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**WATER AND ELECTROLYTE BALANCE
DISORDERS**
(pathophysiological aspects)

Minsk BSMU 2016

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ПАТОЛОГИЧЕСКОЙ ФИЗИОЛОГИИ

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**НАРУШЕНИЯ
ВОДНО-ЭЛЕКТРОЛИТНОГО ОБМЕНА
(патофизиологические аспекты)**

**WATER AND ELECTROLYTE BALANCE
DISORDERS
(pathophysiological aspects)**

Учебно-методическое пособие



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Рассматриваются типовые формы расстройств водно-электролитного обмена, их этиопатогенез, основные механизмы развития отдельных видов отеков и их клинические проявления, принципы диагностики, профилактики и лечения такого рода расстройств.

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MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Water and electrolyte balance is crucial for body homeostasis and is one of the most protected physiological mechanisms in the body. While we can survive for months without food, without water intake we die very quickly. Similarly the body has very strong mechanisms to control salt and water balance, an understanding of which has major implications in clinical practice. The knowledge in this area is necessary to restore and maintain at a constant level of the standard values of the basic physical and chemical constants of body fluids, in particular of composition and volume of blood, and other liquids of internal environment. "The constancy of the internal environment is the condition for free and independent life" (C. Bernard). Due to the fact that the disorders of water and electrolyte metabolism are typical for a number of diseases and pathological conditions which occur in the body the study of the pathogenesis of these disorders has a particular importance for the clinic.

This educational manual describes the main standard forms of disorders of water and electrolyte metabolism disorders, reasons of various types of edema and their pathogenic role for the body.

Lesson purpose: to study the etiology, pathogenesis and clinical manifestations of water and electrolyte metabolism typical disorders.

Lesson objectives: the student should:

1. Know:

- definitions of notions: "water and electrolyte metabolism", "edema", "anasarca", "dropsy", "ascites", "hydropericardium", "hydrothorax", "hydrocele", "hydrocephalus", etc.;
- violations of water and electrolyte metabolism, their forms;
- causes of dehydration, hypohydration and hyperhydration;
- types of edemas;
- main pathogenetic factors of edemas;
- the etiology, pathogenesis and clinical manifestations of the next kind of edemas: pulmonary, cardiac, kidney, toxic, cachectic, angioneurotic;
- the significance of edema for the organism.

2. Be able to:

- justify the conclusion about the causes, mechanisms, principles of pathogenetic therapy of water and electrolyte imbalance;
- solve the situational tasks on topic of the lesson.

3. Be familiar with:

- the experimental methods of edema reproduction in pathophysiological experiment;
- clinical manifestations of water and electrolyte disorders and different types of edema;
- the basic principles of pathogenetic therapy of water and electrolyte imbalance.

Requirements for the initial level of the knowledge. For a successful mastering of the topic student must have a clear understanding of the physiological mechanisms of water and electrolyte metabolism regulation in organism.

The control questions from related disciplines:

1. The body fluids (blood, lymph, intracellular fluid, extracellular fluid, cerebrospinal fluid, etc.), their volume distribution in the body.
2. The concept of the internal environment of the body. Homeostasis.
3. Water and electrolyte metabolism and its regulation mechanisms (antidiuretic hormone, renin-angiotensin-aldosterone system, atrial natriuretic factor).
4. The electrolyte composition of blood plasma. The osmotic pressure of the blood, its role in the exchange of water and electrolytes between blood and tissues.
5. Involvement of kidneys in maintaining of acid-base balance, osmotic pressure, ionic composition and volume of blood, in regulation of water and electrolyte metabolism.

Control questions:

1. Regulation mechanisms of water exchange and their impairment (hypo- and hyperhydrations).
2. Edemas and dropsies (definition).
3. Types of edemas.
4. General pathogenetic factors of edema.
5. Pathogenesis of cardiac, renal, toxic, cachectic, angioneurotic and other kinds of edemas.
6. Pulmonary edema (etiology, pathogenesis, clinical and pathomorphological picture of pulmonary edema).
7. The significance of edema for the organism.

WATER AND ELECTROLYTE METABOLISM AND ITS REGULATION

Water is the most widespread chemical compound — an ideal solvent for organic and inorganic substances and an essential component of metabolic reactions, the main component of the internal environment. The digestion and absorption of nutrients in intestine are carried out in the liquid medium. The life products are eliminated from the body with water. Water is an essential component for the implementation of the majority of an organism vital functions.

Water and electrolyte metabolism is an aggregate of processes of absorption, distribution, consumption and excretion of water and salts in the body of animals and humans. It maintains water balance and permanence of the osmotic pressure, ionic composition and acid-base balance of the internal environment.

The water content in an adult is an average of 60 % by weight, ranging from 45 % (in the elderly with overweight) to 70 % (young men). Depending on weight,

age, sex, the intensity of physical activity, body temperature, ambient conditions (in hot shops, in hot climates) human daily water requirement is on average 30–45 g per kg of body weight that ranges from 2.1 to 3.1 L.

The need of the organism in the water corresponds to the amount of lost fluid (table 1).

Table 1

The average daily intake and water loss in adults

| Water intake, ml/day | Water loss, ml/day |
|--|--------------------------------|
| Drinking and liquid food — 1100–1400 | With urine — 1200–1400 |
| Solid food — 800–1000 | With sweat — 600–700 |
| As a result of oxidative metabolism (endogenous water) — 300 | With the exhaled air — 300–400 |
| | Through the gut — 100–200 |
| Total: 2200–2700 | Total: 2200–2700 |

Water balance consists of three processes:

- 1) water intake with drinking and food;
- 2) formation of water during metabolism (endogenous water);
- 3) release of water from the body.

The amount of drinking water is approximately equivalent to diuresis, and the amount of water supplied with food is approximately equal losses during the perspiration and with sweat.

In the organism water is redistributed between the intracellular and extracellular sectors (table 2).

