Обобщающие уроки клинической патофизиологии

СИСТЕМНЫЙ ПОДХОД К ЕСТЕСТВЕННЫМ ПУТЯМ И ВЗАИМОСВЯЗАННЫМ ЗВЕНЬЯМ ПАТОГЕНЕЗА. НАРУШЕНИЯ ВОДНО-ЭЛЕКТРОЛИТНОГО ОБМЕНА. ЧАСТЬ 2. НАРУШЕНИЯ ОСМОТИЧЕСКОГО ГОМЕОСТАЗА И МОЗГ

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Integrative Lessons in Clinical Pathophysiology

SYSTEMIC APPROACH TO NATURAL PATHWAYS AND NETWORKING OF ETIOPATHOGENESIS. DISORDERS OF FLUIDS AND ELECTROLYTES. PART TWO. DISORDERS OF OSMOTIC HOMEOSTASIS AND BRAIN

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Резюме. В этом номере мы продолжаем серию публикаций для самостоятельной патофизиологической проработки клинических задач. Форма, избранная в виде публикации клинического случая и ситуационных задач, требует активного участия читателей. В соответствии с главной темой данного номера журнала вниманию читателей предлагается алгоритмический разбор механизмов мозговой дисфункции при гемодинамическом шоке и нарушений сознания при диабетическом гиперосмолярном синдроме. Типовые этиопатогенетические кластеры гипонатриемии и гипернатриемии иллюстрируются двумя клиническими случаями Каждый типовой этиопатогенетический кластер гипонатриемии и гипернатриемии иллюстрируется двумя клиническими случаями. Клинико-патофизиологический разбор предполагает обсуждение дисфункции мозга в контексте конкретного данного заболевания / нарушения. Решения для заданий, как для упражнений A–C в алгоритмической части, так и для разделов II и III в части этиопатогенетических кластеров, будут опубликованы для самоконтроля правильности ответов в следующем номере журнала (5 рис., библ. 6 ист.).

Ключевые слова: энергодефицит мозга, гипоэргоз, гемодинамический шок, гиперосмолярный синдром, этиопатогенетические кластеры, гипонатриемия, гипернатриемия, набухание мозга, нарушения сознания, отек мозга.

Abstract. In this issue we continue with the series of self-elaborative pathophysiology of clinical problems. The form of study case imposes an active readers' participation. In accordance with the central thematics of this issue the algorhythmic workout of brain dysfunction during hemodynamic shock and consciousness diorders in diabetic hyperosmolal syndome are presented. The etiopathogenetic clusters (EPC) of hypernatremia and hyponatremia are illustrated with two case studies in each EPC. Each study case considers brain dysfunction within the integral context of given disease / disorder.

The solutions of the tasks, both, for A through C exercizes in algorhythmc and for II and III workout segments of EPC-approach, will be provided for a self-control of correct answers in the upcoming issue of the journal (5 figs, bibl.: 6 refs).

Key words: Brain energy disorders, hypoenergosis, hemodynamic shock, hyperosmolal syndrome, etiopathogenetic clusters, hyponatremia, hypernatremia, brain swelling, consciousness disorders, brain oedema.

ALGORHYTHMIC WORKOUT OF CLINICAL PROBLEM.

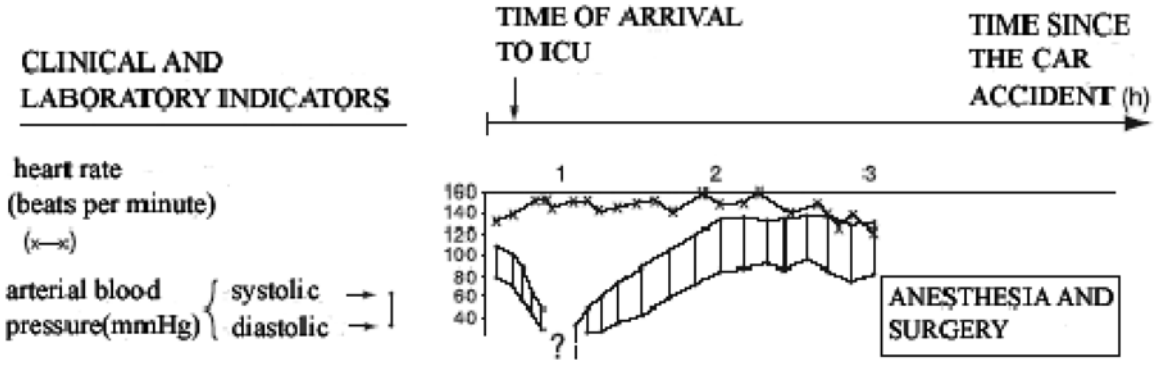
Pathophysiology of the hypovolemic hemodynamic shock syndrome[1]

Readings for this problem are found on pages 133–5, 388–90, 526–32 and 610–11 of your Pathophysiology (5th edition) textbook.

A 23-year old driver involved in a car accident, acquired multiple injuries, facial lacerations, a cut on the shoulder, contusion of the left fist and, in addition, he took a blow to the abdomen and the lower third of the right side of the thorax [1].

Immediately after the accident, he remained conscious and managed to get out of the car wreck by himself. The external bleeding ceased spontaneously soon after. Within the next 25 minutes, he noticed an unpleasant feeling in the abdomen; he slowly grew tired and became lethargic. In the ambulance he became soporous, his skin was extremely pale, cold and clammy, the peripheral pulse was not palpable but was still present on the neck; he developed a tachycardia as well. Systolic arterial pressure during transport ranged from 100→55 mmHg and the diastolic between 75→35 mmHg. Figure 1 shows all of the relevant clinical signs in the course of the disease.

[1] Taken from the book Z. Kovač, S. Gamulin (Ed.) Pathophysiology. Study Guide Algorhythms — Problem Solver. Book Two. Medicinska Naklada Zagreb; 2013: 307–11, with the consent of the Publisher and the author.



						normal values
central venous pressure	0,5	1	1	2	4	1–9 cm H_2O
hourly diuresis		7		18		20–100 mL/h
respiratory frequency	28	30	32	28	24	12–18 breaths /minute
pH	7,36			7,41		7,36–7,44
$PaCO_2$	3,2			3,7		4,6–6,1 kPa
PaO_2	9,2			11,1		10,0–13,3 kPa
base excess	5			-2		±4 mmol/L
erythrocyte count	3,8			4,4		4,5–5,5 × 10^{12}
hematocrit	0,39			0,43		0,45–0,52
carbamide in plasma	8,9			8,1		3,1–7,1 mmol/L
K^+ in plasma	5,4			5,1		3,8–5,0 mmol/L
Na^+ in plasma	140			141		135–145 mmol/L
lactate in plasma	3,6			2,0		0,5–2,2 mmol/L

Fig. 1. Pathogenetic indicators of the hypovolemic shock caused by a traumatic rupture of the liver resulting with internal bleeding. Symbol "?" represents immeasurable values

During the transport, a rapid IV of saline was administered. At the time of arrival to ICU the patient was unable to communicate, could still react to external stimuli by mimicking, however very slowly and incoherently. Arterial pressures became immeasurable at one point. On admittance, blood samples were taken for laboratory analysis and about 10 minutes later, he started receiving a matching blood transfusion via two IV lines. In a half an hour, he had received 1200 ml of blood and his arterial pressure became measurable (see Fig. 1). In the following hour and a half, the arterial and venous pressure normalized and his consciousness improved to a somnolence.

