Обобщающие уроки клинической патофизиологии

СИСТЕМНЫЙ ПОДХОД К ЕСТЕСТВЕННЫМ ПУТЯМ И ВЗАИМОСВЯЗАННЫМ ЗВЕНЬЯМ ПАТОГЕНЕЗА. НАРУШЕНИЙ ВОДНО-ЭЛЕКТРОЛИТНОГО ОБМЕНА. ЧАСТЬ 3. ПАТОФИЗИОЛОГИЯ ЭНДОКРИНОПАТИЙ

З. Ковач

Загребский университет, г. Загреб, Хорватия

Integrative Lessons in Clinical Pathophysiology

SYSTEMIC APPROACH TO NATURAL PATHWAYS AND NETWORKING OF ETIOPATHOGENESIS-DISORDERS OF FLUIDS AND ELECTROLYTES. PART THREE. PATHOPHYSIOLOGY OF ENDOCRINOPHATIES

Z. Kovač

Medical School University of Zagreb, Zagreb, Croatia

Резюме. В этом выпуске мы продолжим серию клинико-патофизиологических задач с пояснениями для самостоятельной проработки. Форма клинико-патофизиологических разборов предполагает активное участие читателей. В соответствии с центральной тематикой данного номера журнала предлагается алгоритмический разбор эндокринных нарушений и расстройств, связанных с альдостероном. Этиопатогенетические кластеры (ЭПК) гиперкалиемии и гипокалиемии проиллюстрированы двумя тематическими случаями для каждого ЭПК. Каждый разбор предусматривает рассмотрение определенной эндокринопатии в качестве интегрального контекстного или иного заболевания / расстройства.

Решение задач как для упражнений A–C в алгоритмической части семинара, так и для II и III сегментов раздела ЭПК будет дано для самоконтроля правильных ответов в следующем выпуске журнала (4 рис., 3 табл., библ.: 7 ист.).

Ключевые слова: альдостерон, гиперальдостеронизм, гипоальдостеронизм, гиперкалиемия, гипокалиемия.

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 algorithmic workout of disorders of aldosteron related endocrinopathies are presented. The etiopathogenetic clusters (EPC) of hyperkalemia and hypokalemia are illustrated with two case studies in each EPC.

Each study case elaborates the selected endocrinopaty asthe integral context of given disease / disorder. The solutions of the tasks, both, for A through C exercizes in algorithmic 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 (4 figs, 3 tables, bibliography: 7 refs).

Key words: aldosterone, hyperaldosteronism, hypoaldosteronism, hyperkaliemia, hypokaliemia.

ALGORITHMIC WORKOUT OF CLINICAL PROBLEM

Pathophysiology of endocrinopathies with aldosterone homeostasis disorders[1]

The problem task was based on data from published paper: C. W. Perrin [6].

Aldosterone endocrinopathies are complex group of disorders with very heterogeneous etiopathogenesis. Table 1 shows etiopathogenetic groups of diseases with aldosterone insufficiency, while Table 2 lists groups of hyperaldosteronemic diseases and syndromes. Figure 1 illustrates interrelationship between aldosteronemia and aldosterone / renin activity ratio in primary and secondary hyperaldosteronisms and aldosterone insufficiencies.

Figure 2 shows genetic enzyme disorders in aldosterone synthesis pathway responsible for certain hereditary diseases.

[1] Taken from the book Z. Kovač, S. Gamulin (eds.) [4], with the consent of the Publisher and the author.

Exercise A: Repetitions of relevant knowledge

(Circle one or more correct answers)

1. According to data in Table 1 and Fig. 1 and 2, pathogenetic mechanisms of mineralocorticoid insufficiency are accurately described by the following claims:

a) Primary aldosterone insufficiency has decreased aldosteronemia to renin activity ratio since, due to absent aldosterone synthesis, hypovolemia-induced hyperreninemia cannot increase aldosterone concentration.

b) Secondary aldosterone insufficiencies mostly maintain physiological aldosteronemia to renin activity ratio despite hypoaldosteronemia.

c) Causes of adrenal *zona glomerulosa* dysfunction followed by aldosterone insufficiency include hereditary genetic disorders, autoimmune processes, infections, hemorrhages and tumor metastases into the adrenal gland.

Table 1. Etiopathogenetic classification of mineralocorticoid insufficiencies

Group of disorder	Disease/syndrome and some attributes of the condition
Hereditary biosynthetic insufficiencies[a]	21-hydroxylase insufficiency (cortisol deficiency, genetic disorder on 6p21.3 chromosome with recessive inheritance)
	aldosterone-synthetase deficiency
	3β-hydroxysteroid deficiency, sexual infantilism
	insufficiency of cholesterol desmolase
Other hereditary diseases	adrenoleukodystrophy (deficiency of peroxisomal enzymes linked with Xp28 chromosome)
	congenital adrenal hypoplasia (commonly associated with Duchenne's muscular dystrophy)
Autoimmune diseases	isolated adrenal autoimmunity
	polyglandular deficiency type I (combined with muco-cutaneous candidiasis and hypoparathyroidism)
	polyglandular deficiency type II (combined with autoimmune thyroiditis and insulin-dependant diabetes mellitus)
Infections	tuberculosis
	sepsis (pneumococcal in particular)
	in a course of AIDS
	cytomegaloviral
Hemorrhages	infant trauma in complicated birth, e.g. breech birth
Metastatic diseases	especially breast carcinoma and pulmonary carcinoma

[a] Compare illustration of biochemical sequence in Figure 2.

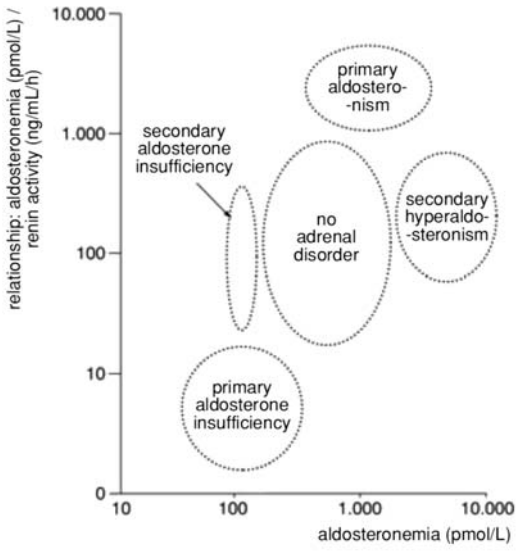

Fig. 1. Relationship between aldosterone concentration in plasma and interrelation of aldosteronemia with plasma rennin activity in various conditions of mineralocorticoid insufficiency or excess

d) In development of chronic tuberculous process in adrenal glands, parenchymatous cells undergo metaplastic transformation into fibroblasts with consequential reactive tissue fibrosis.

e) In type II polyglandular autoimmune disease (with the main autoantigen being 21-hydroxylase enzyme) parenchymatous cell destruction decreases adrenal gland reactivity and quantitatively reduces aldosterone synthesis.

