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ГИПЕРОСМОЛЯРНАЯ КОМА: ДИАГНОСТИЧЕСКИЕ СЛОЖНОСТИ НА КЛИНИЧЕСКОМ ПРИМЕРЕ

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Hyperosmolar Coma: Diagnostic Difficulties on the Clinical Example

Резюме

Гиперосмолярное гипергликемическое состояние является острым осложнением сахарного диабета, летальность при котором достигает 50 %. Одна из причин неблагоприятного исхода — несвоевременная диагностика, которая нередко обусловлена недостаточной осведомленностью врачей в отношении особенностей клинических и лабораторных проявлений данного диабетического осложнения. Гиперосмолярное состояние чаще развивается у пациентов старшего возраста с полиморбидностью, а в клинической картине преобладают неврологические симптомы, что также вносит сложности в диагностику и становится причиной диагностических заблуждений. В статье представлен клинический случай гиперосмолярного гипергликемического состояния, диагностика которого вызвала трудности на всех этапах, включая посмертное патологоанатомическое исследование. Первоначально предполагалось острое нарушение мозгового кровообращения, затем тяжелое состояние пациентки связали с острым инфарктом миокарда, а по результатам патологоанатомического исследования было сделано заключение о сепсисе и септическом шоке. Рецензирование истории болезни пациентки показало, что наиболее вероятным диагнозом было гиперосмолярное состояние вследствие декомпенсации сахарного диабета на фоне воспалительного процесса. Выраженная дегидратация пациентки, как причина ее сопорозного состояния, подтверждалась данными осмотра и лабораторно-инструментального исследования: сухость кожи и слизистых, малое количество мочи, признаки сгущения крови и преренальная острая почечная недостаточность. Вместе с тем отсутствие явных очаговых неврологических нарушений, клинически значимых изменений со стороны сердечно-сосудистой системы, лихорадки и нарушений гемодинамики не позволяли, на наш взгляд, связать тяжелое состояние пациентки с инсультом, инфарктом миокарда или септическим шоком. Дегидратация осложнилась развитием синдрома диссеминированного внутрисосудистого свертывания, желудочно-кишечным кровотечением и геморрагическим шоком с летальным исходом. Данный клинический случай свидетельствует о том, что в дифференциальной диагностике заболеваний ключевым подходом является анализ клинической картины с точки зрения патогенеза нарушений. Разбор подобных клинических ситуаций может служить для врачей подспорьем в вопросах диагностики гиперосмолярного состояния.

Ключевые слова: *гиперосмолярная кома, гиперосмолярное состояние, острая декомпенсация сахарного диабета*

Конфликт интересов

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Abstract

Hyperosmolar hyperglycemic state is an acute complication of diabetes mellitus, the mortality rate of which reaches 50 %. One of the reasons for the unfavorable outcome is untimely diagnosis, which is often due to insufficient awareness of doctors regarding the features of clinical and laboratory manifestations of this diabetic complication. Hyperosmolar state often develops in older patients with polymorbidity, and neurological symptoms predominate in the clinical picture, which also complicates diagnosis and causes diagnostic errors. The article presents a clinical case of hyperosmolar hyperglycemic state, the diagnosis of which caused difficulties at all stages, including postmortem pathological examination. Initially, acute cerebrovascular accident was assumed, then the patient's severe condition was associated with acute myocardial infarction, and based on the results of the pathological examination, a conclusion was made about sepsis and septic shock. Review of the patient's medical history showed that the most probable diagnosis was hyperosmolar state, which developed as a result of decompensation of diabetes mellitus against the background of the inflammatory process. Severe dehydration of the patient, as the cause of her soporous state, was confirmed by the data of examination and laboratory and instrumental examination:

dry skin and mucous membranes, small amount of urine, signs of blood thickening and prerenal acute renal failure. At the same time, the absence of obvious focal neurological disorders, clinically significant changes in the cardiovascular system, fever and hemodynamic disturbances did not allow, in our opinion, to associate the patient's severe condition with acute cerebrovascular accident, myocardial infarction or septic shock. Dehydration was complicated by the development of disseminated vascular coagulation syndrome, gastrointestinal bleeding and hemorrhagic shock with a fatal outcome. This clinical case demonstrates that in differential diagnostics of diseases a more reliable approach is the analysis of the clinical picture from the point of view of the pathogenesis of disorders. Analysis of such clinical situations can serve as an aid for doctors in diagnosing hyperosmolar state.