Ultrasound imaging revealed a large amount of fluid in the peritoneal cavity that was compressing the abdominal organs in addition to ruptured liver tissue. The spleen and the kidneys ultrasonically appeared unaffected, while the other organs could not be distinguished clearly. Emergency chest and abdominal X-rays showed a fractured 8th and 9th rib on the right side. With the arterial pressure being stabile, the patient was referred to a surgical treatment. The midline laparotomy showed a large amount of dark stained blood inside the peritoneal cavity (about 3 L), partly coagulated, and also a rupture of the liver tissue. Gastrointestinal tract was undamaged.

Exercise A: Repetitions of relevant knowledge (Circle one or more correct answers)

1. According to the patient's condition, all of the following claims are correct:

a) Blood transfusions increase the volume of circulating blood, which converts the clinical condition to a compensated phase of circulatory collapse, reflected by the improvement in blood pressure and cerebral functions.

b) During the first 20 minutes after the car accident, the patient remained conscious despite the internal bleeding because the compensatory mechanisms maintained a sufficient blood flow to the brain by centralizing the circulation.

c) The patient developed a decompensated phase of shock since hypovolemia exceeded the compensatory ability of blood vessels despite the maintained pressure producing activity of the heart.

d) Since the heart rate exceeding 180 beats / min shortens diastole too much (2/3 of the physiological length) the venous return and the stroke volume became reduced which rendered tachycardia an inefficient mechanism.

e) As a result of reduced vascular tonus, centralization of the blood flow became inefficient adaptation, otherwise manifested by hypercatecholaminemia, pallor, cold and clammy skin and pale mucous membranes.

2. According to data in Fig. 1, all of the following pathogenetic mechanisms occur in the pathogenesis of hypovolemic shock:

a) A moderate oligocythemia and decreased hematocrit are a consequence of the saline IV administered during the patient transport and do not reflect the vascular "filling" directly.

b) Altered level of consciousness is a result of progressive reduction of the blood flow through the brain, thereby causing dysenzymatic hypoenergosis in the neurons, which consequently cause an electrolyte imbalance of the cell membranes.

c) Pale and cold skin in the patient occur because of skin vasoconstriction and reduced heat release from the central body parts due to the centralization of the blood flow.

d) Infusion of plasma is just as effective as a blood transfusion when it comes to correcting hypovolemia since it contains the proteins that remain inside the blood vessels and oncotically draw the fluid towards the intravascular lumen.

e) Moderate hypoxemia (PaO_2 = 9.2 kPa within the first hour) induces hyperventilation which at the time of hypotension is unable to correct the tissue hypoxia since the main problem lies in a reduced tissue perfusion.

3. Pathogenesis of the hypovolemic shock is distinguishable from the other types of shock (cardiogenic or vasogenic) by all of the following mechanisms:

a) A significant compensatory role in hypovolemic shock is based on venoconstriction and blood flow redistribution, which increase the effective volume of circulating blood; and this mechanism is absent during vasogenic septic shock.

b) Central venous pressure is decreased in hypovolemic shock due to a reduced "filling" of the blood vessels, and either normal or increased in different kinds of shock.

c) Generally speaking, we can say that the compensatory response of the heart and blood vessels is maintained during the hypovolemic shock and impaired in other kinds of shock.

d) Efficiency of the heart and the blood vessel response during compensated phase of the hypovolemic shock is decreased compared to the other kinds of shock since hypovolemia exceeds compensatory capabilities of the heart and the blood vessels.

e) Although the heart function and the vascular adaptive capacity are normal, in decompensated phase of the hypovolemic shock the arterial pressure progressively decreases which is augmented by the development of secondary hypovolemia.

4. All of the following claims pertaining to the general pathogenesis of the hypovolemic shock are correct:

a) Disorders of the electrolyte and water balance can lead to hypovolemic shock (e. g. in Addison's disease, in hyperosmolar syndromes combined with hyponatremia, in diarrhea associated with cholera syndrome).

b) Reduced blood volume approximately bellow 36–45 mL/kg of body weight in women, or 39–48 ml/kg of body weight in men, represents an incompensative hypovolemia which causes a fast shift into a decompensated phase of a shock.

c) Infusion of isotonic solutions is very effective therapy of the hypovolemic shock since most of the infused fluid remains inside the blood vessels and directly corrects the hypotension.

d) Reduced blood volume exceeding the tonus adaptation of blood vessels causes reduced pressures in both arterial and venous systems thereby causing reduced blood flow through the tissues.

e) In decompensated phase of a shock, not even the strongest stimulation by catecholamines can increase the venous return and the stroke volume since the intravascular blood volume is depleted.

5. In the pathogenesis of the three basic types of circulatory shock (cardiogenic, hypovolemic and vasogenic) all of the following common mechanisms are observed:

a) Baroreceptor mediated decrease of the arterial pressure as well as hypovolemia through the volume receptors stimulate pathways of the vasomotor center and neuroendocrine system towards the centralization of the blood flow.

b) In decompensated phase of a shock many hemostatic mechanisms form positive feedback loops, which through their actions deteriorate reduction of arterial-venous pressure difference.

c) On the cellular level, tissues develop hypoenergosis (both hypoxic and substrate) which cause a shift in the metabolism as well as organ dysfunction.

d) A response from the vasomotor center to a loss of arterio-venous pressure difference is identical in all of three pathogenetic types of shock, however, the efficiency of that response depends on the functional state of the blood vessels and the heart (e. g. compare a massive myocardial infarction and an anaphylactic shock).

e) In all three pathogenetic types of shock, it is possible to prove increased pressure in the right atrium caused by activation of the vasomotor center as well as reduced arterial pressure.