2. According to data in Table 1 and Fig. 1 and 2, pathogenesis of hyperaldosteronism is accurately described by the following claims:

a) Excessive uncontrolled aldosterone secretion in adenoma is a consequence of corticotropin receptor expression that regularly appears as a part of dysdifferentiation process of the initial adenomatous cell.

b) Primary hyperaldosteronism (Conn's syndrome) is predominantly a consequence of hormonally active adenomas of adrenal *zona glomerulosa*, while consequential hyperaldosteronemia causes an increase in extracellular space by retention of sodium and water.

c) In primary hyperaldosteronism aldosteronemia to plasma renin activity ratio regularly exceeds 1000 to 10 000 times.

d) Aldosteronemia to renin activity ratio in secondary hyperaldosteronism is mostly within physiological range, but plasma aldosterone concentration is in a supraphysiological level, frequently higher than aldosteronemia in syndromes of primary aldosteronism.

e) Since secondary aldosteronism represents a reactive consequence of plasma volume reduction, decreased interrenal flow or heart failure, it is regularly accompanied by hyperreninemia; thereby aldosteronemia to renin activity ratio does not increase (differing from primary aldosteronism).

3. Electrolyte disorders in hyperaldosteronism are involved in the following pathogenetic mechanisms:

a) Salt and water reabsorption in distal tubule is increased in morphologically unaltered kidney, thus causing hypernatremia, hypervolemia, hypertension, but sodium does not accumulate within the organism, nor edema appear due to "escape" from renal tubules.

b) Carbohydrate tolerance decreases with susceptibility towards hyperglycemia; a mechanism originates from decreased insulin secretion due to hypokalemia that β-cells of endocrine pancreas react upon.

c) In severe prolonged hypokalemia, kidneys can develop kaliopenic nephrosis with decreased urine concentrating capacity (nephrogenic diabetes insipidus) with polyuria and polydipsia.

d) Hypokalemia shows arrhythmogenic effect on the heart (development of extrasystoles, paroxysmal atrial tachycardia with or without atrio-ventricular block, occasionally ventricular fibrillation); pressure-

Table 2. Etiopathogenetic groups of disorders and syndromes of hyperaldosteronism.

Group of disorder	Disease/syndrome and some attributes of the condition
Primary hyperaldosteronism (Conn's syndrome)	adenomas with aldosterone secretion, 65% of patients bilateral hyperplasia of *zona glomerulosa*, 35% of patients unilateral (primary) hyperplasia, 5% of patients
Hyperaldosteronism that responds to glucocorticoid treatment	CYP11B1/CYP11B2, 8q22-linked dominant disorder
Other hereditary diseases	11β-hydroxylase deficiency (CYP11B1) 8q22-linked recessive disorder 17β-hydroxylase deficiency, sexual infantilism (CYP17), to 10th chromosome linked recessive disorder
Secondary (hyperreninemic) hyperaldosteronism	in liver cirrhosis, due to decreased aldosterone biotransformation and hypovolemia

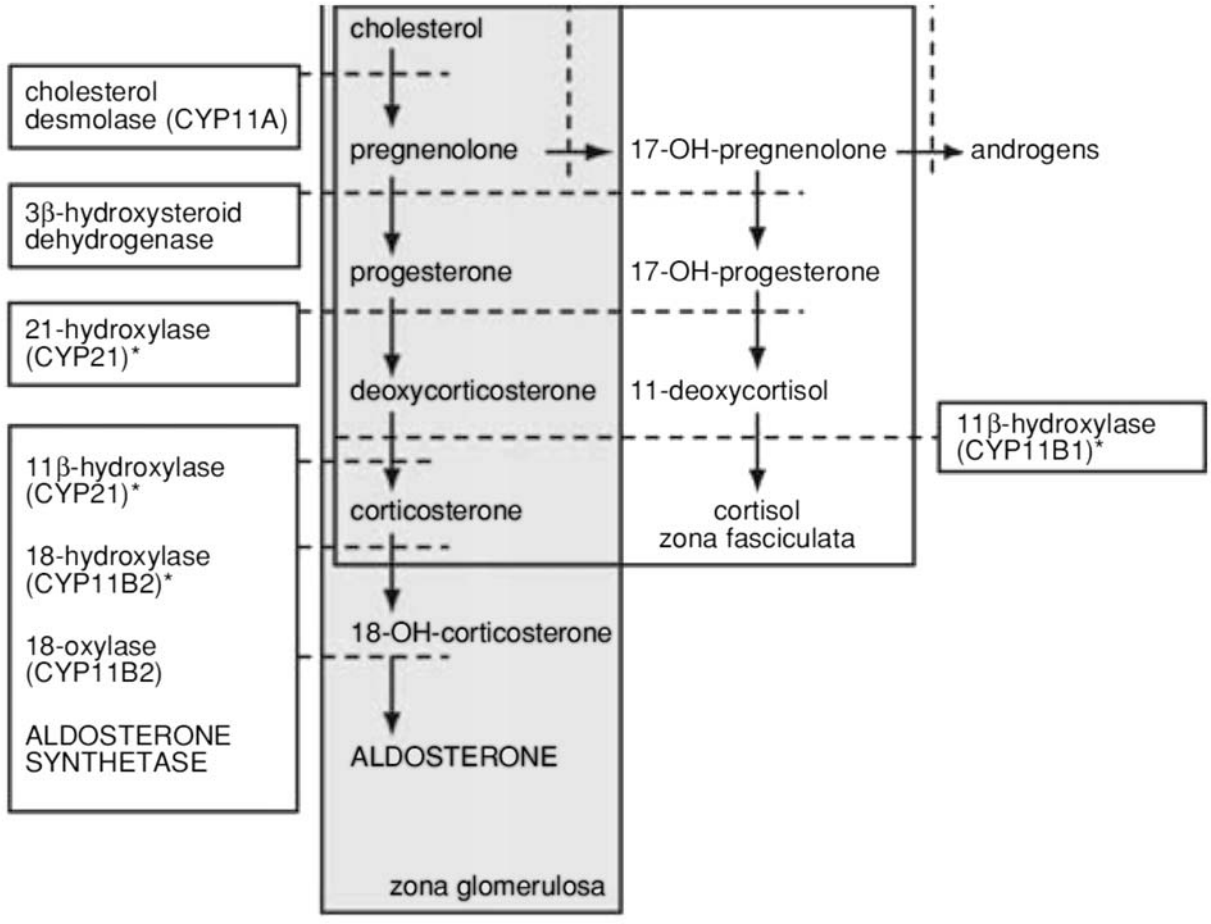

Fig. 2. Schematic representation of genetic disorders within aldosterone synthetic pathway in adrenal gland. Symbol (8) designates enzymes whose hereditary disorders are responsible for certain diseases or syndromes (compare Tables 1 and 2). Dashed lines represent action sites of the annropriate enzyme

forming heart function decreases as well, but, mostly does not precipitate cardiac decompensation.

e) Hypokalemia causes hyperpolarization of muscle membranes, therefore decreasing excitability and aggravating occurrence of contraction that clinically causes skeletal muscle weakness (even muscular paralysis); intestinal dysfunction can cause paralytic ileus.