Table 2

Water distribution in the body

| Sector | Status |
|--|--|
| The intracellular water — 31–45 % of body weight | Related with hydrophilic organic and inorganic substances |
| | Adhered on the surface of colloid molecules |
| | Free. This part of the intracellular water is changing the most significant during the life of cells, both in normal and in the development of pathological processes |
| Extracellular water — 15–25 % of body weight | Intravascular fluid (blood plasma). Circulating plasma water makes up an average of about 4–5 % of body weight |
| | Intercellular (interstitial) fluid. It is 12–15 % of body weight |
| | Paracellular liquid (1.3 % of body weight) is found in various body spaces: |
| | – cerebrospinal fluid; – synovial fluid (joints, tendons, etc.); – gastric and intestinal juices; – oral liquid capsule glomerulus and renal tubules (primary urine); – liquid serous cavities (pleural, pericardial, peritoneal and others); – moisture chamber of the eye |

Extracellular sector includes fluid in the interstitial (extracellular) fluid space and circulating in the bloodstream. Transcellular fluid is localized in the regional cavities (cerebrospinal, intraocular, intraarticular, pleural, and ets.). Extracellular and intracellular fluids are significantly different in composition and concentration

of the individual components, but the overall total concentration of osmotically active materials is about the same. Movement of water from one sector to another occurs at small deviations in their osmotic pressure. Since most of the solutes and water molecules readily pass through the capillary epithelium, a rapid mixing of low molecular weight components between blood plasma and interstitial fluid takes place. Reception, loss or limitation of water consumption, increased salt intake or its deficiency, changes in metabolic rate and etc. capable to change the volume and composition of body fluids. Deviation of these parameters from a normal level activates mechanisms, which correct of water and salt balance violations.

Regulation system of water metabolism is intended for maintenance of optimal fluid volume in the body. This system eliminates the deviation of the liquid and salts content in the body and helps to reduce their severity. The regulation system of water metabolism is closely linked with the control systems of salt metabolism and osmotic pressure.

The system of water and electrolyte metabolism regulation in the body includes *afferent*, *efferent* and *central* units.

The afferent unit includes sensory nerve endings and nerve fibers in various organs and tissues (of the oral mucosa, stomach and intestine, vascular, etc.), as well as distant receptors (mainly visual and auditory). Afferent impulses from receptors of different types (osmo-, chemo-, baro-, thermal receptors) are supplied to the hypothalamic neurons in the thirst center.

The central unit of water metabolism regulation system is the center of thirst. Its neurons are located mainly in the anterior hypothalamus. This center is connected with the areas of the cerebral cortex which are involved in the formation of thirst sensation. Regulatory stimulus from thirst center neurons (nervous and humoral) are transmitted to the effector structures.

The efferent link of the water and electrolyte metabolism regulation system involves the kidneys, sweat glands, intestines, and lungs. These organs provide a removal or retention of water and salts in the body. An important regulators of water metabolism in the body are antidiuretic hormone (ADH, vasopressin), the renin-angiotensin-aldosterone system (RAAS), and atrial natriuretic factor (ANF, atriopeptid), catecholamines (ACTH), prostaglandins, mineralocorticoids (fig. 1).

Irritation of osmoreceptors of hypothalamic area (by increasing the osmotic pressure of blood over 280 ± 3 mOsm/L H_2O), and of the left atrium volumoreceptors (at the blood volume decreasing) increases the release of vasopressin (ADH) by supraoptic and paraventricular hypothalamic nuclei. ADH increases the reabsorption of water in the tubules of nephrons.

Ischemia of the kidneys, activation of the kidney arterioles receptors (at the decreasing of renal blood flow or blood loss) and sodium receptors of tight spots of juxtaglomerular complex (during sodium deficiency) enhance the synthesis and release of renin into the blood. Angiotensin-II, formed under the influence of rennin, stimulates the synthesis and increases the release of

adrenal aldosterone, which increases the reabsorption of sodium in the convoluted tubules of nephrons. Reducing the volume of extracellular fluid and angiotensin-II also stimulates the center in the hypothalamus.

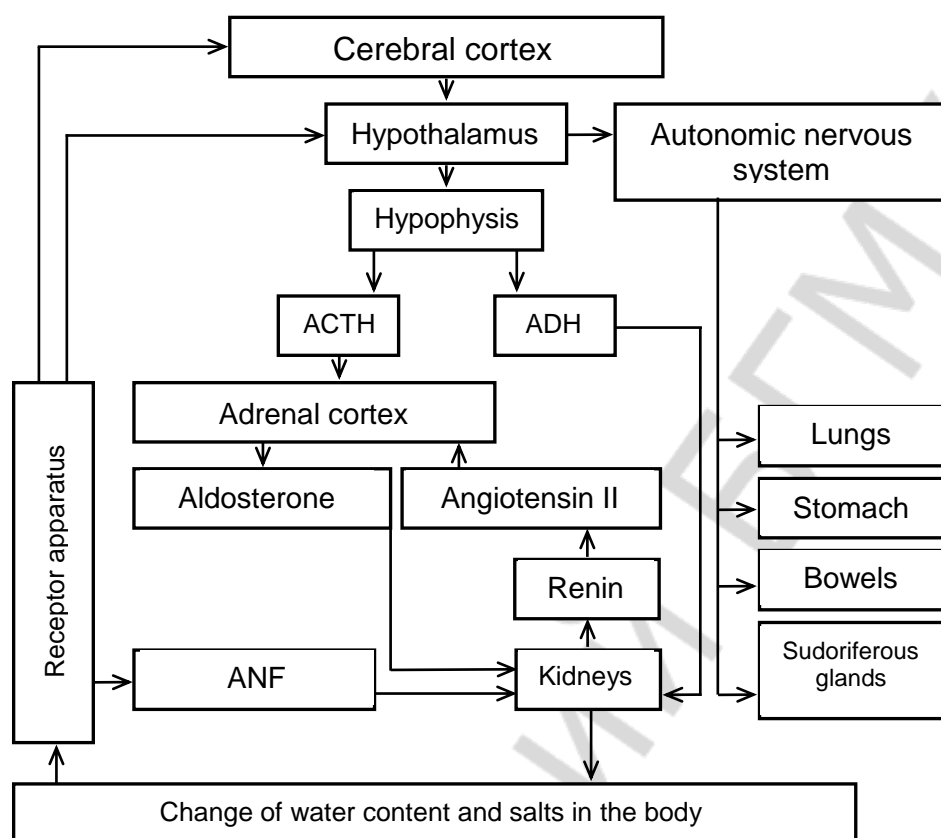


Figure 1. The water metabolism regulation system of the body (by P. F. Litvitsky)

Diuretic and natriuretic mechanisms resist to antidiuretic and antinatriuretic. The main operating factors of these mechanisms are renomedullary renal prostaglandins and atriopeptid. ANF is produced in the cells of the atria and enhances diuresis and natriuresis, decreases the tone of vessels and lowers blood pressure. ANF content in the atria and its secretion in the blood is increased under the influence of the excess water and salt consumption; atrial stretching; during an increase in blood pressure, as well as at the stimulation of vasopressin and α -adrenergic receptors.