Exercise B: Algorhythmic workout of the pathogenesis

Arrange the following terms in causative order:

1. Blood transfusion and plasma infusion
2. Tachycardia
3. Mechanical trauma (a steering-wheel blow to the abdomen)
4. Impaired consciousness
5. Discontinuity of the liver tissue and the Glisson's capsule
6. Vasoconstriction in the skin
7. Hyperlactacidemia
8. Stimulation of volume and baroreceptors
9. Vasoconstriction of the vascular system
10. Reduced arterial-venous pressure difference
11. Hypoenergosis of the cerebral cells
12. Reduced flow thorough the renal arteries
13. Hypovolemia
14. Hypoxia
15. Prerenal kidney failure
16. Strong stimulation of the vasomotor center
17. Internal bleeding
18. Oliguria
19. Stimulation of sweat glands
20. Increased intravascular volume
21. Increased efficiency of the vascular and cardiac compensatory mechanisms
22. A shift in the energy metabolism
23. Hypercatecholaminemia
24. Reduced blood flow through the cerebral blood vessels
25. Extreme deceleration of a car during a crash
26. Reduced substrate delivery into the brain

Exercise C: Feedback integration of the problem
(Solve the tasks in following way; Correct claim + correct claim + mutually related = a; correct claim + correct claim + mutually non-related = b; correct claim + incorrect claim = c; incorrect claim + correct claim = d; inorrect claim + incorrect claim = e)

1. In a decompensated phase of the shock, tissue hypoenergosis leads to organ dysfunction (see claim 1c) such as impaired consciousness (claim 2b, terms 4 and 11 of the algorithm) and renal failure (see Fig. 1, terms 15 and 18 of the algorithm).

because

decreased concentration of ATP inhibits energy dependant metabolic processes, which leads to a metabolic arrest and a loss of ionic concentration gradients across the cell membranes.

a b c d e

2. The patient developed a decompensated phase of hypovolemic shock due to the internal bleeding from the ruptured liver (claim 1b, terms 13 and 14 from the algorithm)

because

there is a primary decrease in the efficiency of adaptive mechanisms due to the increased tonus of blood vessels and capillaries as well (compare claims 1d, 1e and 2d).

a b c d e

3. In mechanical trauma, external force of the blow was greater than the elastic forces of the liver, which caused a tissue to rupture and led to a massive bleeding (claim 3b)

because

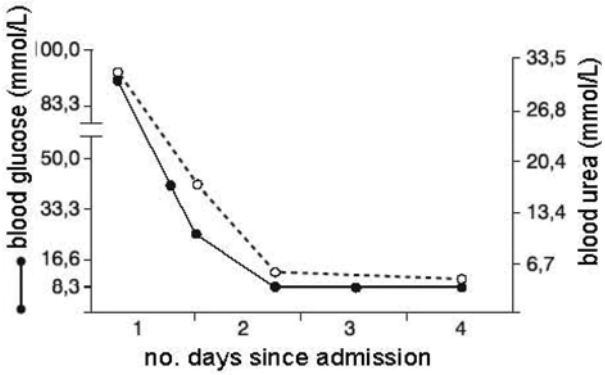
the pressure in the peritoneal cavity is basically lower than the average pressure in the pleural and alveolar space, which facilitates the bleeding from the ruptured hepatic vessels.

a b c d e

Additional questions:

4. Name three etiopathogenetic groups of hypovolemic shock and list two clinical examples for every group.

5. The relationship between the heart rate (beats / min) and the mean arterial pressure (mmHg) is termed Allgower's index, which in the compensated phase of



Serum	NHD[a]	Days of management				Normal values
		1st	2nd	3rd	4th	
Osmolality, mOsm/L		396	294	286		
Sodium, mmol / L		144	138	135		
Potassium, mmol / L		3.0	3.5	3.5		
Bicarbonate,mmol / L		20	23	23		
Ketonemia		–	–	–	–	
Blood pH		7.35	7.40	7.41		7.36–7.44
Urine						
Glucosuria	+++	++++	++++	++	–	–
Ketonuria	–	–	–	–	–	–0.6–1.6
Volume, L / day	0	0.5	1	2	–	
Therapy						
Insulin, units		500	300	100	150	
Infusion, liters		8	4	1.5	1.5	

Fig. 2. Relevant laboratory indicators for the patient with hyperosmolal hyperglycemic syndrome obtained in the first four days of management. (Symbol "–" stands for non-provable and symbol "+" for semiquantitative arbitrary units.)
[a]NHD = data obtained from the nursing home, a night prior to admission.

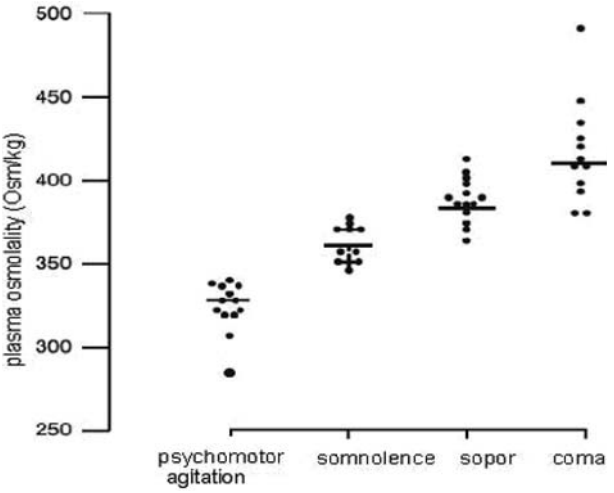


Fig. 3. Relationship between plasma osmolality and sensory and perception disturbances in 53 patients with hyperglycemic hyperosmolality

the cardiovascular collapse exceeds 1. According to the data in Fig. 1, it is obvious that the chronotropic compensatory mechanism in the patient is inefficient with respect to maintaining the arterio-venous pressure difference. Illustrate by graphic representation of the heart work curve ($\Delta V \times \Delta T$) why this mechanism became inefficient in the particular patient.

ALGORHYTHMIC WORKOUT OF CLINICAL PROBLEM.

Pathophysiology of the hyperosmolal syndrome in the course of newly diagnosed diabetes mellitus[2]

In order to workout this problem, study pages 115–6, 156–62, 249, 385–6 and 538–43 of the Pathophysiology, 5th edition.

A 78-year-old man was brought to the emergency room in a state of impaired consciousness, dehydrated, tachycardic and anuric, weighing 68 kg [2]. According to heteroanamnestic data and the enclosed medical documentation, the patient had none previous records of diabetes. The patient has lost about eight kilograms of body mass over the previous month. Three weeks ago he started to complain of excessive and frequent urination. He constantly complained of thirst and consumed approximately 5–7 liters of water daily. Two days ago he became confused, lethargic and somnolent; yesterday he was barely in contact. Upon admission the patient was comatose, very dehydrated, hypotensive (75–90 / 40–50 mmHg), tachycardic (110–146 beats / minute), anuric. Small laboratory in his nursing home determined glycosuria and absence of ketones by urinanalysis. Laboratory indicators of the disease obtained during initial four days of hospitalization are shown in Fig. 1. Neither vomiting, acidosis nor Kussmaul's breathing were observed in the patient. Rehydration was carried out by hypotonic solution during first three days, followed by isotonic fluids as shown in Fig. 2. Upon rehydration and regulation of diabetes, the patient has significantly recovered within five days, became conscious, communicative and normotensive.

Consciousness impairment in hyperosmolal hyperglycemic syndrome correlates well with extracellular space osmolality, as shown in Fig. 3. Measured plasma osmolality in the patient corresponded to "sopor-coma" values (compare data in Fig. 1).

[2] Taken from the book Z. Kovač, S. Gamulin (Ed.) Pathophysiology. Study Guide Algorhythms — Problem Solver. Book Two. Medicinska Naklada Zagreb; 2013: 178–82, with the consent of the Publisher and the author.