4. In mineralocorticoid disorders, acid-base alterations occur in the organism and involve following mechanisms:

a) Increased aldosterone concentration in distal nephron tubules causes increased excretion of hydrogen ions, thus leading to metabolic alkalosis with urinary pH in the acid value range.

b) In hyperaldosteronism syndromes, plasma proteins with buffering decreased hydrogen ion concentration increase affinity and increasingly bind calcium, thus causing ionic hypocalcaemia, that rarely leads to tetany, since irritability of excitable tissues decreases simultaneously with hypokalemia.

c) Metabolic alkalosis is not chloride dependent in primary aldosteronism, because of increased extracellular volume and decreased sodium reabsorption in proximal tubules.

d) Hypervolemia and hyperosmolality in primary hyperaldosteronism contribute to correction of metabolic alkalosis, since hydrogen ions are being "extracted" from the cells.

e) In mineralocorticoid adrenal insufficiency (e. g. in the course of Addison's disease) hyperkalemia and metabolic acidosis develop as direct consequences of hypoaldosteronemia and decreased renal secretion; hyperkalemia itself increases acidosis on cellular level in the organism.

5. In the course of mineralocorticoid insufficiency the following pathogenetic mechanisms occur:

a) Clinical symptoms and signs of insufficiency appear at >90% loss of parenchymal mass in both adrenal glands, for instance due to autoimmune or inflammatory-infective processes in the Addison's disease.

b) Mineralocorticoid insufficiency causes increased natriuresis, hyponatremia; while plasma volume reduction leads to prerenal azotemia, orthostatic hypotension and circulatory shock.

c) Autoimmune, infective, hemorrhagic and metastatic etiopathogenetic processes in adrenal gland have atendency towards selective destruction of *zona glomerulosa*; that explains rare occurrence of combined disorders of glucocorticoids, sex hormones or catecholamines together with mineralocorticoid disorders.

d) In chronic mineralocorticoid adrenal insufficiencies, stress response of the organism is decreased, since internal environment homeostasis is deranged due to electrolyte, acid-base and volume disorders.

e) Hyponatreamia hypovolemia occurs in the syndrome of insufficiency due to hypoaldosteronemia that is pathogenetically categorized as hypovolemic shock with blood volume being reduced below adaptive cardiovascular capacity, thus leading to hypotension.

Exercise B: Algorithmic workout of the pathogenesis

(Construct the etiopathogenetic algorithm of the disease by using elements given below)

1. Hypokalemia
2. Paresthesias
3. Uncontrolled aldosterone secretion (Conn's syndrome)
4. Adenoma in adrenal *zona glomerulosa*
5. Hyperaldosteronemia
6. Increased potassium and hydrogen ion excretion
7. Hyporeninemia
8. Increased extracellular fluid volume
9. Increased sodium and water reabsorption
10. Metabolic alkalosis
11. Kaliopenic nephropathy
12. Muscle weakness and paralysis
13. Polyuria
14. Myocardial hypertrophy according to the Laplace's law
15. Hyperbicarbonatemia
16. Acid urine
17. Ionic hypocalcaemia
18. Susceptibility towards paralytic ileus
19. Arterial hypertension
20. Cardiac pressure overload
21. Membrane hyperpolarization
22. Increased neuromuscular excitability
23. Increased affinity of hemoglobin for oxygen and decreased release into tissues
24. Nephrogenic *diabetes insipidus*
25. Vacuolization of nephron cells

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. Disorders of aldosterone synthesis, function and degradation have significant pathogenetic and clinical implications on blood pressure, electrolyte homeostasis and acid-base balance (see claims 1a, 2b, 3a, 4a, 5d and 5e)

because

genetic disorders of aldosterone synthetase (see Fig. 2) regularly cause hypercortisolemia through increased local concentrations of steroid intermediary products in adrenal *zona fasciculata*.

a b c d e

2. Angiotensin II in cells of adrenal *zona glomerulosa* induces increased gene expression for aldosterone synthetase (see Fig. 2) that contains cytochrome P450 (CYP11B2) in its structure and thereby increases aldosterone concentration in plasma

because

structurally, aldosterone is a peptide, metabolized predominantly in liver by processes of biotransformation that include conjugation with sulfuric and

glucuronic acid, thereby augmenting polarity of the conjugate.

a b c d e

3. By means of determining ratio between aldosteronemia and renin activity, disorders can be clearly separated into four distinct groups (see Fig. 1 and claims 1a, 1b, 2c, 2d and 2e)

because

alterations in aldosteronemia (hypoaldosteronemia and hyperaldosteronemia) directly induce extracellular volume alterations and thereby renin activity and, vice versa, alterations in renin activity due to changed aldosterone concentration in plasma (negative feedback loop mechanism).

a b c d e

Additional questions

4. Name two examples for three structural hormone groups as well as their metabolic pathways within the organism.

5. Normal values of aldosteronemia in orthostasis exceed the normal values in supine position at rest (20–415 in relation to 97–831 pmol/L). Elaborate the mechanism by which upright posture load causes a relative increase in plasma aldosterone concentration.

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 clustering points are important for understanding of the nature of disease. The EPCs are important networking elements in biological reactivity. In Fig. 3 and 4 EPC-rosettes outline various groups of diseases/conditions, regardless of their etiologies — which are associated with the same ECP, **the EPC of Hyperkalemia** and **the EPC of Hypokalemia**, respectively. The rosettes are followed by two case studies within each EPC.

CASE STUDY 3.9. HYPERKALEMIA — WITHIN HYPORENINEMIC HYPOALDOSTERONISM IN A PATIENT WITH DIABETES MELLITUS TYPE II AND CONSEQUENTIAL DEVELOPMENT OF DIABETIC NEPHROPATHY[2]

Thecase study has been adopted from the article of C. van Nieuwkoop et al. [7].

[2] Taken from the book Z. Kovač, S. Gamulin (eds.) [5], pg. 55–6 with the consent of the Publisher and the author. Case study code number 3.9 corresponds to the group of processes outlined in the EPC rosette in Fig. 4.

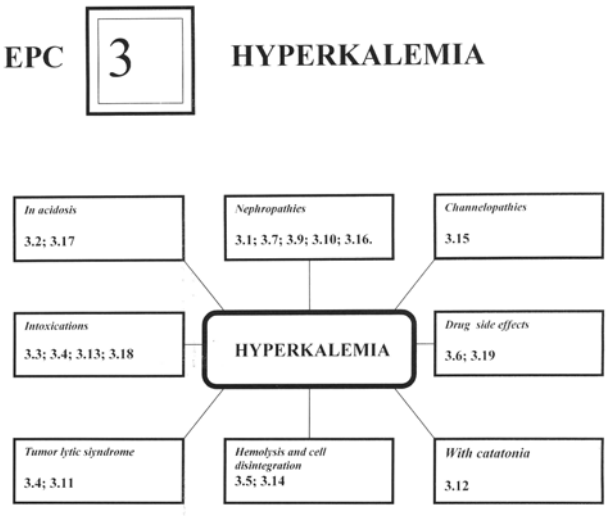

Fig 3. Introductory rosette of (EPC) of hyperkalemia serves as navigation scheme among multiple groups conditions, all related to this electrolyte disorder. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book

