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Acute complications of diabetes – the present state of knowledge. Part II. Non-ketotic hyperosmolar hyperglycemia

Ostre powikłania cukrzycy – aktualny stan wiedzy. Część II. Nieketonowa hiperglikemia hiperosmolalna (zespół hiperglikemiczno-hiperosmolalny)

D e f i n i t i o n . Non-ketotic hyperosmolar hyperglycemia (NKHH) is, besides diabetic ketoacidosis, a second most serious acute complication of diabetes. It is characterized by severe hyperglycemia, hyperosmolarity and dehydration in the absence of ketosis [1, 2, 6, 10].

E p i d e m i o l o g y . NKHH occurs mainly in patients with type 2 diabetes, particularly in elderly people who are unable to maintain adequate fluid intake or are unaware of developing hyperglycemia. It may be the first manifestation of previously undiagnosed type 2 diabetes, especially in elderly patients [3,5,6,9]. Rarely, NKHH is diagnosed in type 1 diabetes patients, including children [4,6]. NKHH is 5-6 times less frequent than DKA but its mortality rate is three times higher, approaching 15% [2,3,7].

P a t h o g e n e s i s . NKHH is initiated by partial or relative insulin deficiency accompanied by elevated level of counter-regulatory hormones including catecholamines, growth hormone, glucagon and cortisol [3,10]. Diminished effective action of insulin leads to impaired glucose intake by peripheral tissues, increased hepatic glycogenolysis, and enhanced hepatic and renal gluconeogenesis. The result is hyperglycemia followed by glycosuria and osmotic diuresis with water loss and a rise in serum osmolality (>320mosm/kg water). If a patient is unable to maintain appropriate fluid intake, dehydration results. This, in turn, causes plasma volume contraction and contributes to the development of renal insufficiency with diminished renal glucose excretion. This further increases hyperglycemia and serum osmolarity. When osmolarityr (estimated as 1.86 x Na [mmol/l]+glucose [mmol/l] + urea [mmol/l]) exceeds 380mosm/kg water, mental obtundation and coma develop. Despite severe hyperglycemia, ketosis does not develop in NKHH. It is prevented by the presence of at least small amounts of endogenous insulin. The residual concentration of insulin is believed to inhibit lipolysis in adipose tissue thus limiting the availability of free fatty acids necessary to hepatic ketone bodies formation. Hypernatremia (>150 mmol/l), which is often observed in NHH, implicates severe intracellular water loss and is partially responsible for patients' mental disorders [1–4,10]. The general overview of the pathogenesis of NKHH is presented in Fig. 1.

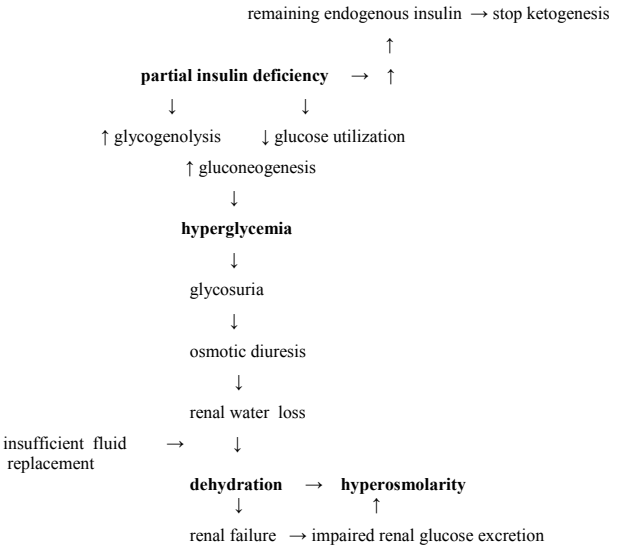

Fig. 1. The overview of the pathogenesis of non-ketotic hyperosmolar hyperglycaemia

Precipitating factors. The main precipitating factors include infection (most commonly pneumonia, urinary tract infection), acute pancreatitis, myocardial infarction, cerebrovascular accident. NKHH can be also elicited by certain drugs which impair insulin secretion or cause insulin resistance, for example: corticosteroids, diuretics, phenytoin, immunosuppressive agents. The key factor initiating and exacerbating NKHH is dehydration [3, 9].

Clinical features. NKHH develops gradually, over several days or weeks. The initial symptoms such as polyuria and polydipsia usually remain unnoticed especially in elderly patients. The majority of patients present with mental disorders including memory, orientation and association problems [3,5,6,9]. The natural history of NKHH eventually leads to lethargy and coma. Physical examination of a patient reveals severe dehydration (loss of skin turgor, dry mucous membranes, tachycardia, hypotension), tachypnoe, face reddening. Patient may also present with neurological deficits including aphasia, partial loss of sight, paresis or nystagmus [8, 9].

Diagnosis is established based on blood glucose level over 600 mg/dl, normal arterial blood pH (at least 7.3), increased plasma osmolality (>320 mosm/kg water) and bicarbonate level over 15 mmol/l. In about 50% of patients hypernatremia is present (> 150 mmol/l). Ketone bodies are not present in the urine or, if so – only in a small amount. Additionally, usually an increased level of creatinine and urea is observed as a mainifestation of renal failure [6, 8–10].