Exercise A: Repetitions of relevant knowledge (Circle one or more correct answers)

1. For development of hyperglycemic hyperosmolal syndrome all of the following claims are accurate:

a) The condition develops in patients with uncontrolled diabetes mellitus with only partially decreased insulin function, thereby they are not prone to ketoacidosis.

b) In the initial phase of the disease a considerable amount of sodium is being lost by polyuria due to glycosuric osmotic diuresis, thus causing hyponatremia with approximate decrease rate of 1.6 mmol/L per glucose increase of 5.5 mmol/L.

c) Hyperosmolality of the extracellular space causes cellular edema, whereas osmolality of intracellular fluid remains constant.

d) Due to consciousness impairment developed in the last two days prior to admission to the hospital, the patient has decreased water intake despite preexisting extracellular hyperosmolality, which led to water-depletion within the organism, hypernatremia and further increase in hyperglycemia.

e) It can be expected that anion deficit in the syndrome is not altered significantly, since laboratory tests for keto-acids in urine in plasma proved negative.

2. For certain symptoms within the syndrome as observed in the described patient, all of the following pathogenetic processes are responsible:

a) Malaise develops as a consequence of cellular substrate hypoenergosis, hyperosmolality as well as impaired volume and composition of the extracellular fluid.

b) Prior to consciousness impairment the patient has, by polydipsia, regularly caused extracellular hypoosmolality with water shift back into cells.

c) Body mass loss experienced one month prior to his admission was a consequence of gradual dehydration due to osmotic diuresis with polyuria that caused fluid loss greater than the peroral substitution by water intake.

d) Polydipsia results from activation of osmoreceptors in the hypothalamic thirst center in response to extracellular hyperosmolality, accompanied by concomitant activation of the neurohypophysis with augmented vasopressin (ADH) secretion, thus increasing urine osmolality.

e) Cessation of fluid intake due to gradual deterioration of consciousness caused the patient to rapidly lose extracellular volume with sudden increase in plasma osmolality.

3. For the pathogenesis of the patient's condition all of the following claims are true:

a) Severe polyuria coupled with consciousness impairment and sensory deficits may lead to dehydration of the organism, hypovolemia and hypotension, possibly leading to hypovolemic circulatory shock (patient's condition upon admission).

b) Bicarbonate concentration and pH values remained practically normal (see Fig. 1), since glucose directly acts as a buffer for hydrogen ions.

c) In diabetic hyperosmolal syndrome, there is a very small increase in plasma free fatty acids in relation to ketoacidosis severity, since the present insulinemia, though moderately decreased, inhibits lipolysis.

d) On admission, the patient was in a decompensated circulatory shock that is pathogenically classified into complex form of circulatory shock, because of involved concomitant hypovolemic and vasohypotonic pathogenetic components.

e) The patient had ketogenesis limited by suppressed lipolysis consequential to activity of available insulin due to which acetoacetic and β-hydroxybutyric acids did not form.

4. In development of diabetes mellitus, clinical manifestation in the form of acute syndromes (hyperosmolal syndrome or syndrome of diabetic ketoacidosis) are determined by all of the following pathogenetic mechanisms:

a) Moderate decrease of insulinemia diminishes facilitated diffusion of glucose into the cell with simultaneously maintained lipid metabolism regulation which results from lower metabolic threshold for lipid, in relation to the glucose regulation.

b) Ketoacidosis develops as a compensatory energetic metabolic pathway, enabled by simultaneous lipolysis increase which activates ketogenesis and increases anion gap.

c) In hyperosmolal syndrome Kussmaul's respiration does not occur, bicarbonate concentration is not significantly lowered and pH plasma value is > 7.30, since marked metabolic acidosis does nor occur.

d) In both acute syndromes of diabetes, ketoacidosis and hyperosmolal syndrome, disenzymatic hypoenergosis develops intracellularly, anionic gap increases with comparable accumulation of endogenous osmolutes within cells.

e) As a result of hyperglycemia, glycosylation of available proteins takes place (non-enzymatic protein alterations) due to which, among others, dysfunction of basement membranes occurs.

5. As a part of hyperglycemic hyperosmolal syndrome, all of the following pathogenetic mechanisms can occur:

a) In very high hyperglycemia (approximately > 35mmol/L), a considerable amount of glucose is being transported into cells without insulin-mediated facilitation; thus enabling its utilization as intracellular energy source, especially facilitated by muscle work.

b) Due to hyperosmolality of extracellular space, cell dehydration and volume decrease occur, with simultaneous intracellular synthesis of endogenous osmolutes (such as sorbitol, polyols, myoinositol, methylamines) that increase intracellular space osmolality.

c) Although powerful mechanisms of urine concentration are being activated in order to preserve water within the organism, the patient developed hypotension as a consequence of excessive cell dehydration including smooth muscles within blood vessels.

d) Extracellular hyperosmolality causes intracellular hyperosmolality through dehydration and stimulation of endogenous osmolute production, which cause intracellular edema to appear during rapid therapeutic hypoosmolal infusions.

e) As a part of the syndrome, neurological symptoms may appear (such as sensomotor aphasia, hemiparesis, visual hallucinations, focal epilepsy, hyperreflexia) as a consequence of dehydration, hyperosmolality and electrolyte imbalance in central nervous system cells.

Exercise B: Algorhythmic workout of the pathogenesis

Arrange the following terms in causative order:

1. Decreased transmembrane glucose transport within tissues
2. Substrate hypoenergosis of the insulin dependent cells
3. Insulin system insufficiency
4. Extreme hyperglycemia
5. Cellular dehydration
6. Polydipsia
7. Hyponatremia (compare claim 1b)
8. Severe osmotic diuresis
9. Glucosuria and polyuria
10. Consciousness impairment (see Fig. 2)
11. Increased synthesis of endogenous intracellular osmolutes
12. Decrease and cessation of water intake *per os*
13. Hypernatremia
14. Water deficiency in relation to plasma Na^+ and Cl^-
15. Hyperkalemia
16. Oliguria and anuria
17. Hypovolemia and hypotension
18. Acute renal failure
19. Inhibition of lipolysis
20. Decreased lipid degradation
21. Hyperosmolality of the extracellular space
22. Increased natriuresis due to glycosuric osmotic diuresis
23. Tachycardia
24. Infusions of hypoosmolal fluids
25. Strong stimulation of vasomotor center
26. Glucose filtration in glomeruli considerably exceeds the transport maximum

Exercise C: Feedback integration of the problem (Solve the tasks in following way; Correct claim + correct claim + mutually related = a; correct claim + correct claim + mutually non-related = b; correct claim + incorrect claim = c; incorrect claim + correct claim = d; inorrect claim + incorrect claim = e)

1. In diabetes, hyperosmolal hyperglycemic syndrome occurs as a consequence of absent glucose regulation by insulin, whereas lipid and amino acid metabolism regulation remain maintained (claims 3c, 3e, 1a)

because

in type II diabetes which is predominantly insulin independent diabetes, insulinemia and c-peptide concentrations may be increased or physiological; in some tissues insulin resistance can occur.