Described mechanisms are working constantly and provide the restoration of water and electrolyte homeostasis during blood loss and dehydration; excess water in the body, as well as at the changes in the osmotic concentration of the extracellular fluid.

Changes or violation of water metabolism are referred to as positive (excess accumulation in the body of water) or negative (water deficit in the body) balance. If the efficiency of the water balance regulation system is not sufficient, different versions of water metabolism disorders develop.

TYPICAL FORMS OF WATER EXCHANGE DISORDARCES

Disorders of water metabolism (dyshidria) are divided into *hypo-*, *dehydration* and *hyperhydration* which are characterized by a reduction, absence or excess of fluid amount in the body respectively.

In turn, depending on changes in osmolarity concentration (ratio of water and electrolytes), hypohydration and hyperhydration are divided into *isoosmolar*, *hyposmolar* (the plasma osmolality is less than 280 mOsm/kg H₂O) and *hyperosmolar* (plasma osmolality is 300 mOsm/kg H₂O).

HYPOHYDRATION

Hypohydration (dehydration) is a form of water and electrolyte metabolism violation when there is a negative water balance, i. e. when removing water from the body exceeds its receipt.

Extreme dehydration is called **exicosis**.

Dehydration syndrome which is characterized by loss of water and electrolytes, blood circulation disorders, acidosis, disorders of the central nervous system, kidneys, gastrointestinal tract and other organs and systems can occur when:

- there is limitation or deprivation of water in the body in combination with a diet rich in protein;
- organism is deprived of water and salts during the oral administration of magnesium sulphate (as a laxative);
- during intravenous administration of hypertonic solutions of different sugars (osmotic diuresis);
- repeated evacuation of gastric juice or administration of emetics (apomorphine, etc.);
- intraperitoneal dialysis;
- artificial narrowing of the pyloric part of the stomach or the initial part of the duodenum with a permanent diverting out the secret of the pancreas, and others.

These methods lead to the primary loss of body water or electrolyte (along with the juices of the gastrointestinal tract), and rapid development of dehydration, increase blood viscosity, disturbance of microcirculation with a subsequent violation of the internal environment, and functions of various organs and systems. A special place in this case belongs to a discordance of the cardiovascular system. Violation of circulation is accompanied by a decrease in blood pressure, hypovolemia which result in disorders of the central nervous system, breathing, and renal system.

Isoosmolar hypohydration develops in cases of the equivalent loss of water and electrolytes. This happens sometimes during polyuria, intestinal auto-intoxication, as well as at the first minutes after acute blood loss. This reduces the volume of extracellular fluid without changing its osmolarity.

Hypoosmolar hypohydration develops when the body loses large quantities of water and electrolytes with the preferential loss of salts. It develops with the loss of gastric and intestinal juices (uncontrollable vomiting, pregnancy, profuse diarrhea), as well as sweating. The decrease in the osmotic pressure of the extracellular environment leads to a transition of water into the cells, whereby their swelling occurs, hypovolemia, blood clots, increasing of blood viscosity, which leads to circulatory disorder.

Dehydration and electrolyte loss often lead to a violation of the acid-base status. Thus, dehydration during the gastric juice loss, is accompanied by the loss of chlorides and H^+ ions, leads to the excretory alkalosis. Loss of pancreatic and intestinal juices containing more sodium and bicarbonates, on the contrary, leads to the excretory acidosis.

Hyperosmolar hypohydration develops when water loss exceeds the loss of electrolytes (especially sodium), during hyperventilation, profuse sweating, loss of saliva (sweat and saliva are hypotonic with towards to blood), as well as diarrhea, vomiting and polyuria, when additional water consumption is not enough. Under these circumstances extracellular fluid volume decreases and increases its osmotic pressure. Water leaves the cell, its dehydration begins, which manifests with feeling of thirst, despite sufficient water in the body. Under these conditions, there is increased production of vasopressin, which limits the loss of water by renal and extrarenal ways.

Sometimes an increase of aldosterone secretion leads to sodium retention and to amplifying of hyperosmolarity.

Water distribution in the intracellular and in the extracellular sectors at the hypohydration is presented in table 3.

Table 3

Distribution of water in the intracellular and extracellular sectors at hypohydration

| Index | Isoosmolar | Hypoosmolar | Hyperosmolar |
|----------------------------|--|--|---|
| Causes | The initial stage of acute massive blood loss (prior to the development of short-term effects of compensated mechanisms). Profuse vomiting. Profuse diarrhea. Burns a large area. Polyuria caused by higher doses of diuretics | Hypoaldosteronism. Long profuse sweating with the release of large amounts of salt. Repeated, uncontrollable vomiting. Diabetes insipidus or mellitus. Profuse diarrhea. Improper or unreasonable conduct of cleansing procedures | Insufficient water intake. Excessive and prolonged sweating. Polyuria (at diabetes mellitus and diabetes insipidus). Prolonged artificial lung ventilation by insufficient moisturized gas mixture. Drinking the seawater at hypohydration conditions. Parenteral injections of high osmolar solutions |
| Extracellular fluid volume | ↓↓ | ↓↓ | ↓ |
| Intracellular fluid volume | = (at burns ↓) | ↑ | ↓ |

| Index | Isoosmolar | Hypoosmolar | Hyperosmolar |
|----------------|---|--|--|
| Manifestations | Reduction of the circulating blood volume. Increased blood viscosity (HCT↑). Violation of the microcirculation. Disorders of acid-base balance. Hypoxia | Reduction of the circulating blood volume. Increased blood viscosity (HCT↑). Reduction of the systolic volume and the blood flow minute volume. Hypoperfusion of organs and tissues. Disorders of acid-base balance: – hypoxia; – dryness of mucous membranes and skin, hyposalivation; – ↓ diuresis; – thirst | Reduction of the circulating blood volume. Increased blood viscosity (HCT↑). Systemic circulatory disorders. Violations of the of acid-base balance. Hypoxia. Fever. Neuropsychiatric disorders. The painful, irresistible thirst |

HYPERHYDRATION

Hyperhydration is a form of violation of water and electrolyte metabolism, which occurs due to excessive intake of water (water intoxication), or lack of its excretion, i. e. when there is a positive water balance.