Differential diagnosis. 1. Diabetic ketoacidosis – usually in type 1 diabetes patients. Characterized by acute onset (<24 hrs), with polyuria, polydipsia, vomiting, stomachache. Kussmaul respiration may be present. Arterial blood pH and plasma bicarbonate levels are low, ketone bodies are present in the urine. 2. Hepatic or uraemic coma – should be considered in patients with a history of renal/hepatic failure. In these patients blood glucose is not very elevated (with tendency to hypoglycemia in hepatic failure). 3. Intoxications. 4. Central nervous system disorders [6].

T r e a t m e n t . There are three main aspects of treatment, which include: fluid replacement, insulin therapy and potassium replacement. Simultaneously, a search for the precipitating factors of NKHH should be initiated:

1. Fluid replacement. Owing to the fact that dehydration is a crucial element in the pathogenesis of NKHH, fluid replacement is of paramount importance. It is recommended to replace 50% of fluids within the first 12 hours of treatment. In the case of hypotension, fluid therapy should be begun with 0.9% NaCl. In all other cases, 0.45% NaCl is preferable. Within first hour of therapy, 1000-2000 ml of 0.45% NaCl should be given intravenously. During the next three hours, administration of another 3 liters of hypotonic saline solution is recommended. Further fluid therapy depends on plasma sodium concentration and osmolarity. Besides, fluid infusion rate has to be adjusted to the capacity of the cardiovascular system of the patient. In the case of cardiac failure, it might be necessary to slow down infusion even twice, compared to healthy individuals [6,10].
2. Insulin therapy. In NKHH, insulin therapy seems to be less important than fluid replacement. Insulin doses needed to restore normoglycemia are usually lower than in DKA. In fact, fluid replacement alone can decrease glycemia considerably. Insulin is given intravenously. An initial bolus of 4–8 units of short acting insulin is followed by uninterrupted infusion at a low rate e.g. 0.1 U/kg/h. The expected glucose lowering should not exceed 50–75 mg% per hour. It is not recommended to lower plasma glucose too fast as it promotes rapid fluid and electrolytes movements from extra to intracellular compartment with the risk of cerebral oedema, decreased perfusion in the central nervous system and in other organs. On the other hand, if the glucose level goes down below 50–75 mg/d/hour, the insulin infusion rate should be increased twice every hour until the desired glucose lowering is achieved. When the glucose level reaches 200 mg/dl, the insulin infusion rate should be reduced twice. It is advised to maintain this glycaemia until the mental state of the patient is improved. It might demand additional glucose solution supplementation [3, 6, 10].
3. Potassium replacement. Insulin therapy and fluid replacement cause a decrease in the potassium level. Therefore, in order to avoid hypokalaemia, the potassium replacement should be started when its level drops below 5.3 mEq/l. It is recommended to add 20 mmol of potassium chloride per hour to the fluid given intravenously. Potassium has to be administered very carefully in patients with pre-existing renal failure or oliguria [3, 9].

M o n i t o r i n g . Blood pressure, heart and respiration rate and blood glucose have to be recorded every hour. Potassium, sodium, phosphorus and calcium level should be measured every 4 hours or, if necessary, even more frequently [3, 6, 9, 10]. Furthermore, the patient's mental state has to be estimated systematically. Worsening of consciousness after the initial amelioration might suggest too rapid reduction in plasma osmolarity or too rapid rehydration. Constant improvement in the patient's mental status confirms that the treatment is appropriate [9].

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SUMMARY

Non-ketotic hyperosmolar hyperglycemia (NKHH) is**,** besides diabetic ketoacidosis, a second most serious acute complication of diabetes. It occurs mainly in patients with type 2 diabetes, particularly in elderly people who are unable to maintain adequate fluid intake or have partial renal insufficiency. It is characterized by severe hyperglycemia, hyperosmolarity and dehydration in the absence of ketosis. It carries a 15% mortality risk. The aim of this study is to present the current state of knowledge about NKHH including epidemiology, pathogenesis, clinical features and treatment directives.

Keywords: non-ketotic hyperosmolar hyperglycemia, type 2 diabetes, epidemiology, pathogenesis, treatment directives

STRESZCZENIE

Zespół hiperglikemiczno-hiperosmolarny, określany również jako nieketonowa hiperglikemia hiperosmolalna, to drugie, obok cukrzycowej kwasicy ketonowej, najpoważniejsze ostre powikłanie cukrzycy. Dotyczy głównie chorych z cukrzycą typu 2, zwłaszcza osób w wieku podeszłym z zaburzeniami regulacji pragnienia i głodu bądź osób z częściowo upośledzoną funkcją nerek.

Podstawą rozpoznania jest stwierdzenie znacznej hiperglikemii, hiperosmolalności osocza oraz odwodnienia przy jednoczesnym braku cech kwasicy. Śmiertelność tej patologii sięga 15%. Praca przedstawia stan wiedzy na temat zespołu hiperglikemiczno-hiperosmolarnego w zakresie epidemiologii, patogenezy, obrazu klinicznego, a szczególnie bieżących standardów leczenia.

Słowa kluczowe: zespół hiperglikemiczno-hiperosmolarny, nieketonowa hiperglikemia hiperosmolalna, cukrzyca typu 2, epidemiologia, patogeneza, obraz kliniczny, standardy leczenia