a b c d e

2. In the course of treatment of hyperosmolal syndrome, rapid administration of hypoosmolal fluid may cause the syndrome of brain edema, since the intercellular space becomes hypotonic in relation to the intracellular space

because

development of hyperosmolal syndrome in the course of diabetes involves increase in intracellular osmolality by dehydration and activation of endogenous osmolute production (claims 5b and 5c); that newly formed hyperosmolality reverses the cell volume back to normal.

a b c d e

3. Hyperosmolal (non-ketotic) coma develops in about 33% of diabetic comas, with diagnostic criteria (blood glucose > 33 mM, serum osmolality >340 mOsm/kg, HCO_3^- > 15 mM, low ketone values, sensory depression, pH > 7.3) that reflect the basic pathogenesis of the condition (compare the algorithm)

because

effects of insulin deficiency rely on different sensitivity of individual reactions (glucose transport at about 40 µU/mL, lipolysis inhibition at 15 µU/mL, inhibition of gluconeogenesis and glycogenolysis at 12 and 6 µU/mL, respectively); during which a moderate insulin decrease causes absence of lipolysis activation (compare claims 1a, 1e, 3c, 3e, 4a).

a b c d e

Additional questions

4. Calculate the approximate value of osmol surplus in extracellular and intracellular spaces in the patient on the day of admission.

5. Calculate a deficit of water volume within the organism according to the following equation:

Water deficit = 0.6 × body mass (in kg) × (1–140/corrected sodium).

In hyperglycemia above 8.25 (compare claim 1b) corrected sodium concentration is calculated according to the expression:

Corrected sodium = measured sodium + (1.5 × (glycemia – 8.25)/5.5).

All concentration are in mM.

Compare the calculated water deficit with the volume infused in the course of treatment.

EPC — WORKOUT OF CLINICAL PROBLEM

Various etiopathogenetic pathways have natural tendency to influence each other, to come together and integrate within the units called **etiopathogenetic clusters (EPC)**. Analysis and consideration of such nodes are important for understanding of the nature of disease. The EPCs are important networking elements in biological reactivity. In Fig. 4 and 5 EPC-rosettes outline various groups of diseases/conditions, regardless of their etiologies — which are associated with the same ECP, **the EPC of Hypernatemia** and **the EPC of Hyponatremia**, respectively. The rosettes are followed by two case studies within the each EPC.

Case study 1.2. HYPERNATREMIA — with somnolence, hyperosmolality of the plasma, polyuria and extrapontine myelinolysis as components of pituitary diabetes insipidus[3].

The case study has been adopted from the article of Chang et al. Unusual occurrence of extrapontine myelinolysis associated with acute severe hypernatremia caused by central diabetes insipidus. Clin. Endocrinol. 2005; 63: 232–7.

I. **Medical history** [3]. 55 years-old female was admitted through an emergency department with the symptoms of psychiatric disorders, somnolence and polyuria despite the reduced fluid intake. The anamnestic data did not suggest possible etiology of the disorder. At the time of admittance she was hypotensive (BP was 91/57 mmHg, normal range: 110/70–135/80 mmHg) with the heart rate of 86 bpm (normal range: 60–100 bpm), orientated, and was unable to perform all required tasks for the complete neurological examination. The patient was hypernatremic (172 mmol/L, normal range: 136–144 mmol/L) and hyperglycemic (7 mmol/L, normal range: 3.3–5.5 mmol/L). Excessively low osmolality of the urine (230 mmol/kg, normal range: 50–1200 mmol/L) in the comparison with the hyperosmolality of the serum (370 mmol/kg, normal range: 278–305 mmol/kg) indicated diabetes insipidus.

Intravenous fluid replacement was started with 12L of physiological saline solution during three hours with the intranasal administration of the desmopressin (DDAVP, synthetic analogue of arginine vasopressin), resulting in the increase of the urine osmolality to the 444 mmol/kg. Patient was still hypotensive, developed non-cardiogenic lung edema and the short episode of bradycardia with electrical activity without a pulse which was treated with the atropine. Patient had hypocortisolism (210 mmol/L, normal range: 220–660 mmol/L) with the low levels of ACTH in contrast to the conditions of the acute stress (167 pmol/L, normal range: 154–1123 pmol/L) which led to the introduction of the high dose of corticosteroids into therapy. Patient, which was in a menopause, had low levels of serum FSH (<1.2 IU/L, normal range: >40 IU/L) and LH (3.8 IU/L, normal range: >40 IU/L). 3 mm formation in the area of the lower hypothalamus was observed on the nuclear magnetic resonance images (NMR), with the thickening of the pituitary stalk, which indicated infundibulo-hypophysitis; and bilateral changes in the area of the cerebral peduncles and corpus callosum which indicated extrapontine myelinolysis.

Blood pressure, sodium levels and osmolality of the serum were normalized over the course of the next two days. After removing DDAVP from the therapy, there was a decrease in the osmolality of the urine to the 90 mmol/kg with hyperosmolality of the serum (319 mmol/kg, normal range: 285–295 mmol/kg) which indicated persistent diabetes insipidus. Neurological follow up examination, the serum levels of prolactin, growth hormone and thyroid hormones and ACTH stimulating test were all normal with the significant regression of observed changes on the follow up NMR images.

ADDITIONAL INSIGHT: Lymphocytic infundibulo-hypophysitis is autoimmune disorder of the pituitary gland which usually occurs in the females during late pregnancy or postpartum. Usually it is located in the adenohypophysis, but in 20–30% of the cases it can also occur in the neurohypophysis.

Heavy acute hypernatremia leads to the rapid intracellular dehydration and axonal demyelination, extrapontine myelinolysis respectively, while sudden restoration of hyponatremia (>10–15 mmol/L/24h) often causes pontine myelinolysis. Gradual development of hypernatremia does not lead to the myelinolysis due to the compensatory retention of electrolytes and endogenous production of organic osmolytes in the nerve cells, which maintains isotonic compositions of the cells in comparison with the serum thus preventing osmotic stress.

II. Etiopathogenesis of the disease (Using the given elements compose an etiopathogenetic algorithm of the disease)

1. Severe acute hypernatremia
2. Axonal demyelination — myelinolysis

[3] Taken from the book Z. Kovač. **Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One**. Medicinska Naklada Zagreb; 2013: 4–5, with the consent of the Publisher and the author dr Lada Bradic. Case study code number **1.2** corresponds to the group of processes outlined in the EPC rosette in Fig. 4.