During the water poisoning, water quantity increases and the osmotic pressure decreases both outside and inside the body's cells. Water poisoning occurs in humans, if the water flow exceeds the ability of the kidneys to its excretion, for example during some renal diseases (hydronephrosis et al.), as well as at conditions involving a sharp cessation of urination (in surgical patients in the postoperative period, in patients in shock, and others). Patients with diabetes who take large amounts of fluid during treatment with antidiuretic hormones can suffer from the water poisoning.

Because of excessive water inflow blood volume increases (oligocythemich hypervolemia). There is a relative decrease of proteins content, blood electrolytes, hemoglobin, and also hemolysis of erythrocytes, and hematuria develops. Diuresis is initially increased, and then begins to lag relative to the amount of incoming water but during hemolysis and hematuria diuresis decrease.

Isoosmolar hyperhydration can occur after administration of the excess volume of 0.9 % sodium chloride, Locke–Ringer, Ringer–Tyrode, Krebs–Ringer solutions. Developing hyperhydration is temporary and usually is quickly eliminated in case of normal functioning of water exchange system.

Hypoosmolar hyperhydration as a form of violation of water and electrolyte metabolism is associated with the accumulation of water when it is greater than the intake of the excretory capacity of the kidneys. In this state, the osmotic pressure decreases in the extracellular environment, water enters to the cells. There is cell swelling, water intoxication develops. Hypoosmolar intracellular hyperhydration is accompanied by gross violations of ion and acid-base balance

and cell membrane potential. Clinically, patients have swelling of the face, legs, ascites develops, edema of the lungs and brain. During the water poisoning, nausea, repeated vomiting, convulsions, coma may develop. This pathology in clinical practice can occur when repetitive cleansing enemas are used, after the surgery, when the renal function is lowered and oliguria comes.

Hyperosmolar hyperhydration may occur while the body is enriched by large amount of water and electrolytes which occurs, for example, during forced using of seawater for drinking. The rapid increase in the level of electrolytes in the extracellular environment leading to acute hyperosmia. The water exits from the cells, their dehydration occurs that manifests with thirst, despite sufficient water in the body. This type of violation is accompanied by the development of the same symptoms as when hyperosmolar dehydration develops.

Water distribution in the intracellular and extracellular sectors during hyperhydration are presented in table 4.

Table 4

Distribution of water in the intracellular and extracellular sectors at hyperhydration

| Index | Isoosmolar | Hypoosmolar | Hyperosmolar |
|----------------------------|---|--|---|
| Causes | The infusion of large amounts of isotonic solutions. Increase the permeability of the microvessels walls. Hypoproteinemia. Chronic lymphostasis | Excessive introduction into the body of water (water intoxication). High blood ADH due to its overproduction in the hypothalamus (syndrome of inappropriate antidiuretic hormone secretion [Parhon's Syndrome]). Renal failure | Forced drinking of seawater. Injetion into the body solutions with a high salt content. Hyperaldosteronism. Renal failure |
| Extracellular fluid volume | ↑↑ | ↑ | ↑↑↑ |
| Intracellular fluid volume | = (↑) | ↑ | ↓↓↓ |
| Manifestations | Increasing of circulating blood volume. Increased blood pressure, cardiac output and systemic vascular resistance. The development of heart failure. Formation of edema | Increasing of circulating blood volume and hemodilution. Polyuria. Hemolysis of red blood cells. Vomiting and diarrhea. Neuropsychiatric disorders: drowsiness, apathy, impaired consciousness, convulsions. Insufficiency of blood flow with the development of edema | Hypovolemia, ↑circulating blood volume. Increased blood pressure and cardiac output. Increasing of central venous blood pressure. Brain and lungs edema. Hypoxia. Neuropsychiatric disorders. Great thirst. Hyperosmolar syndrome with cell hypohydration |

TYPICAL FORMS OF ELECTROLYTE METABOLISM VIOLATIONS

Mostly minerals present in the organism in dissolved forms as electrolytes or in connection with proteins. The basic electrolytes include sodium, potassium, chlorine, calcium, phosphorus and magnesium, whose role in the life of an organism is various and uncertain.

Table 5

Clinical and laboratory manifestations of electrolyte imbalance

| Type of violation | Main reasons | Signs and symptoms | Clinical and laboratory parameters |
|--------------------------|---|--|---|
| Hypo-natremia | Increased loss of Na ⁺ with urine and sweat. Insufficient production of aldosterone. Long-term use of sulfonamides and their derivatives — saluretics enhancing excretion by the kidneys. Profuse diarrhea, prolonged vomiting | Muscle weakness and cramps. Lethargy, confusion, epileptic seizures, coma. Hypotension, tachycardia. Nausea, vomiting, intestinal colics. Oliguria, anuria | Reduction of the sodium content in the blood serum below 135 mmol/L |
| Hyper-natremia | Excessive intake of salt. Hypernatremia due to violation of Na ⁺ excretion by the kidneys (glomerulonephritis, long-term use of glucocorticoids). Enhanced Na ⁺ reabsorption in the renal tubules by excessive secretion of aldosterone | Anxiety, restlessness, fever. Increased muscle tone, seizures. Hypertension, tachycardia, edema, excessive weight gain, thirst, increased saliva viscosity, coarse tongue. Shortness of breath, respiratory arrest, death | Increase the sodium content in the blood serum over 145 mmol/L |
| Hypo-kalemia | Insufficient intake of K ⁺ with food. Chronic profuse diarrhea. Uncontrollable vomiting. Excessive excretion of K ⁺ with urine due to the reduction of its reabsorption in the renal tubule under the influence of long-term treatment with glucocorticoids and corticotropin. Hyperaldosteronism | Dizziness, hypotension, arrhythmia, ECG changes, cardiac arrest and breathing. Nausea, vomiting, anorexia and diarrhea, decreased intestinal peristalsis, bloating and paresis of the ileum. Muscle weakness, fatigue and cramps in the legs | Decrease of potassium in the blood serum less than 3.5 mmol/L |
| Hyper-kalemia | Excessive intake K ⁺ with food. Violation of the K ⁺ excretion by the kidneys. Hypoaldosteronism. Damage and destruction of cells due to the redistribution of potassium in blood cells | Tachycardia and followed bradycardia, ECG changes, cardiac arrest. Nausea, diarrhea, muscle cramps of the abdominal wall. Muscle weakness, flaccid paralysis | Content of potassium in serum of more than 5.0 mmol/L |