I. Medical History. A 55-year-old man who was suffering from diabetes mellitus type II with advanced diabetic retinopathy and polyneuropathy for three years had recently developed proteinuria (0.54–2.19 g/day, normal range < 0.15) within diabetic nephropathy. There were no signs of nephrotic syndrome. The rest of the test results for urine, electrolytes, glomerular filtration, glycosylated hemoglobin levels, and blood pressure were normal. In the treatment of diabetic nephropathy, he received valsartan (an angiotensin II receptor antagonist). Of other drugs, he received metformin (belongs to the biguanides group which inhibits gluconeogenesis, decreases intestinal absorption of glucose, and increases glucose utilization in peripheral tissues), glibenclamide (a derivative of sulfonylurea which, by activating its receptors on the β cells of the islets of Langerhans, stimulates endogenous insulin secretion) and alfuzosin (an α-adrenergic blocker which, other than as a hypotensive, is commonly used to treat benign prostatic hyperplasia, since it facilitates urination). Laboratory test results confirmed hyperkalemia (6.8 mmol/L, normal range 3.9–5.1). Then, valsartan was removed from his therapy, which led to the normalisation of kalemia, but also to the increase of proteinuria. About 4 weeks after the discontinuation of valsartan, hyperkalemia was confirmed again as a result of hyporeninemic hypoaldosteronism. For the normalisation of kalemia, hydrochlorothiazide (an inhibitor of Na-Cl cotransport in the distal tubules of the kidneys, which increases kaliuresis as well) was introduced into his therapy, and normalisation of potassium to 4.6 mmol/L followed. Subsequently, he received an ACE inhibitor, enalapril (an angiotensin-converting enzyme inhibitor), potassium levels remained under control, and proteinuria decreased.

Additional Insight. Diabetes mellitus is the leading cause of hyporeninemic hypoaldosteronic hyperkalemia. The most common cause of hyporeninemia in diabetes mellitus is function damage of the juxtaglomerular apparatus, but the retarded conversion of renin precursors to active renin, the insufficient sympathetic stimulation of renin-producing cells due to diabetic nephropathy, or even the inhibition of renin release due to hyperkalemia are also possible. Diabetic nephropathy commonly manifests as nephrotic syndrome, and diffuse glomerulosclerosis is usually in the basis of this event, which manifests as diffuse proliferation of mesangial matrix and thickening of the basement membrane. Valsartan is a drug that acts as an angiotensin II receptor antagonist, which leads to decreased aldosterone secreation with resulting hyperkalemia and hyponatremia. Therefore, the discontinuation of valsartan normalises the level of potassium.

ACE inhibitors block ACE (localised primarily in the lungs), which cleaves the C-terminal peptide (histidyl-leucine-dipeptide) from angiotensin I and converts it into the potent octapeptide angiotensin II. It acts on the AT1 and AT2 receptors. It stimulates aldosterone secretion, and has mitogenic and trophic effect on smooth muscle cells.

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

1. Diabetes mellitus
2. Hypoaldosteronism
3. Hyporeninemia
4. Hyperkalemia
5. Diabetic nephropathy
6. Proteinuria
7. ACE inhibitors therapy
8. Antagonists of angiotensin II receptors therapy

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition. According to data presented in this case study please outline a) 5 etiological features; b) 8 features of pathogenesis; c) 7 features of disease spread and chronobiology; d) 5 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS***specified on page 150 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 3.16. HYPERKALEMIA — THE EFFECT OF FLUDROCORTISONE TREATMENT ON END-STAGE CHRONIC RENAL INSUFFICIENCY[3]

Thecase study has been adopted from the article of Dong-Min Kim et al. [3].

[3] Taken from the book Z. Kovač, S. Gamulin (eds.) [5], pg. 64–5, with the consent of the Publisher and the author. Case study code number 3.16 corresponds to the group of processes outlined in the EPC rosette in Fig. 3.

I. Medical History. A group of 21 patients were included in a prospective study on the effect of fludrokortisone on kalemia in chronic renal insufficiency. The criteria for selecting patients to be included in the study were: End-stage chronic renal insufficiency, >6 months of hemodialysis for a period of 4 hours 3 times a week, >18 years of age, serum potassium 5.0 mmol/L at least 3 consecutive months. Laboratory test results, including serum potassium, sodium, urea, creatinine and total protein/albumin, were measured monthly. The concentration of plasma aldosterone was also measured in all patients. Body weight was taken before and after each hemodialysis, and blood pressure before each hemodialysis. Before and after each hemodialysis, serum potassium levels were also measured. There were no significant differences in age or gender of the patients included in the study. The median age was 50 (28–72), 48% of patients were male. The main cause of chronic renal insufficiency was chronic glomerulonephritis. Other causes included diabetic, hypertensive, and urate nephropathy. Serum potassium levels in the tenth month after treatment with fludrocortisone acetate (FCA) were not significantly different between the group that received treatment and the control group: 5.2 mmol/L versus 5.8 (normal range 3.9–5.1). The tenth month after FCA treatment, kalemia was significantly reduced in comparison to the potassium levels before treatment (5.2 mmol/L versus 6.1). With FCA treatment, other laboratory test results, such as sodium, chloride, urea, creatinine, body weight between dialysis and blood pressure before dialysis, showed no significant difference between the control group and those who received treatment. There were also no significant differences in these findings before and after treatment with FCA. Not a single patient who received treatment developed hypervolemia or hypertension. The conclusion of the study was that fludrocortisone treatment significantly reduced the level of potassium in patients during end-stage chronic renal insufficiency.

Additional Insight. In patients with end-stage chronic renal insufficiency, hyperkalemia develops due to constant potassium intake and a simultaneous reduction in excretion from the body. The progressive loss of nephron function, metabolic acidosis, oligoanuria, mineralocorticoid deficiency, treatment with ACE inhibitors, β-blockers, and non-steroidal antirheumatics indirectly or directly contribute to hyperkalemia. Fludrocortisone is a synthetic glucocorticoid with potent mineralocorticoid activity and moderate glucocorticoid activity. Fludrocortisone significantly decreases kalemia in patients with chronic renal failure by increasing the excretion of potassium through the digestive system (colon). This is achieved by stimulating Na-K-ATP-ase activity in intestinal epithelial cells. Such extrarenal regulation of potassium excretion is particularly important in a state of chronic failure.

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

1. Metabolic acidosis
2. Normokalemia
3. Diabetic nephropathy
4. Arterial hypertension
5. Chronic glomerulonephritis
6. Hyperkalemia
7. Chronic renal insufficiency
8. Fludrocortisone acetat treatment

III. Classification of etiopathogenetic nature and development of disease / disorder/ condition. According to data presented in this case study please outline a) 4 etiological features; b) 18 features of pathogenesis; c) 16 features of disease spread and chronobiology; d) 14 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS*** specified on page 150 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.)

CASESTUDY 4.18. — HYPOKALEMIA – ASSOCIATED WITH PALPITATIONS, SKELETAL MUSCLE SPASM AND ATRIAL FIBRILLATION DUE TO PRIMARY HYPERALDOSTERONISM (CONN'S SYNDROME)[4]

The case study has been adopted from the article of Al-Aloul B. et al. [1].

I. Medical history. A 58-year-old African has visited his physician complaining about palpitations, chest pain, a sense of insecurity and skeletal muscle spasms. He described palpitations as „flutter in the chest" that appeared suddenly and irregularly and disappeared spontaneously during the past two weeks. The symptoms would last for a few hours.