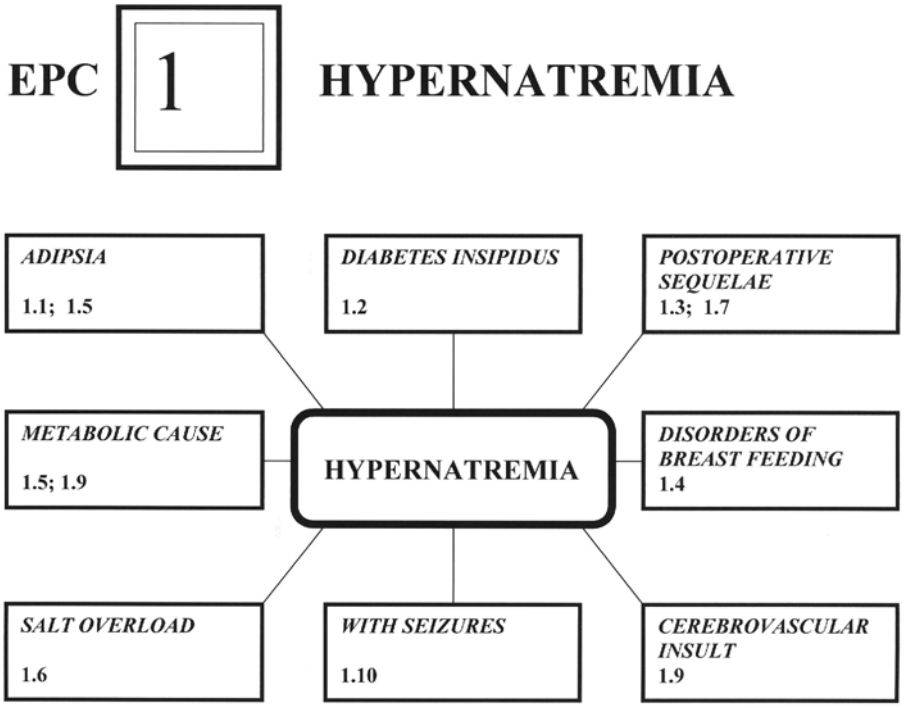


Fig 4. Introductory rosette of (EPC) of hypernatremia serves as navigation scheme among multiple groups conditions, all related to this electrolyte disorder. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book

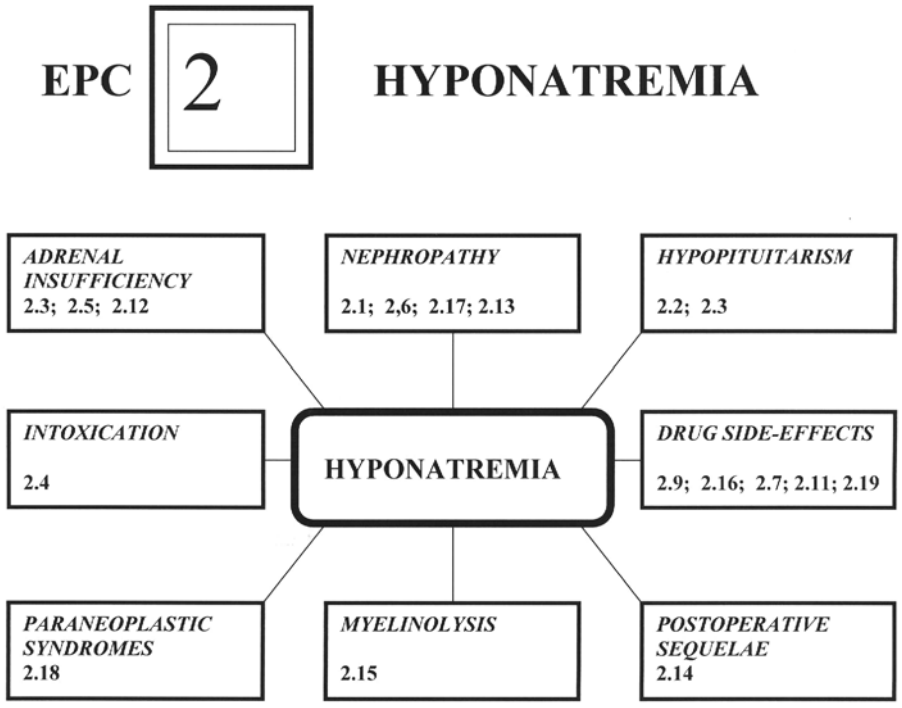


Fig. 5. Introductory rosette of etiopathogenetic cluster (EPC) of hyponatremia serves as navigation scheme among multiple groups conditions, all related to this electrolyte disorder. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book

3. Pituitary diabetes insipidus with decrease in the ADH secretion
4. Excretion of large quantities of hypotonic urine
5. Lymphocytic infundibulo-hypophysitis
6. Adenohypohpysis insufficiency
7. Neurological symptoms (psychiatric disorders, somnolence)
8. Intracellular brain dehydration

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition. According to data presented in this case study please outline a) 7 etiological features; b) 23 features of pathogenesis; c) 16 features of disease spread and chronobiology; d) 12 feature of clinical elaboration (diagnosis, therapy) — using the classification features specified on page … of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable. (Please write the decimal number-codes of the features.)

Case study 1.9.
HYPERNATREMIA — wirh hypernatriuria, hyperchloremia hypokalemia and hyperosmolality in patient with disabilties due to cerebrovascular insult one year ago[4]

The case study has been adopted from the article of Park Y. J. et al. Successful treatment in the patient with serum sodium level greater than 200 mEq/l. J. Korean Med. Sci. 2000; 15: 701–3.

I. Medical history [4]. The 52-year-old woman has been driven into ER in comatose condition without any verbal or motoric response. Heteroanamnesis shows that she has had a fever with significantly decreased mental capability for the last two days, and that she had become comatose on the day of arrival in the ER. She was last hospitalised one year ago because of hemorrhagic insult of the basal ganglia. She has been addicted to somebody's care since then.

At arrival, she was not contactable; she was breathing spontaneously, shallow and rapidly (20 respirations/min, normal range 12–18). She was hypertensive (150/100 mmHg, normal range 110/70–135/80) and afebrile (36.4 °C axillary, normal range 36.0–37.5), dry mucous membrane. Her pupils were normal in size, symmetrical and reactive, and Babinsky's reflex was bilaterally negative.

Patient was hypernatremic (206 mmol/l, normal range 135–145), hypokalemic (2.2 mmol/l, normal range 3.5–5.3) and hyperchloremic (157 mmol/l, normal range 95–108) with hyperosmolar serum (427 mmol/l, normal range 270–290) and urine osmolarity of 872 mmol/kg (normal range 500–1200). She had increased concentration of sodium in urine (300 mmol/l, normal range 36–65). Computerized tomography (CT) of her brain showed numerous lesions of the basal ganglia with degenerative and atrophic changes.

Due to dehydration with estimated water lack of 8 L she started to receive treatment of fast intravenous and per oral fluid compensation. Although the correction of sodium was too fast (1.9 mmol/l/h, normal range < 1), she didn't have any clinically visible neurological consequences. The patient became contactable already the day after with appearance of spontaneous movements and on the third day, when serum sodium was completely normalised, she could complete commands.