| Type of violation | Main reasons | Signs and symptoms | Clinical and laboratory parameters |
|-------------------|---|---|---|
| Hypo-chloremia | Pathology of the gastrointestinal tract, accompanied by the loss of Cl^- . Cholera. Acute intestinal obstruction. Diuretics with saluretic action which depress Na^+ reabsorption in the renal tubules and caused a significant increase in Cl^- excretion with urine | Hyperreflexia and tetany. Superficial, respiratory depression. Symptoms commonly associated with hyponatremia: muscular weakness and cramps | Reduction of chlorine ion in serum below 95 mmol/L |
| Hyper-chloremia | Excessive consumption of salt. Acute glomerulonephritis. Violation of the urinary tract patency. Chronic circulatory insufficiency. Hypothalamic-pituitary insufficiency. Prolonged hyperventilation | Hyperpnoea, tachypnea. Weakness. Acidosis. Lethargy leading to coma | Increase in the content of chlorine ion in serum more than 108 mmol/L |
| Hypo-calcemia | Low calcium levels in foods. Increased transition of Ca^{2+} from the plasma into the bone tissue during overproduction of calcitonin. Delay of calcium in bone tissue during overproduction of parathyroid hormone. Violation of calcium absorption in the intestine at hypo- and avitaminosis D | Anxiety, irritability. Weakness. Hypotension. Arrhythmia due to reduced incoming Ca^{2+} into the cells. Laryngospasm. Anxiety. Epileptic attack | Decrease in calcium concentration in blood serum below 2.23 mmol/L |
| Hyper-calcemia | Washout of calcium from bones and increased its output in the blood at hyperparathyroidism. Reduction in blood calcitonin or hypervitaminosis D | Muscle weakness. Cardiac arrest. Anorexia, nausea, vomiting. Caries. Osteoporosis | Increase the total calcium content in serum over 2.75 mmol/L |
| Hypo-magnemia | Reduction of magnesium intake during starvation or violation magnesium absorption in the intestine and increase its excretion by the kidneys. Alcohol abuse. Prolonged diarrhea. High levels of aldosterone, thyroid hormone or vasopressin. An increase in magnesium excretion by the kidneys. Treatment with diuretics, anti-fungal agents or anti-cancer agents | Increased excitability of the central nervous system. Arrhythmias. Vasodilation. Hypotension. Weakness and mental disorder (mental confusion, anxiety, aggressiveness). Tetanic convulsions. Loss of appetite, nausea and vomiting. Drowsiness | Decrease in magnesium concentration in blood serum below 0.65 mmol/L |

| Type of violation | Main reasons | Signs and symptoms | Clinical and laboratory parameters |
|--------------------|--|--|---|
| Hyper-magnemia | Long-term, excessive intake of magnesium from food. Kidney failure. Patients who take magnesium salts or medicines, containing, for example, some antacids or laxatives | Reduction of tactile sensitivity. Drowsiness, nausea and vomiting. Severe decrease in blood pressure. Breathing disorders. Paralysis, paresis | Increasing magnesium levels in serum over 1.1 mmol/L |
| Hypo-phosphatemia | Alcohol abuse. Respiratory alkalosis. Malabsorption in the intestines. Reception means linking phosphate. Binge eating. Severe burns. Treatment of diabetic ketoacidosis. Vitamin D deficiency. Hyperparathyroidism. Acute tubular necrosis after kidney transplantation. Hereditary hypophosphatemia. Fanconi syndrome | Violation of the function of erythrocytes, leukocytes. Muscle weakness. Loss of appetite. Malaise, weakness. Paresthesias in extremities. Bone pain. Violation of the oxyhemoglobin dissociation. Myopathy. Cardiomyopathy. Rachitis. Osteomalacia | Serum phosphorus content less than 0.81 mmol/L |
| Hyper-phosphatemia | Renal failure. Hypothyroidism. Pseudohypoparathyreosis. Rhabdomyolysis. Disintegration of tumors. Metabolic and respiratory acidosis | Hypocalcemia. Hyperreflexia. Flaccid paralysis. Muscle weakness. Violation of bone maturation | Increase the phosphorus concentration in the blood serum over 1.45 mmol/L |

EDEMA

One of the most common types of water and electrolyte balance disorders is edema. **Edema** is a typical pathological process, which is characterized by an accumulation of water and electrolytes in the tissues and interstitial spaces due to violations of water exchange between the blood plasma and perivascular fluid.

The main pathogenetic factors of edema:

1. *Positive water balance* is a state in which the amount of water or an electrolyte excreted from the body is less than that ingested. For example renal dysfunction, drinking of large amounts of osmotic active substances and others.

2. *Hydrodynamic factor* (increasing filtration pressure: a) increase of venous pressure (general venous congestion associated with heart failure, violation of patency of venous of veins and insufficiency of venous valves, etc.); b) the restriction of venules).

Osmotic factor (reduction of the osmotic pressure gradient between the blood and interstitial environment due to accumulation of osmotically active substances (electrolytes, metabolic products) in the intercellular space.

Oncotic factor. Reduction of oncotic pressure of the blood, or to enhance its raise in tissue and interstitial fluid. Blood hypoconia is most often caused by a reduction of protein levels and mainly albumin because of: a) insufficient protein intake; b) violation of albumin synthesis; c) excessive loss of blood plasma proteins with urine at certain renal diseases;

Factor of capillary vessels permeability. Increase of capillary vessels permeability due to: a) action of humoral factors (histamine, serotonin, kinins, prostaglandins, etc.); b) vascular trophism violation owing to impaired neurotrophic support, starvation, hypoxia, etc.