For the past four years the patient has been treated with labetalol due to arterial hypertension. The patient was taking anticoagulant therapy (warfarin) due to paroxysmal atrial fibrillation. The patient does not smoke, does not drink alcohol and there have been no heart diseases in his family.

At physical examination the patient presents with tachyarrhythmia (about 120 bpm, normal range 70–100), normal blood pressure (with antihypertensive therapy) and 2 / 6 mesosystolic heart murmur which is the loudest at the base of the heart.

[4] Taken from the book Z. Kovač, S. Gamulin (eds.) [5], pg. 95–6, with the consent of the Publisher and the author. Case study code number 4.18 corresponds to the group of processes outlined in the EPC rosette in Fig. 4.

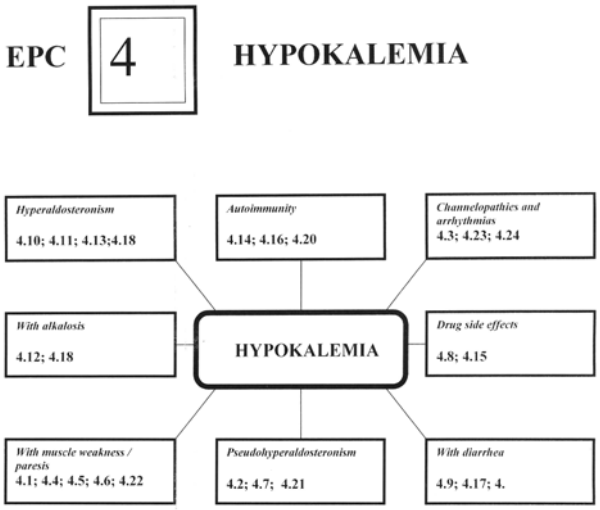

Fig. 4. Introductory rosette of (EPC) of hypokalemia serves as navigation scheme among multiple groups conditions, all related to this electrolyte disorder. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book

Laboratory analysis confirmed hypokalemia (2.7 mmol/L; normal range 3.5–4.5 mmol/L) with no other electrolyte disbalances. Electrocardiography (ECG) showed atrial fibrillation with rapid ventricular response and prominent U-wave.

Normokalemia and therefore sinus rhytm have been re-established with the potassium chloride therapy (80 mEq during 8 hours).

Furthermore, laboratory tests showed hyperaldosteronemia (82.7 ng/mL, normal range interval 4.0–31.0) and decreased plasma renin activity (0.07 ng/mL/h, normal range 0.7–5.0).

Computed tomography (CT scan) showed a node in left suprarenal gland. After that, spironolacton was added to therapy and dosage of pottasium-chloride has been adjusted to maintain serum pottasium above 3.8 mmol/L.

Medical documentation from the past four years showed that the patient always had hypokalemia associated with paroxysmal atrial fibrillation.

ADDITIONAL INSIGHT: Hypokalemia disturbs heart rhytm in four mutually connected ways: 1) it changes transmembranous electrical currents during repolarization (especially in 2nd, 3rd and 4th phase of action potential); 2) it increases resting membrane potential; 3) it impairs transmembranous flow of other electrolytes; 4) it indirectly increases sodium and calcium cytoplasmic concentrations by blocking Na/K-ATPase.

Shortening of refractory period increases automatic discharge of sinoatrial node, increases activity of ectopic pacemakers and alters direction of currents in atrial cells. Various clinical arrhythmias and conduction blocks are caused by combinations of mentioned potassium electrophysiological effects.

Hyperaldosteronism causes hyperkaliuria and therefore hypokalemia. Retention of water and salt contributes to isoosmolalhyperhidration (i. e. increase in intravascular volume) and therefore arterial hypertension. Juxtaglomerular apparatus decreases excretion of renin (hyporeninemia) as a compensatory response. It is also possible that aldosteron has a direct effect on heart cells.

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

1. Isoosmolal hyperhydration and arterial hypertension
2. Hyperaldosteronism and decreased plasma renin activity
3. Hypokalemia
4. Suprarenal gland tumor with uncontrolled excretion of mineralocorticoids
5. Appearance of U-wave in ECG
6. Atrial fibrillation with rapid ventricular response
7. Decreased Na/K-ATPase activity, shortened refractory period, disorder of repolarization
8. Palpitations, flutter of the heart, skeletal muscle spasms

Table 3. Laboratory test result in patient

Lab test	1st hospitalization	2nd hospitalization	Normal range
Hemoglobinemia	77	72	104–175 g/L
Lactate dehydrogenase	4349	703	91–180 U/L
Total bilirubin	723	629	6.8–34.2 mmol/L
Direct bilirubin	381	407	1.7–8.5 mmol/L
Cholic acid	38.1	38.2	<3.1 mmol/L
Chenodeoxycholic acid	170	234	<9.9 mmol/L
Urin volume	5.7	2.93	0.6–1.6 L/24 h
Kaliuresis	165	137	40–80 mEq/24 h
Natriuresis	245	49	75–200 mEq/24 h
Aldosterone (serum)	2	10	<28 ng/dL
Cortiosol (serum)	6.9	14.1	6–21 mg / dL
Corticotropin (serum)	12	9	7–50 pg/dL
Kalemia	2.5	3.1	3.6–5.1 mEq/L
Natremia	137	136	136–144 mEq/L
Transtubular Potassium gradient	9.9	17	<3 in Hypokaliemia

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition. According to data presented in this case study please outline a) 4 etiological features; b) 11 features of pathogenesis; c) 9 features of disease spread and chronobiology; d) 8 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS*** specified on page 150 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 4.21. HYPOKALIEMIA — DUE TO APPARENT MINERALOCORTICOID EXCESS IN SICKLE CELL CRISIS, WITH POLYURIA, HYPERBILIRUBINEMIA AND HYPERBILACIDEMIA[5]

The case study has been adopted by article of M. Jaitly et al. [2].

I. Medical history. Hypokaliemia was detected in 23-year-old American with who has sickle cell anemia during sickle cell crisis. The patient is an adipose person. Physical examination detected jaundice, arterial hypertension, hepatomegaly, edema and polyuria. Laboratory tests revealed hyperbilirubinemia, elevated cholic acid and deoxycholic acid plasma levels, normonatremia, normal blood pH, hypohemoglobinemia and elevated lactate dehydrogenase plasma activity (see Table 1). He was treated with exchange transfusion. He was referred to ambulatory treatmen with potassium replacement therapy.

When he was hospitalized for second time because of sickle cell crisis, 4 months after the first eposide, he presented with upper GI bleeding and died in hypovolemic shock. He was ggain hypokalemic, hyperkaliuric, normonatremic and polyuric (Table 3).

ADDITIONAL INSIGHT

11β-hydroxysteroid dehydrogenase (11β-HSD) converts cortisol to cortisone in kidneys and colon (it is expressed in those tissues), thus protecting mineralocorticoid receptors from cortisol activity. Cortisol and aldosterone affinity for those receptors is similar, and 11β-HSD activity locally decreases cortisol concentration and mineralocorticoid effect.