Key words: *hyperosmolar coma, hyperosmolar state, acute decompensation of diabetes mellitus*

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BP — blood pressure, APTT — activated partial thromboplastin time, BBC — blood biochemistry, DIC — disseminated intravascular coagulation, CT — computer tomography, INR — international normalised ratio, MRI — magnetic resonance imaging, CBC — complete blood count, ACVA — acute cerebrovascular accident, CRP — C-reactive protein, EGDS — esophagogastroduodenoscopy, RR – respiratory rate, HR — heart rate, ECG — electrocardiography, echoCG — echocardiography

Hyperosmolar hyperglycaemic state is an acute complication of diabetes mellitus, which manifests with marked hyperglycaemia and associated dehydration and altered state of consciousness. Unlike ketoacidotic hyperglycemic coma, this condition is approximately 10 times less common; at the same time, it is associated with high mortality rates, which can be as high as 50 %. One of the reasons is poor awareness of healthcare providers, making timely diagnosis challenging. Unfortunately, there are just a few articles and clinical case studies on this topic.

Hyperosmolar coma develops in type 2 diabetes mellitus, which is associated with partially preserved insulin secretion, therefore no ketones are present. It is induced by factors contributing to dehydration: acute GIT pathology associated with vomiting and diarrhoea, severe inflammation with fever, restricted fluid intake, and a number of other factors. Hyperglycaemia can be more severe than in ketoacidotic coma, and the values can reach 60–80 mmol/L, because in the presence of ketones, the patient does not have vomiting or nausea, which would make them seek medical attention sooner. It results in more severe dehydration, and fluid deficiency can exceed 10 litres.

Patients in hyperosmolar state are usually elderly, which is partially a result of age-related changes in water-electrolyte metabolism regulation, predisposing them to dehydration: reduced thirst and poorer renal concentrating ability. In the first instance, severe rehydration affects the brain, that is why clinical symptoms are dominated by neurological signs, which are often mistakenly interpreted as cerebrovascular events. A typical sign is altered state of consciousness, spanning from confusion and disorientation to coma, transient focal symptoms — facial asymmetry (downturning mouth), hemianopsia, hemiparesis, hemiplegia, etc.; seizures are also possible. At the same time, nervous system involvement is usually beyond the clear focal syndrome; cerebral damage is more pronounced than local signs; clinical manifestations are unstable and resolve as soon as hyperosmolarity is treated. Brain computer tomography is advisable if neurological symptoms persist despite improvement in hyperosmolarity [1].

Diagnosis of hyperosmolar hyperglycaemic state should take into account clinical and laboratory signs of dehydration: dry skin and mucosa, reduced diuresis and dark. concentrated urine. Complete blood count shows elevated haematocrit and RBC levels. Blood biochemistry results show hyperazotaemia resulting from acute renal failure, in addition to hyperglycaemia. Blood sodium levels are also elevated; test results should be adjusted for hyperglycaemia, because higher blood glucose levels results in higher natriemia values.

The following formula is used to evaluate adjusted sodium levels:

Adjusted sodium levels = measured sodium+1.6 (glucose mmol/L–5.5)/5.5.

Blood biochemistry results and adjusted sodium levels can indicate plasma osmolarity, with the normal values being 285–295 mOsm/L; while in hyperosmolar state, they can be as high as 330 mOsm/L and above.

Plasma osmolarity = 2 (sodium mmol/L+potassium mmol/L)+glucose mmol/L.

Unlike ketoacidotic coma, hyperosmolar state is not associated with metabolic acidosis; however, in some cases, mild acidosis can be possible because of lactic acid accumulation, resulting from impaired microcirculation and tissue hypoxia.

Severe dehydration with pronounced microcirculation impairment causes disseminated intravascular coagulation (DIC) syndrome, which is seen in coagulation profile. DIC leads in gut ulceration, which can be complicated by bleeding.

Usually the cause of death is acute circulatory collapse; postmortem examination often shows advanced thrombosis resulting from disseminated intravascular coagulation.