Lymphatic factor. Violation of the outflow of lymph, lymph stagnation in the body (damage or obstruction of the lymphatic vessels, elephantiasis, and others).

Violation of the nervous and humoral regulation of water-electrolyte metabolism (violation of volumo-, osmoreceptors sensitivity, secondary aldosteronism; hypothyroidism, etc.).

These factors are involved in the pathogenesis of all forms of edema; however, their role in the mechanisms of different types of edemas development is not the same. In its pure form the monopathogenic edema occur very rare, usually the mentioned pathogenetic factors are combined.

Violation of water and electrolyte metabolism develops in a number of diseases and pathological conditions and they are accompanied by edemas. For example, portal hypertension during hepatic insufficiency is characterized by an accumulation of fluid in the abdomen — *ascites*; destruction of inguinal and pelvic lymph nodes is manifested by accumulation of serous fluid between the parietal and visceral plates of tunica vaginalis testis — *hydrocele*; at the severe heart failure or renal disease a transudate accumulation in the pericardial cavity can be observed (hydropericardium) or sharp swelling of the legs, torso and genitals, swelling of subcutaneous fat — *anasarca*; malabsorption is accompanied with excess formation of fluid in the brain cavities and the difficulty of its outflow (for example at the tumors) (*hydrocephalus* develops). There are different types of edema.

Classification of edemas

Depending on the causes and mechanisms of development are distinguished: *cardiac, renal, cachectic, inflammatory, toxic, lymphogenous, allergic edema*, etc. Some of them are specific to certain parts of the body and they are called local, while others may be more generalized — general edema.

Depending on the speed of development — *a fulminant* (after snake or insect bite), *acute* (pulmonary edema, myocardial infarction) and *chronic* (nephrotic, cachectic) edemas.

Depending on the underlying pathogenetic factor there are *osmotic, oncotic, hydrodynamic, lymphogenous, membranogenic* edema.

CARDIAC EDEMA

Cardiac edema develops during a heart failure. Attenuation of heart force leads to a decrease in cardiac output, a decrease in blood flow minute volume.

Neurohumoral link in the complex mechanism of cardiac edema is characterized by activation of sympathoadrenal and renin-angiotensin-aldosterone systems with increased production of ADH and, as a consequence, increased renal reabsorption of sodium and water. Under these conditions, protein synthesis in the liver is reduced and enhanced their elimination through the kidneys, followed by reduction of blood oncotic pressure. Along with this, at a heart failure the permeability of the capillary walls increases and blood proteins pass into interstitial fluid, increasing its oncotic pressure. All this facts contribute to water retention and the accumulation in the tissues during heart failure. Increased pressure in the superior vena cava causes a spasm of the lymphatic vessels, leading to lymphatic insufficiency, which further aggravates swelling.

Thus, the development of edema at heart failure is the result of the combined action of all inter-potentiating actions of pathogenetic factors: hydrodynamic, osmotic, oncotic, membranogenic and lymphatic.

Cardiac edemas are characterized by several features: 1) they start with the legs and the lower abdomen, in bedridden patients the edemas are arranged symmetrically; 2) they develop slowly, gradually, over weeks or months; 3) they are tight, leave a hole after press; 4) they accompanied by an increase of liver and possibly ascites. They combine with shortness of breath (which is increased in the supine position), tachycardia, pallor, cyanosis of the lips, poor exercise tolerance. The edema disappears when the compensation reactions progress.



Figure 2. Pitting edema and ascite (Bloom and Ireland, 1992)

PULMONARY EDEMA

Pulmonary edema is the pathological process that is caused by transudation of liquid part of blood from the blood capillaries into the interstitial lung tissue, and then to the alveoli and is characterized by a sharp violation of gas exchange in the lungs.

Pulmonary edema is the most severe manifestation of left ventricular heart failure (myocardial infarction, hypertensive crises, cardiomyopathy, defects of heart valvulars, etc.), as well as it's observed at the mitral stenosis, thrombosis and embolism of pulmonary vessels, during uremia and other endogenous and exogenous intoxications, at the anaphylactic shock, and parenteral administration of a liquid.

The pathogenesis of pulmonary edema at various diseases is different. In most cases it develops because of hemodynamic disturbances, usually caused by a pathology or acute cardiac overload (cardiogenic pulmonary edema) or damage of blood-air barrier by toxic substances (toxic lung edema), food allergy (allergic pulmonary edema), due to hypoxia; rarely developing of pulmonary edema is associated with impaired state of colloid-osmotic pressure of the blood plasma.

There are three main pathogenetic mechanisms of pulmonary edema. These mechanisms include:

1. A sharp rise of the filtration pressure in the capillaries of the pulmonary circulation.

2. *Violation of the capillary walls permeability.*

3. *Reducing of transudate outflow into the lungs lymphatic system.*

Increasing of the filtration pressure in the capillaries of the pulmonary circulation occurs due to increase of hydrostatic blood pressure in them and decrease of colloid-osmotic pressure of plasma. Reduced blood oncotic pressure due to hypoproteinemia is one of the main causes of pulmonary edema in patients with protein starvation, and liver and kidney diseases.

Violation of vascular permeability and alveolar walls is a result damage of the alveolar-capillary membrane by the protein-polysaccharide complex. This pathogenetic factor may have a leading role in the development of pulmonary edema in anaphylactic shock, uremia, liver failure, severe infectious intoxication, inhalation of phosgene and other toxic substances.

Pulmonary edema develops initially only in the interstitium (interstitial phase), then transudation occurs in the alveoli (alveolar phase). In connection with impregnation of interalveolar septa by edematous liquid, their thickness increases by 3–4 times, which complicates of gas diffusion, particularly oxygen, through the blood-gas barrier. As a result hypoxemia develops which in the initial phase of edema is combined with hypocapnia and alkalosis due to severe hyperventilation. In the phase of alveolar edema abundant foamy sputum is formed, which hampers of alveolar ventilation and further prevents the diffusion of gases. This leads to hypercapnia and respiratory acidosis. Increasing hypoxia is accompanied by damage of alveolar capillaries membranes and an increase of their permeability for proteins. Pulmonary edema is usually fast-paced pathological process, and it's clinical picture depends on the speed of the transition from interstitial phase to the alveolar phase of pulmonary edema.