In this patient elevated levels of bile acids (see Table 1), especially chenodeoxycholic acid, inhibited 11β-HSD activity and therefore increases cortisol's kaliuretic effect despite normonatremia. Gliciretinic acid, a derivative of liqurice has similar effect on 11β-HSD. 11β-HSD inhibiton presents as pseudoaldosteronism,

[5] Taken from the book Z. Kovač, S. Gamulin (eds.) [5], pg. 98–9, with the consent of the Publisher and the author. Case study code number 1.2 corresponds to the group of processes outlined in the EPC rosette in Fig. 4.

which is also called AME syndrome (*apparent mineralocorticoid excess*).

Etiopathogenesis of polyuria involves kidney tubular function impairment, while angiomural edema is caused by general endothelial and capillary wall dysfunction in rheological and occlusive effects of rigid drepanocytes.

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

1. Hereditary mutation of β globin chain causes polymerization of hemoglobin
2. Normoaldosteronemia with normonatremia, but increased transtubular gradient and hyperkaliuria
3. Hypokalemia
4. Hemolityic crisis causing tissue ischemia, erythrocyte breakdown and pain
5. Hyperbilirubinemia and elevated plasma bile acid level
6. Intrahepatic cholestasis due to necrosis, partial fibrosis and cirrhosis
7. Increased cortisol mineralocorticoid effect with normocortisolemia
8. Decreased conversion of of cortisol to cortisone in renal collecting duct by 11βHSD.

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) 11 features of pathogenesis; c) 8 features of disease spread and chronobiology; d) 12 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS***specified on page 150 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.)

БИБЛИОГРАФИЯ

1. *Al-Aloul B., Li J. M., Benditt D., Tholakanahalli V.* Atrial fibrillation associated with hypokalemia due to primary hyperaldosteronism (Conn's syndrome). Pacing and Clinical Electrophysiology. 2006; 29: 1303–5.
2. *Jaitly M., Mohan S., Park C. M., Anderson H. L., Cheng J. T., Pogue V. A.* Hypokalemia during sickle cell crisis apparently due to intermittent mineralocorticoid excess. Am. J. Kidney Dis. 2008; 51: 319–25.
3. *Kim D.-M., Chung J. H., Yoon S. H., Kim H. L.* Effect of fludrocortisone acetate on reducing serum potassium levels in patients with end-stage renal disease undergoing haemodialysis. Nephrol. Dial. Transplant. 2007; 22: 3273–6.
4. *Kovač Z., Gamulin S., eds*. Pathophysiology. Study Guide Algorithms — Problem Solver. Book Two. Zagreb: Medicinska Naklada; 2013: 163–7.
5. *Kovač Z., Gamulin S., eds.* Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One. Zagreb: Medicinska Naklada; 2013.
6. *Perrin C. W.* Disorders of aldosterone biosynthesis and action. New Engl. J. Med. 1994; 331: 250–8.
7. *van Nieuwkoop C., Ijpelaar D. H., Bolk J. H.* Treating proteinuria in a diabetic patient despite hyperkaliemia due to hyporeninaemic hypoaldosteronism. Neth. J. Med. 2007; 65: 75–7.

REFERENCES

1. *Al-Aloul B., Li J. M., Benditt D., Tholakanahalli V.* Atrial fibrillation associated with hypokalemia due to primary hyperaldosteronism (Conn's syndrome). Pacing and Clinical Electrophysiology. 2006; 29: 130–35.
2. *Jaitly M., Mohan S., Park C. M., Anderson H. L., Cheng J. T., Pogue V. A.* Hypokalemia during sickle cell crisis apparently due to intermittent mineralocorticoid excess. Am. J. Kidney Dis. 2008; 51: 319–25.
3. *Kim D.-M., Chung J. H., Yoon S. H., Kim. H. L.* Effect of fludrocortisone acetate on reducing serum potassium levels in patients with end-stage renal disease undergoing haemodialysis. Nephrol. Dial. Transplant. 2007; 22: 3273–6.
4. *Kovač Z., Gamulin S., eds*. Pathophysiology. Study Guide Algorithms — Problem Solver. Book Two. Zagreb: Medicinska Naklada; 2013: 163–7. (in Croatian)
5. *Kovač Z., Gamulin S., eds.* Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One. Zagreb: Medicinska Naklada; 2013. (in Croatian)
6. *Perrin C. W.* Disorders of aldosterone biosynthesis and action. New Engl. J. Med. 1994; 331: 250–8.
7. *van Nieuwkoop C., Ijpelaar D. H., Bolk J. H.* Treating proteinuria in a diabetic patient despite hyperkaliemia due to hyporeninaemic hypoaldosteronism. Neth. J. Med. 2007; 65: 75–7.

УВЕДОМЛЕНИЕ

Автор заявляет об отсутствии конфликта интересов применительно к публикации данной статьи. Вся работа выполнена одним автором.

СВЕДЕНИЯ ОБ АВТОРЕ

Ковач Зденко — профессор, кафедра патофизиологии, медицинский факультет, Загребский университет, Госпитальный центр КВС, Хорватия, Загреб, Кишпатичева ул., д. 12; e-mail: zdenko.kovac@mef.hr

ACKNOWLEDGEMENT

The author declares no conflict of interest in relation to the publication of this article. All work is done by one author.

INFORMATION ABOUT AUTHOR

Kovač Zdenko — professor, Department of Pathophysiology, Medical School University of Zagreb, KBC-Hospital Centre, Kišpatićeva 12, Zagreb Croatia, e-mail: zdenko.kovac@mef.hr

Z Kovač. Integrative Lessons in Clinical Pathophysiology:

CLASSIFICATION AND DISAMBIGUATION OF ETIOPATHOGENETIC CHARACTER AND COURSE OF DISEASE PRESENTED IN THE EPC CASE STUDY — ELEMENTS

a) Etiological characteristics of a patient's condition.)

1. **Biological etiology**; 1.1 genetic, 1.2 monogenic, 1.3 polygenic, 1.4 infectious, 1.5 bacterial, 1.6 viral, 1.7 plasmodial, 1.8 infestive, 1.9 parasitic, 1.10 fungal, 1.11 transplant reaction, 1.12 developmental anomaly, 1.13 fetomaternal unit disorder

2. **Physical etiology**; 2.1 mechanic, 2.2 trauma, 2.3 hypoosmolar, 2.4 hyperosmolar, 2.5 hyperhydration, 2.6 hypohydration, 2.7 hypovolemic, 2.8 oncotic, 2.9 burn injury, 2.10 hyperthermia, 2.11 hypothermia, 2.12 electrical injury, 2.13. ultrasound, 2.14 vibration, 2.15 obstructive, 2.16 overload, 2.17 hyperviscous, 2.18 deceleration, 2.19 acceleration, 2.20 acoustic, 2.21 hydrostatic, 2.22 decreased tissue elasticity, 2.23 environmental pressure change, 2.24 immobilization, 2.25 radiation

3. **Chemical etiology**; 3.1 intoxication, 3.2 hypovitaminosis, 3.3 hypervitaminosis, 3.4 corrosive, 3.5 biological poisoning (insects, snakes, mushrooms, marine organisms etc.), 3.6 xenobiotics, 3.7 drug overdose, 3.8 endogenous metabolite accumulation, 3.9 carbohydrate disorder, 3.10 protein disorder, 3.11 lipid disorder

4. **According to etiopathogenesis**; 4.1 endogenous, 4.2 exogenous, 4.3 iatrogenic, 4.4 medicamentous, 4.5 professional, 4.6 malnutrition, 4.7 lifestyle-related, 4.8 smoker, 4.9 addiction, 4.10 suicidal, 4.11 accidental, 4.12 deficiency of basic metabolic substances, 4.13 deficiency of specific metabolic substances, 4.14 congenital, 4.15 spontaneous, 4.16 explosive, 4.17 induced, 4.18 alcohol abuse

b) Characteristics of pathogenesis, natural course, degree of dysfunction and outcome of a disease.