The key therapeutic strategies are fluid replacement, insulin therapy and potassium level adjustment. Fluid replacement starts with administration of 1 litre of normal saline solution (0.9 %), then adjusted sodium levels are evaluated. If the results exceed 165 mmol/L, then 2.5 % glucose solution is used. Where sodium concentrations are 145–165 mmol/L, it is recommended to initiate infusion therapy with hypotonic (0.45 %) NaCl solution. Once adjusted sodium levels reach 145 mmol/L, saline administration continues. Taken high insulin sensitivity in DM2, insulin therapy should be low-dose (0.5–2 U/h). The target blood glucose level is 13.9–16.7 mmol/L, i.e. higher than in diabetic ketoacidotic coma, where day 1 glycaemic target is 13–15 mmol/L due to a higher risk of cerebral oedema in case of hyperosmolarity. Protection against cerebral oedema is also taken into account in recommendations on the rate of glycaemia reduction: 4 mmol/L/h, plasma osmolarity: 3–5 mOsm/L/h; and sodium levels: 10 mmol/L/day.

Potassium deficiency is usually more pronounced than in ketoacidotic coma because of more severe osmotic diuresis. Potassium deficiency is corrected with blood potassium testing. Recommended concomitant treatment includes broad-spectrum antibiotics due to a high risk of infection, as well as low molecular heparins due to a high risk of blood-clotting [2, 3].

Case study

Female patient R., 74 years old, brought in by the ambulance on August 28, 2021 in semicoma. Her condition had been deteriorating for the past 7–10 days, with increasing atony and lethargy, up to no reactions, which was the reason to call the ambulance. According to the patient's daughter, the patient had had type 2 diabetes mellitus for 25 years, arterial hypertension — for 10 years; four and two years before admission, she was diagnosed with dementia and arrhythmia, respectively. During the past two years, blood sugar levels were corrected with basal-bolus insulin therapy; for the cardiovascular condition, the patient was taking angiotensin-converting enzyme inhibitor (lisinopril), beta blocker (bisoprolol) and antiplatelet (acetylsalicylic acid); for dementia — neurotropic drug (memantine). For the past year, the patient had a medical attendant caring for her.

Upon admission, the condition was severe; level of consciousness — semicoma. Examination revealed dry skin and tongue, reduced skin tightness. Blood pressure (BP) was 100/75 mm Hg; heart rate (HR) — 65 bpm; respiratory rate (RR) — 17/min; O2 saturation — 96 % (with oxygen support); body temperature: 36.4 °C.

Complete blood count (CBC) showed elevated RBC count of 6.34×10^{12}/L (up to 4.7×10^{12}/L; reference values are given in brackets), Hb — 177 g/L (up to 140), hematocrit — 52.4 % (up to 42), WBC — 22.8×10^{9} (up to 8.5), and low platelets count — 154×10^{9}/L (from 200). Blood biochemistry (BBC) showed elevated blood glucose levels — 55.96 mmol/L (up to 5.9), creatinine — 244 μmol/L (up to 84), urea — 29.64 mmol/L (up to 6.7), sodium — 151 mmol/L (up to 145), C-reactive protein (CRP) — 98.07 mg/L (up to 5), lactic dehydrogenase — 453.1 IU/L (up to 230), aspartate aminotransferase — 81.6 U/L (up to 35), creatine phosphokinase — 394.8 IU/L (up to 170). Coagulation profile showed elevated activated partial thromboplastin time (APTT) — 48.4 s (up to 37), APPT index — 1.51 (up to 1.2) and international normalised ratio (INR) — 1.25 (up to 1.2). Urinalysis results: dark urine, glucosuria up to 20 mmol/L, protein traces — 0.033 g/L, no acetone.

Electrocardiography (ECG) showed atrial fibrillation 85–180 per minute without any signs of damage. An ultrasound examination revealed multiple stones in gall bladder opening, elevated echogenicity and diffuse structural inhomogeneity of pancreas, uneven kidney contour, uneven renal parenchyma and diffuse echogenicity heterogeneity. Small amount of urine in bladder. Brain and chest computer tomography (CT): unremarkable.