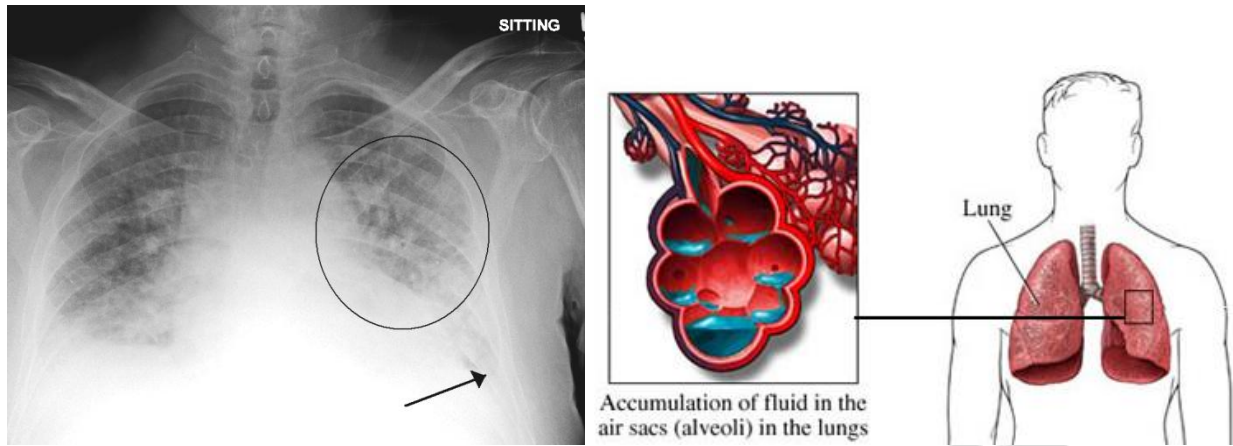


Figure 3. Pulmonary edema with small pleural effusions on both sides

RENAL EDEMA

Nephrotic and nephritic edemas can arise at the kidney diseases. In the event of *nephrotic edema* associated with the destruction of renal parenchyma, reducing the amount of blood plasma proteins (hypoproteinemia) plays an important role due to a great loss of proteins (mainly albumin) through urine. Albuminuria is associated with increased permeability of the glomeruli and with violated protein reabsorption of reuptake by the proximal part of the renal tubules. Strengthened fluid transudation from blood vessels into the tissues and the development of a dynamic lymphatic insufficiency contribute hypovolemia, reduction in renal blood flow, followed by activation of the renin-aldosterone mechanism of sodium retention and antidiuretic mechanism of water delay in the organism. Thus, in the pathogenesis of nephrotic edema oncotic and osmotic mechanisms play a significant role.

Nephritic edema. It takes place at inflammatory kidney diseases of autoimmune origin, mostly during the glomerular dysfunction of the nephron. Acute renal inflammation leads to a reduction in the number of functioning nephrons and as a result, a decrease in glomerular filtration volume. In the patients which suffered from nephritis an increased concentration of aldosterone and ADH is observed. Aldosterone hypersecretion is a result of disturbed renal blood flow and the subsequent activation of the renin-angiotensin system. An angiotensin-II formed under the influence of renin through a number of intermediates activates the secretion of aldosterone directly. Thus, a mechanism of aldosterone sodium retention is mobilized. Hypernatremia through osmoreceptors activates the secretion of ADH, which rises the hyaluronidase activity not only of the renal tubules epithelium and collecting ducts of the kidneys, but also a large part of the capillary system of the body (generalized capillaries). There is a decrease of water removal through the kidneys and the increase in capillary permeability, in particular, blood plasma proteins. Therefore hallmark of nephritic edema is a high protein content in interstitial fluid hyperhydropexy and protein in urine. Therefore, osmotic, oncotic and membrane factors play a crucial role in the pathogenesis of nephrotic edema.

Renal edema appears first on the face, around the eyes. Edema is soft, loose, skin is pale. They are developing very quickly. There are no shortness of breath and other symptoms of heart failure. There are symptoms of kidneys damage — general weakness, headache, back pain, possible change the color of urine, reducing diuresis, and proteinuria.



Figure 4. Hyperhydropexy and protein in urine

ASCITES

Ascites is a significant accumulation of fluid in the abdominal cavity. The reason of the development is portal hypertension of various origins, chronic heart failure, alimentary dysfunction, lymph drainage by the thoracic duct. At the liver dysfunction ascites develops much faster. During advanced cirrhosis of the liver, one of the main manifestation of which is the portal hypertension usually occurs ascites, whose origin is attributed to several factors. Firstly, with hemodynamic factor (stagnation in the system v. Portae). With an increase in hydrostatic pressure in the portal vein is sharply increased lymph flow in the liver. With the development of ascites fluid transsudation exceed transport capacity of the lymphatic pathways (dynamic lymphatic insufficiency).

Second, an important role in the mechanism of the total fluid accumulation at the liver cirrhosis is a hormonal factor. Blood deposition in the abdominal cavity leads to the renin-angiotensin-aldosterone system activation and the active retention of sodium and water in the body. The hypokalemia and hypernatremia develop. A large number of aldosterone in the body appears due to rising of its production, and due to reduction of its metabolism in the liver (secondary hyperaldosteronism).

If abnormal liver's ability to synthesize albumin decreases oncotic blood pressure also decreases due to hypoalbuminemia, and it means that oncotic factor is involved in the development of edema, at the same time with factors listed above.

Similar pathogenesis of ascites occurs in the portal (stagnant) cirrhosis of the liver, which is observed in patients with chronic congestive heart failure.