5. **Characteristics of pathogenetic character of a process**; 5.1 inflammatory, 5.2 neoplastic, 5.3 ischemic, 5.4 metabolic, 5.5 autoimmune, 5.6 immunodeficiency, 5.7 alloreactivity, 5.8 atopic, 5.9 allergic, 5.10 anaphylactic, 5.11 anabolic, 5.12 catabolic, 5.13 degenerative, 5.14 electrolyte disorder, 5.15 acid-base disorder, 5.16 hypoenergosis, 5.17 substrate deficiency, 5.18 dysenzymatic, 5.19 glycation, 5.20 hypoglycemic, 5.21 hyperglycemic, 5.22 dyslipidemia, 5.23 hypoxemia, 5.24 hypoxia, 5.25 carbonylation, 5.26 methylation, 5.27 dysregulatory, 5.28 hypertensive, 5.29 hypotensive, 5.30 spastic-paralytic, 5.31 channelopathy, 5.32 hypothermic, 5.33 hyperthermic, 5.34 fibrosis, 5.35 maldigestion, 5.36 malabsorption, 5.37 hemorrhagic, 5.38 protein-loss, 5.39 necrotic, 5.40 apoptotic, 5.41 atherosclerotic, 5.42 arrhythmogenic, 5.43 epileptogenic, 5.44 edema, 5.45 infiltrative, 5.46 granulation, 5.47 tetanic, 5.48 acidotic, 5.49 alkalotic, 5.50 amyloidotic, 5.51 DNA repair disorder, 5.52 translation disorder, 5.53 excitotoxicity, 5.54 oxyfority disorder, 5.55 coagulopathy, 5.56 mitochondrial dysfunction, 5.57 lysosomal disorder, 5.58 membranous dysfunction, 5.59 proliferation, 5.60 endoplasmic reticulum disorder, 5.61 shock, 5.62 acute stress, 5.62 chronic stress, 5.64 compartmentalisation, 5.65 septic, 5.66 hypertrophic, 5.67 tamponade, 5.68 hypoproteinemic, 5.69 cachectic, 5.70 hemolytic, 5.71 hypermetabolic, 5.72 hypometabolic, 5.73 receptor dysfunction, 5.74 neoangiogenic, 5.75 tesaurismosis, 5.76 reduced catabolism of self molecules, 5.77 thrombogenic, 5.78 hypercytokinemia, 5.79 tissue transplant reaction, 5.80 flaccid paralysis, 5.81 asfixia, 5.82 hyperventilation, 5.83 hypoventilation, 5.84 hypercapnia, 5.85 hypocapnia, 5.86 embolic

6. **Characteristics according to disease course**; 6.1 irreversible, 6.2 reversible, 6.3 progressive, 6.4 remission, 6.5 acute, 6.6 subacute, 6.7 chronic, 6.8 fulminant, 6.9 primary, 6.10 secondary, 6.11 n-th pathogenesis, 6.12 subclinical

7. **Characteristics according to the degree of dysfunction and disease outcome**; 7.1 compensated, 7.2 decompensated, 7.3 latent insufficiency, 7.4 manifest insufficiency, 7.5 hyperreactivity, 7.6 hyporeactivity, 7.7 afunction, 7.8 moribund, 7.9 terminal, 7.10 urgent condition, 7.11 intensive-care, 7.12 elective treatment, 7.13 vegetation state, 7.14 lethal, 7.15 vital threat

c) Characteristics of disorder staging and chronobiology of a patient.

8. **Characteristics based on process dissemination in organs, tissues, compartments and body fluids;** 8.1 cutaneous, 8.2 osseus, 8.3 articular, 8.4 cerebral, 8.5 vascular, 8.6 venous, 8.7 arterial, 8.8 interstitial, 8.9 intracellular, 8.10 pulmonary, 8.11 bronchial, 8.12 diaphragmal, 8.13 neural, 8.14 intestinal, 8.15 hepatic, 8.16 biliary, 8.17 pancreatic, 8.18 muscular, 8.19 cardiac, 8.20 epithelial, 8.21 hematologic, 8.22 lymphatic, 8.23 cerebrospinal, 8.24 mammary, 8.25 utero-vaginal, 8.26 penile-testicular, 8.27 abdominal, 8.28 renal, 8.29 vesico-ureteral, 8.30 extracellular, 8.31 ascitic, 8.32 mono-organic, 8.33 multi-organ, 8.34 pleural, 8.35 with integral affection of specific body parts (foot, leg, arm, eye, ear, throat, nose, neck, mediastinum etc.), 8.36 pericardial, 8.37 tracheal, 8.38 capillary, 8.39 prostatic

9. **Characteristics according to the population affected**; 9.1 epidemic, 9.2 infectious, 9.3 pandemic, 9.4 endemic, 9.5 familial

10. **Characteristics according to functional system affection**; 10.1 hemodynamic, 10.2 respiratory, 10.3 thermoregulatory, 10.4 endocrine, 10.5 neurovegetative, 10.6 immune, 10.7 renal-urinary, 10.8 hematological, 10.9 locomotor, 10.10 genital-reproductive, 10.11 osseous-connective tissue, 10.12 peripheral sensory disorder, 10.13 peripheral motor disorder, 10.14 central nervous system disorder, 10.15 gastrointestinal

11. **Chronobiological characteristics of a patient**; 11.1 embrional, 11.2 fetal, 11.3 neonatal, 11.4 developmental, 11.5 childhood, 11.6 adolescent, 11.7 opstetric, 11.8 reproductive, 11.9 postmenopausal, 11.10 adult, 11.11 geriatric, 11.12 fertilization disorder

d) Characteristics of clinical diagnostics and treatment modalities.