A preliminary diagnosis was made on the basis of examination and test results. Primary diagnosis: Complex origin encephalopathy (dysmetabolic, residual) with moderate cognitive damage, social and domestic maladaptation, decreased level of consciousness (semicoma). Acute cerebrovascular accident (ACVA) cannot be ruled out. Secondary diagnosis: Stage III hypertensive disease, risk 4. Type 2 diabetes mellitus, insulin therapy. Chronic kidney disease C4. Ischaemic heart disease with rhythm disturbances. Tachysystole atrial fibrillation. Complications: Chronic heart failure 2A.

Based on the diagnosis, intensive care was initiated in ICU.

Next day (August 29, 2021) the patient had black faeces; she was examined by the on-call surgeon and underwent esophagogastroduodenoscopy (EGDS), which showed acute erosive esophagitis and recent bleeding. Antiulcer and anticoagulation reversal therapy was recommended.

It is worth noting that despite recent bleeding, blood draws dated August 29, 2021 and August 30, 2021 showed

persistently high levels of RBC, Hb and haematocrit. WBC levels remained high as well, while platelet count decreased to 80×10^9/L (should be at least 200). Blood biochemistry still showed hyperazotaemia, hyperenzymemia, and high CRP levels. Blood sodium concentration was 158 mmol/L (up to 145). Troponin I test came back positive.

On hospitalisation day three (August 30, 2021), neurological symptoms included restricted active movements, more in the right arm. Ischaemic ACVA of the left carotid pool was diagnosed. In order to confirm the diagnosis, magnetic resonance imaging (MRI) and echocardiography (echoCG) were performed. MRI results showed individual subcortical ischaemia foci in the right occipital and parietal lobes (infarctions). Atrophic changes in cerebral hemispheres. EchoCG results: induration of ascending aorta, coronary tendons and aortic and mitral valve cusps with calcifications. Dilated left atrium. Left ventricle myocardial hypertrophy. Left ventricle diastolic dysfunction.

Based on the clinical symptoms and changes seen on MRI scans, the diagnosis was corrected; primary diagnosis: ischaemic ACVA of both carotid pools, cardioembolic subtype, with right-sided hemiparesis, motor aphasia, pseudobulbar syndrome.

The patient was treated with infusion therapy (sterofundin), antihyperglycemic drugs (insulin), diuretics (furosemide), antimicrobials (moxifloxacin, cefotaxime), metabolic therapy (mexidol, ceraxon), lipid-lowering drugs (atorvastatin), proton pump inhibitor (omez), anticoagulants (heparine), beta blocker (metoprolol), and received enteral feeding (Nutricomp, water). Infusion therapy amounted to 1,500 to 2,150 mL/day.

Follow-up CBC dated August 31 and September 01, 2021: elevated RBC and WBC levels and low platelet count. BBC results: persisting values of nitrogenous waste, enzymes, CRP and sodium, the concentration of which was 150 to 163 mmol/L (up to 145). Coagulation profile: even worse coagulation system impairment — APTT was 116.5–168 s (up to 37), APTT index — 3.6–5.3 (up to 1.2), INR — 2.6 (up to 1.2), Quick's value — 38 % (NLT 75).

At 08.00 a.m. on hospitalisation day five (September 02, 2021), the patient had loose stool with haemorrhagic contents; body temperature rose to 37°C, RR — to 20 per minute, and HR — to 90 bpm; BP dropped to 88/59 mm Hg. Pressor agent dopamine 10 μg/kg/min was started for haemodynamic support. EGDS was performed, which showed coffee grouts-like stomach contents (up to 20 mL); no active bleeding was observed during examination; conclusion: erosive haemorrhagic esophagitis, atrophic hyperplastic gastritis. The patient was examined by a surgeon, who diagnosed acute erosive esophagitis with recent bleeding. At 08.45 a.m., clinical death and asystole were recorded; resuscitation was ineffective. The patient was pronounced dead at 09.15 a.m.

In the postmortem report, the primary diagnose was revised and changed to ischaemic heart disease, acute myocardial infarction of unknown location dated September 02, 2021, complicated by cardiogenic shock. Concurrent diagnosis: erosive haemorrhagic esophagitis with gastrointestinal haemorrhage of unknown origin and grade III haemorrhagic shock.