Figure 5. Adapted from H. J. Bruyere (2009). 100 case studies in pathophysiology. Philadelphia, PA: Lippincott Williams & Wilkins

ALLERGIC EDEMA

Allergic edema, which is based on a membrane factor, occurs during allergy as a result of the complex pathochemical reactions resulting in a released large amount of histamine, which causes a sharp vasodilation and increased permeability of the vessels, so that the liquid portion of the blood begins to rapidly go into a tissue (urticaria, angioedema, allergic rhinitis, and others). Often angioedema is often connected with allergic reactions, and it is characterized by swelling of facial tissues. In most cases, angioedema is determined by IgE-mediated degranulation of mast cells to release histamine during the contact with the allergen or by physical factors (immediate-type of allergic reaction).

Edema of facial tissue usually develops quickly, within a few minutes or hours, sometimes can be diffuse, soft and symmetric. Typically, swollen of eyelids, lips. Skin color, usually does not change or becomes reddish. It is also possible edema of tongue, mouth floor and limbs, and can swell larynx, bronchospasm occurs, causing suffocation. Acquired angioedema resolves spontaneously, has a relapsing course and is not harmful to the patient. Complaints are usually limited to the itching and burning sensation.



Figure 6. Allergies to hair dye



Figure 7. Swelling of the lips

Inherited form of angioedema is transmitted by the autosomal dominant type. The mechanism at this form of edema is determining by the activation of the complement system caused by an esterase inhibitors deficiency (type I) or its functional disability (type II).

TOXIC EDEMA

Toxic edema occurs when organism is poisoning. The main factor in the mechanism of the edema is, apparently, the damage of the capillaries with an increase of their permeability and disruption of the autonomic innervations. Toxic edema may be caused by food, drugs, poisons, insect bites and by toxic substances with smothering action (chlorine, phosgene, diphosgene, etc.) with pulmonary edema development. As in the case with allergic edema, the main development mechanism is the membrane factor.

CACHECTIC EDEMA

Cachectic (hungry) edema develops at malnutrition (starvation) and usually accompanies cachexia of various origins, in particular due to tumors, infection, anorexia, alcoholism. The cause of edema is thus a significant reduction of the protein level in blood plasma (hypoproteinemia) and reduction of oncotic pressure of the blood compared with tissue oncotic pressure. Hypoproteinemic edema has a soft consistency; skin over them is dry, thinned, transparent. Swellings are symmetrical and occur gradually; quickly shifted when changing body position. Basically shin, foot, face are swollen.



Figure 8. Kwashiorkor

SIGNIFICANCE OF EDEMA FOR THE ORGANISM

In the formation of various types of edema (cardiac, renal, hepatic, cachectic, toxic, and others) common mechanisms are involved.

This circumstance, as well as a higher rate of edema at various pathologies of the body enables it to refer to the typical pathological processes. As with any pathological process, edema includes elements of both damage and protection.

Development of edema leads to mechanical compression of the tissue and impaired blood flow in them, and will accordingly exert a pathogenic effect. The excess of interstitial fluid prevents the exchange of substances between the blood and cells. Due to the violation of trophism swollen tissue is easier to become infected, and sometimes with development in their connective tissue. If edematous fluid is hyperosmotic, dehydration sets of cells with a painful sense of thirst, fever, restlessness develops. If the edematous fluid is hypoosmotic, cells edema develops with clinical signs of water intoxication. Electrolyte imbalance can lead to disruption of the acid-base balance of body fluids. Risk of edema is largely determined by its localization. Accumulation of fluid in the cavities of the brain, heart bag, the pleural cavity upsets the function of important organs and often is life threatening.

On the other hand, edematous fluid has a beneficial and protective effect due to reduction of the concentration of various chemical and toxic substances capable to induce the edema. During inflammatory, allergic, toxic and other types of edema due to the difficulty of outflow of blood and lymph from the lesion, absorption and dissemination of various toxic substances (bacteria, toxins, allergens etc.) in the body decrease. Developing inflammatory edema contributes to the migration of phagocytes in inflammatory focus.

PRINCIPLES OF PATHOGENETIC THERAPY OF EDEMA

Treatment of edema requires treatment of the underlying disease that caused edema — compensation of heart failure, correction of renal excretory function, etc.

But there are general guidelines:

1. Limit fluid intake to 0.8–1.0 liters per day.
2. It is necessary to limit salt intake to 1.0–1.5 g per day.
3. Daily diuresis monitoring (fluid intake should roughly correspond to the volume of urine).
4. Purpose of diuretics with control of blood electrolytes (especially potassium ions). Partial compensation of lost potassium may be supported by eating of potassium-rich foods such as dried fruit (raisins, dried apricots), baked potatoes, wild rose, rice, oatmeal.

A BRIEF GLOSSARY OF MAIN TERMS

Anasarca is the massive and generalized edema of the body tissues with profound subcutaneous swelling.

Ascites — an abnormal accumulation of fluid within the abdominal cavity.

Dropsy — accumulation of fluid in the cavities and organs of the body.

Hydrothorax is a type of pleural effusion in which serous fluid accumulates in the pleural cavity.

Hydropericardium — this is a condition where excessive fluid accumulates in the pericardial cavity.

Hydrocele is the accumulation of fluids around a testicle.

Hydrocephaly — this is a condition in which there is an abnormal accumulation of cerebrospinal fluid (CSF) in the brain.

Hydrostatic pressure is the pressure that is exerted by a fluid at equilibrium at a given point within the fluid, due to the force of gravity.

Oncotic pressure, or colloid osmotic pressure, is a form of osmotic pressure exerted by proteins, notably albumin, in a blood vessel's plasma (blood/liquid) that usually tends to pull water into the circulatory system. It is the opposing force to hydrostatic pressure.

Osmotic pressure is the minimum pressure which needs to be applied to a solution to prevent the inward flow of water across a semipermeable membrane. It is also defined as the measure of the tendency of a solution to take in water by osmosis.

Transudate is extravascular fluid with low protein content and a low specific gravity (< 1.012). It has low nucleated cell counts (less than 500 to 1000 /microlit) and the primary cell types are mononuclear cells: macrophages, lymphocytes and mesothelial cells. For instance, an ultrafiltrate of blood plasma is transudate. It results from increased fluid pressures or diminished colloid oncotic forces in the plasma.

Exudates is fluid rich in protein and cellular elements that oozes out of blood vessels due to inflammation and is deposited in nearby tissues. The altered permeability of blood vessels permits the passage of large molecules and solid matter through their walls.

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