12. **Characteristics of diagnostic and therapeutic interventions**; 12.1 anamnestic, 12.2 physical-examination, 12.3 laboratory, 12.4 imaging modalities, 12.5 dynamic tests, 12.6 endoscopic, 12.7 stereotactic, 12.8 ultrasound, 12.9 radionuclide, 12.10 molecular, 12.11 pathohystological, 12.12 pathoanatomical, 12.13 cytological, 12.14 genetic analysis, 12.15 symptomatic, 12.16 causal, 12.17 curative, 12.18 palliative, 12.19 conservative, 12.20 medicamentous, 12.21 operative, 12.22 cytostatic, 12.23 antibiotic, 12.24 immunosuppressive, 12.25 substitution, 12.26 diuretic, 12.27 cardiotonic, 12.28 functional x-ray imaging, 12.29 invasive, 12.30 fine needle aspiration, 12.31 tissue transplant, 12.32 autopsy, 12.33 anesthesia, 12.34 transfusion, 12.35 fluid replenishment, 12.36 hypolipemic, 12.37 immunostimulatory, 12.38 antihypertensive, 12.39 antiepileptic, 12.40 antidepressive, 12.41 sympathomimetic, 12.42 sympatholytic, 12.43 parasympathomimetic, 12.44 parasympatholytic, 12.45 antiemetic, 12.46 radiotherapy, 12.47 antipyretic, 12.48 anti-inflammatory, 12.49 with euphenic diet, 12.50 hemodialysis, 12.51 peritoneal dialysis, 12.52 plasmapheresis, 12.53 biological therapy (humanized antibodies, recombinant proteins etc.), 12.54 desensibilization, 12.55 anticoagulant treatment

Z. Kovač. INTEGRATIVE LECTURES IN CLINICAL PATHOPHYSIOLOGY — Solutions of two algorithmic workouts and four case studies of the EPC — workout of clinical problem — presented in Clin. Pathophysiol. 2016; 1: 142–54.

SOLUTIONS OF THE ALGORITHMIC WORKOUT OF CLINICAL PROBLEM — Pathophysiology of the hypovolemic hemodynamic shock syndrome

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

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

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

4. Three types of hypovolemic shiock syndome with examples:

1. Hypovolemic shock due to bleeding caused by rupture of the aorta, or, arterial bleeding in peptic ulcer disease.

2. Hypovolemic shock due to water and electrolytes loss, like in cholera syndrome (due tzo secretory diarrhoea), or, in heat shock syndrome due to excessive sweating.

3. Hypovolemic shock due to plasma loss in burn disease, or peritonitis.

5. In principle, shape of DT × DV curve is no altered, but DV is significantly reduced due to reduction of venous blood return caused by the hypovolemia due to bleeding.

SOLUTIONS OF THE ALGORITHMIC WORKOUT OF CLINICAL PROBLEM — Pathophysiology of the hyperosmolal syndrome in the course of newly diagnosed diabetes mellitus

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

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

Exercise C: 1a, 2a, 3a.

4. The osmolyte excess is approximatelly 10 mOsm/kg body weight. In intracellular space total excess is estimated approximatelly 2500 mOsm, whereas, in the extracellular space the excess is approximatelly 1500 mOsm.

5. Calculated water volume deficiency is 6,53 L. During the first day of therapy patient was infused 8 L, and voided out 0.5 L of fluid, respectivelly.

SOLUTIONS OF THE EPC — WORKOUT OF CLINICAL PROBLEM.

Case study 1.2. HYPERNATREMIA

II. Etiopathogenesis of the disease

1–8; 2–7; 3–4; 4–1; 5–3, 6; 6 –3; 8–2, 7

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition

a) *Etiological features*: 1.1; 2.4; 2.6; 2.7; 3.9; 4.1; 4.15;

b) *Features of pathogenesis*: 5.1; 5.4; 5.5; 5.13; 5.14; 5.21; 5.27; 5.29; 5.42; 5.44; 5.45; 5.46; 5.62; 6.1; 6.2; 6.5; 6.10; 7.2; 7.4; 7.6; 7.10; 7.11; 7.14;

c) *Features of disease spread and chronobiology*: 8.4; 8.8; 8.9; 8.10; 8.13; 8.19; 8.30; 8.33; 8.35; 10.1; 10.2; 10.4; 10.5; 10.14; 11.9; 11.10;

d) *Feature of clinical elaboration* (*diagnosis, therapy*): 12.1; 12.2; 12.3; 12.4; 12.5; 12.15; 12.16; 12.17; 12.19; 12.20; 12.25; 12.35.

SOLUTIONS OF THE EPC — WORKOUT OF CLINICAL PROBLEM.

Case study 1.9. HYPERNATREMIA

II. Etiopathogenesis of the disease

1→4; 1 →5; 2→1; 2 →3, 6; 3→6; 5 →4; 6→7; 7→5, 8; 7 →6; 8→1; 8 →7

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition

a) *Etiological features*: 2.4; 2.6; 2.7; 4; 4.2; 4.17;

b) *Features of pathogenesis*: 5.13; 5.14; 5.28; 5.37; 5.44; 5.62; 5.63; 5.82; 6.2; 6.5; 6.10; 7.2; 7.4; 7.10; 7.11; 7.14; 7.15;

c) *Features of disease spread and chronobiology*: 8.4; 8.5; 8.6; 8.7; 8.8; 8.9; 8.13; 8.30; 8.33; 10.1; 10.2; 10.14; 11.10;

d) *Feature of clinical elaboration* (*diagnosis, therapy*): 12.1; 12.2; 12.3; 12.4; 12.16; 12.17; 12.19; 12.35.

SOLUTIONS OF THE EPC — WORKOUT OF CLINICAL PROBLEM.

Case study 2.7. HYPONATREMIA

II. Etiopathogenesis of the disease

1→5; 3→8; 4→1, 7; 5→2; 6→4; 8→6

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition

a) *Etiological features*: 1.1; 1.3; 2.3; 2.5; 3.6; 4.1; 4.2; 4.3; 4.4; 4.17;

b) *Features of pathogenesis*: 5.4; 5.14; 5.21; 5.27; 5.43; 5.62; 5.64; 6.2; 6.3; 6.5; 6.10; 7.2; 7.4; 7.5; 7.10;

c) *Features of disease spread and chronobiology*: 8.4; 8.9; 8.13; 8.17; 8.18; 8.23; 8.30; 8.33; 10.4; 10.7; 10.9; 10.14; 11.10;

d) *Feature of clinical elaboration* (*diagnosis, therapy*): 12.1; 12.2; 12.3; 12.4; 12.15; 12.16; 12.17; 12.19; 12.20; 12.25; 12.39; 12.40.

SOLUTIONS OF THE EPC — WORKOUT OF CLINICAL PROBLEM.

Case study 2.12. HYPONATREMIA

II. Etiopathogenesis of the disease

1→6, 7; 2→7; 4→2, 8; 5→1, 4; 6→3; 6→1, 8; 8→6, 7

III. Classification of etiopathogenetic nature and development of disease/disorder/ condition

a) *Etiological features*: 1.1; 1.3; 2.3; 2.6; 2.7; 4.1; 4.15;

b) *Features of pathogenesis*: 5.4; 5.5; 5.14; 5.15; 5.16; 5.17; 5.20; 5.24; 5.27; 5.2; 5.49; 5.61; 5.62; 5.72; 5.82; 5.85; 6.1; 6.2; 6.5; 6.7; 6.9; 7.2; 7.4; 7.6; 7.10; 7.15;

c) *Features of disease spread and chronobiology*: 8.1; 8.4; 8.5; 8.7; 8.9; 8.13; 8.19; 8.20; 8.21; 8.28; 8.30; 8.33; 10.1; 10.2; 10.4; 10.5; 10.7; 10.14; 11.6;

e) *Feature of clinical elaboration* (*diagnosis, therapy*): 12.2; 12.3; 12.15; 12.16; 12.17; 12.19; 12.25; 12.35.