Postmortem examination showed multiple apical abscesses of maxilla and mandible, as well as numerous organ damage: necrotising nephrosis, centrolobular haemorrhage in the liver, acute erosive ulcerative gastroenteritis, gastrointestinal haemorrhage (approximately 300 mL of blood clots in intestine postmortem), subpleural bleeding in the lungs, myocardial necrosis area on the posterior left ventricle wall (type 2), 3.5×2 cm, 3–5 days old, liquid blood in heart cavities and large vessels, haemorrhage in cortex of kidneys, focal haemorrhage in adrenals, acute general congestion, pulmonary oedema, cerebral oedema.

Discrepancy between the clinical and postmortem diagnosis was recorded. According to medical examiners, the primary diagnosis was acute purulent periodontitis with odontogenic sepsis, systemic inflammatory response syndrome (WBC dated September 02, 2021 — 22.8×109/L), multiple organ damage, disseminated coagulation syndrome in hypocoagulation phase, pulmonary and cerebral oedema; cause of death: septic shock.

The final diagnoses, both clinical and postmortem, require revision.

Discussion

In this clinical case study, the clinical manifestations in the patient were mostly cerebral, whereas signs of focal damage appeared on hospitalisation day three and did not correspond to the degree of impairment of consciousness; that is why ACVE was unlikely, which was confirmed with CT, MRI and postmortem examination results. The severity of the patient's condition could not be a result of myocardial infarction, taken preserved haemodynamics, no ECG and echoCG signs of myocardial damage up to day 5 of follow-up, when the patient died. These findings necessitated the search for metabolic causes of the severe condition of the patient.

The diagnosis "odontogenic sepsis with septic shock" as the primary cause of the disease is also plausible, given the lack of fever and impaired haemodynamics in the patient in semicoma. As far as leukocytosis is concerned, its bacterial origin is inconclusive because of the lack of inflammatory changes seen in complete blood count results (elevated erythrocyte sedimentation rate and left deviation).

The concurrent diagnosis stated in postmortem report needs attention: "erosive haemorrhagic esophagitis with gastrointestinal haemorrhage of unknown origin and grade III haemorrhagic shock". As a matter of fact, haemorrhagic contents of faeces with drop in BP is a sign of massive blood loss. The consecutive asystole implies that the haemorrhagic shock was the cause of death. It is likely that gastrointestinal haemorrhage was caused by DIC syndrome.

The following sequence of events can be suggested.

Acute purulent periodontitis resulted in diabetes mellitus decompensation and marked hyperglycaemia. Apparently, late call for medical assistance was caused by cognitive disorders in the patient, her sensory diabetic neuropathy after 25 years of diabetes mellitus, which disguised the pain syndrome, and by probable misjudgement of the patient's health condition by caregivers. Severe hyperglycaemia up to 55.96 mmol/L was the cause of severe dehydration and hyperosmolar state. Dehydration was confirmed during examination: dry skin with decreased tightness, dry tongue, dark urine, as well as laboratory and instrumental test results — high RBC count, high levels of nitrogenous waste, enzymes, sodium; small amount of urine in the bladder.

High WBC count could also be caused by dehydration and tissue damage resulting from impaired microcirculation. Besides, high WBC values could be induced by blood loss, which could also happen before hospitalisation, confirmed by black faeces on hospitalisation day two and finding ulcerative damage to esophagus mucous seen during EGDS. Blood loss worsened dehydration, and RBC counts remained high because of severe dehydration.

Using the above formulae, adjusted sodium levels upon admission were 160.8 mmol/L, whereas the upper limit of normal is 145; plasma osmolarity was 389.52 mOsm/L, with the reference value being up to 295. Significantly higher osmolarity resulted in severe brain tissue dehydration and semicoma, as well as in impaired microcirculation and DIC syndrome with blood clots, consumption thrombocytopenia, and poor coagulation profile. These damages caused areas of infarction in the brain, myocardium and erosive ulcerative damage to GIT with haemorrhagic shock. Although the postmortem examination showed approximately 300 mL of blood, which is not a fatal blood loss, the severe condition of the patient as well as her elderly age can make her highly susceptible to less blood loss.

This clinical case demonstrates challenging diagnosis of hyperosmolar state, despite involvement of various specialists and advanced laboratory and instrumental capacities. We believe that this is an example of the significance of clinical interpretation taking into account pathological mechanisms [4, 5]. Understanding the clinical symptoms makes it possible to avoid both overestimation and underestimation of laboratory and instrumental results, as well as diagnostic misconceptions, including hyperosmolar state.

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