ADDITIONAL INSIGHT: Most frequently hypernatremia is a consequence of non-compensated loss of water by gastrointestinal or respiratory system. In outside-hospital environment, generally it can be seen in elderly or mentally retarded people. In the described case, severe dehydration was a consequence of incapability of independent consummation of liquid after CVI and also fever.

Natremia above 160 mmol/l is considered to be severe hypernatremia, and it is accompanied by 60–70% mortality. It is considered that duration and speed of its correction affect the percentage of neurological recovery. Recommendations say that correction of hypernatremia shouldn't be faster than 0.7–1.0 mmol/l/h or 10% natremia per day. Recommended compensation of water is the half of estimated deficiency during first 24 h until full compensation during next 2–3 days. Too fast compensation of liquid can lead to cerebral swelling because of an osmotic shift of liquid into brain cells.

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorhythm of the disease.)

1. Osmotic shift of liquid into brain cells
2. Too fast compensation of hypernatremia
3. Dehydration because of incapability of liquid consummation in a patient with CVI
4. Cerebral swelling
5. Dehydration of brain cells
6. Hypernatremia
7. Osmotic shift of liquid from brain cells
8. Compensatory entrance of electrolytes and organic resin into brain cells

III. Classification of etiopathogenetic nature and development of disease / disorder / condition. According to data presented in this case study please outline a) 6 etiological features; b) 17 features of pathogenesis; c) 8 features of disease spread and chronobiology; d) 13 feature of clinical elaboration (diagnosis, therapy) — using the classification features specified on page … of this issue. Only the features which come

[4] Taken from the book Z. Kovač. **Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One**. Medicinska Naklada Zagreb; 2013: 12–13, with the consent of the Publisher and the author dr Lada Bradic. Case study code number **1.9** corresponds to the group of processes outlined in the EPC rosette in Fig. 4.

out of presented medical history and etiopathogenetic elaboration of processes are acceptable. (Please write the decimal number-codes of the fe

Case study 2.7.
HYPONATREMIA — with hypoosmolality, hypochloremia, seizures and inappropriate ADH secretion as a side effect of citalopram therapy[5]

The case study has been adopted from the article of Flores G et al. Severe symptomatic hyponatremia during citalopram therapy — a case report. BMC Nephrol. 2004; 5: 2–5.

I. **Medical history** [5]. A 61-year-old male referred to the hospital because of a 3-day history of malaise, progressive confusion, and tonic / clonic seizures. Two weeks before, he had been started on a regimen of antidepressant citalopram (20 mg at the evening). The patient and his wife reported that he became progressively confused, lethargic and had difficulty performing simple tasks. He is a type 2 diabetics treated with metformin 500 mg twice daily and glyburide 2.5 mg once daily.

Upon admission, the patient was afebrile with normal vital signs. He appeared euvolemic without evidence of congestion or dehydration. Neurologic examination was normal except for decreased strength on lower extremities. Laboratory findings revealed hyponatremia of 124 mmol/L (normal range 136–145), potassium of 4.3 mmol/L (normal range 3.5–4.5), hypochloremia of 86 mmol/L (normal range 98–106), blood urea nitrogen of 3.2 mmol/L (normal range 3.6–7.1), creatinine of 79.56 μmol/L (normal range < 133), glucose of 10.49 mmol/L (normal range 4.2–6.4), uric acid of 150 μmol/L (normal range 150–480) and serum hypoosmolality of 263 mOsm/ L (normal range 285–295). Urine sodium and urine osmolality were elevated, 141 mmol/L, and 400 mOsm/L, respectively. A computed tomography (CT) of the head and an EEG were both normal. Morning cortisol level, thyroid-stimulating hormone (TSH) and free thyroxine levels were within normal limits. Results of a urine toxicology screen revealed no presence of ethanol or recreational drugs. A citalopram pill count confirmed compliance with the drug regimen without evidence of overdose.

A diagnosis of SIADH (Syndrome of inappropriate ADH secretion) was made based on clinical euvolemia in the presence of hyponatremia with a urine osmolality and sodium that were inappropriately high. Normal renal, thyroid and adrenal function with relative hypouricemia, all supported SIADH.

On the day of admission, citalopram was discontinued and the patient was treated with two liters of intravenous 0.9% sodium chloride, phenytoin (5 mg/kg), and subcutaneous insulin. Approximately, 24 hours after admission the patient›s serum sodium increased to 129 mmol/L, and the chloride increased to 89 mmol/L. Thereafter, fluids were restricted to 1200 mL/day. His mental status improved over the next 48 hours. Five days after admission, serum sodium was 134 mmol/L and serum chloride was 99 mmol/L. Patient was fully alert, had no more seizures and was subsequently discharged. At this time, phenytoin treatment was stopped. A follow up serum sodium three weeks after discharge was 135 mmol/L.

ADDITIONAL INSIGHT: Citalopram is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class. Experimental data indicate that the synthesis of ADH in the hypothalamic supraoptic nucleus is under serotoninergic control. In cases of inappropriate secretion of ADH reabsorption of urate in the proximal renal tubules is reduced.

Transmembrane shift of water due to hypoosmolality causes intracellular oedema, which in central nervous system neurons induces general response to be inappropriate stimuli manifested as the occurrence of paroxysmal excessive neuronal discharge (epileptic activity) with subsequent tonic / clonic convulsions.

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorhythm of the disease)

1. Hyponatremia and serum hypoosmolality
2. Neurological symptoms (confusion, lethargy, epileptic seizures)
3. Citalopram therapy
4. Increased water reabsorption in the renal distal and collecting tubules and a positive water balance
5. Intracellular oedema of the CNS neurons
6. Inappropriately high synthesis and secretion of ADH in the neurons of the hypothalamic supra optic nuclei
7. Urine hyperosmolality
8. Increased serotonergic neuronal activity

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition. According to data presented in this case study please outline a) 10 etiological features; b) 15 features of pathogenesis; c) 13 features of disease spread and chronobiology; d) 12 features of clinical elaboration (diagnosis, therapy) — using the classification features specified on page … of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable. (Please write the decimal number-codes of the features.)

[5] Taken from the book Z. Kovač. **Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One**. Medicinska Naklada Zagreb; 2013: 25–6, with the consent of the Publisher and the author dr Hrvoje Jakovac. Case study code number **2.7** corresponds to the group of processes outlined in the EPC rosette in Fig. 5.

Case study 2.12.
HYPONATREMIA — with hypoglycemia, alkalosis, loss of orthostatic balance and collapse in acute adrenal insufficiency (Addison's crisis syndrome) with hypothyroidism[6]

The case study has been adopted from the article of Nayback A. M. Hyponatremia as a consequence of acute adrenal insufficiency and hypothyroidism. J. Emerg Nurs. 2000; 26:130–3.

I. **Medical history** [6]. A 19-year-old man suddenly collapsed from the state of full consciousness while standing in line for movies. He was pale, sweated, pupils were 3 mm in diameter, with weakened pupillary reflexes. Palpatory measured systolic blood pressure was 120 mmHg (normal range 100–139), the heart rate was 90 bpm (normal range 60–100), and respiration rate was 16 breaths/min (normal range 12–20). Venous line could not me made. During transport in the ambulance patient becomes extremely disorientated and aggressive. With on-hand glucometer hypoglycemia of 1.6 mmol/L (normal range 4.2–6.4) was found, but the patient refused to take glucose by mouth.

On admission examinations showed sinus tachycardia of 120 bpm, systolic blood pressure of 80 mmHg, decreased peripheral pulse, and tachypnea of 22 breaths/min, with the administration of 10 L of oxygen by «Ambu» mask. Mucous membranes were dry and the skin had «marbled» pigmentation. Urine was not obtained by Foley's catheter. The concentration of glucose in the blood could not be measured with glucometers. After establishment of venous access the patient received a bolus injection of a 50% glucose solution and Ringer's lactate, but glycemia remained undetectable. After the second ampoule of 50% glucose infusion and 2 L of Ringer's lactate mental status of patients improved, glycemia reached 14,6 mmol/L, and blood pressure rised to 130/55 mmHg with a heart rate of 110 bpm.

Laboratory tests reveal hyponatremia of 112 mmol/L (normal range 137–145), hypochloremia of 81 mmol/L (normal range 98–107), hyperkalemia of 5.4 mmol/L (normal range 3.5–5.0) and elevated urea of 18.9 mmol/L (normal range 2.8–8.3). Arterial blood gas analysis determined hypocapnia of 16 mmHg (normal range 35–45), elevated PO_2 of 208 mmHg (normal range 80–95) with oxygen therapy, hypobicarbonatemia of 13 mmol/L (normal range 18–23), and pH of 7.53 (normal range 7.35–7.45), suggesting respiratory alkalosis. Due to progressive hypoglycemia during the next 2 hours, two ampoules of 50% dextrose solution were infused, and the infusion of 10% solution was continued. Saline infusion was introduced for rehydration and correction of electrolytes. Further laboratory tests in patients revealed severe hypocortisolemia (<0.2 μg/100mL, normal morning range from 6.2–29.1), and elevated concentrations of ACTH (1745 pg/mL, normal range 9–52) and TSH (55 mU/mL, normal range 0.35–4.94). Based on these and previous findings and clinical symptoms, the diagnosis of Addison›s disease (Morbus Addison, primary adrenal cortex insufficiency) and primary hypothyroidism was established.

ADDITIONAL INSIGHT: Of the many causes of damage to the adrenal cortex and its consequential hypofunction, the most common is an autoimmune process. The patient can also develop autoantibodies against adrenal and thyroid antigens, resulting in failure of both primary glands (Schmidt›s syndrome — an autoimmune polyendocrine syndrome type 2, and type 1 which is Addison›s and hypoparathyroidism with candidiasis — Whitaker›s syn.). The patient experienced typical Addison›s crisis (acute adrenal insufficiency, adrenal crisis), characterized by severe hyponatremia, low blood pressure and hypovolemic shock and hypoglycemia. Different stress conditions (sudden need for cortisol) are often triggers of such crisis. Hypoglycemia is the result of an inadequate secretion of cortisol, a key instigator of gluconeogenesis, while the lack of mineralocorticoids is the reason of inadequate sodium reabsorption with consequential hypovolemia, hypotension and hypovolemic shock, with simultaneous retention of potassium.

Although adrenal insufficiency leads to mild metabolic acidosis (decreased aldosterone-induced renal secretion of H^+ ions), compensatory hyperventilation with tachypnea (further induced by strong activation of the sympathetic nervous system) causes respiratory alkalosis.

Neuropsychological symptoms are result of joint effects of hypoenergosis (a substrate hypoenergosis due to hypoglycemia and hypoxic hypoenergosis due to hypoperfusion during circulatory shock), electrolyte imbalance and alkalosis on CNS.

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorithm of the disease)

1. Hypoglycemia
2. Hyponatremia, hyperkalemia
3. Tachycardia, tachypnea, miosis, paleness, sweating
4. Reduced activity of Na^+/K^+ pump in renal epithelial tubule cells
5. Lack of corticosteroids and hypothyreosis with hypercorticotropinema and hypertireotropinemia
6. Compensatory activation of sympathetic system
7. Neurological symptoms, disorientation
8. Hypovolemia, hypotension and circulatory shock

[6] Taken from the book Z. Kovač. **Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One**. Medicinska Naklada Zagreb; 2013: 31–3, with the consent of the Publisher and the author dr Hrvoje Jakovac. Case study code number **2.12** corresponds to the group of processes outlined in the EPC rosette in Fig. 5.

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition. According to data presented in this case study please outline a) 7 etiological features; b) 26 features of pathogenesis; c) 19 features of disease spread and chronobiology; d) 8 feature of clinical elaboration (diagnosis, therapy) — using the classification features specified on page … of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable. (Please write the decimal number-codes of the features.)

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6. Ibid. Idem. Pp. 31–3.

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ОТВЕТЫ К КЛИНИЧЕСКИМ ЗАДАЧАМ З. Ковача

(см.: Клин. патофизиол. 2015; 4: 89–98)

SOLUTIONS OF THE ALGORHYTHMIC WORKOUT OF CLINICAL PROBLEMS BY Z. KOVAČ

(Clin. Pathophysiol. 2015; 4: 89–98)

Diabetes insipidus

Exercise A: 1. a,c,d,e; 2. a,c,d,e, 3. b,c,d,e, 4.a,c,d,e, 5b,c,d,e.

Exercise B: 3→10,16; 4→25; 5→17; 6→5; 8→5; 9→18,20; 10→4; 11→15; 12→21; 13→1,3; 14→11; 15→2,13; 16→8,17; 17→6; 19→7; 20→7; 21→11; 22→14; 23→2; 24→9, 25→24.

Exercise C: 1c, 2c, 3b.

4. Ratio between maximal and minimal urine concentration is approximately 30:1

5. Intracellular and extracellular fluid loss is approximately 1.8 L and 0.9 L, respectively.

SOLUTIONS OF THE ALGORHYTHMIC WORKOUT OF CLINICAL PROBLEM — Fluid infusion adaptations.

Exercise A: 1d, 2a, 3a, 4e, 5b.

Exercise B: 2→4,10,15,17,26; 3→7; 5→8,19,23; 5→3; 6→25; 7→25; 9→25; 11→20; 12→11; 14→18; 15→3;16→24; 17→14,16; 17→3; 18→1,3; 18 →17; 19→20; 21→13; 22→1,4; 22→17; 24→19,22; 25→5; 26→20.

Exercise C: 1e, 2c, 3b.

4. A 0.9% NaCl solution has osmolarity of 310 mOsm/L, and 5% glucose solution has osmolality of 278 mOsm/L.hence, the difference is 32 mOsm/L.

5. During infusion of saline the contents of salt is increased by 309 mmol, which causes roughly 10% increase of total salt (i.e. 309mmol/3909mmol) in the extracellular space. During infusion of glucose solution there is no change in salt contents in body.