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POSSIBILITIES OF PATHOGENETIC CORRECTION OF HYPERKINETIC DISORDERS TAKING INTO ACCOUNT AN ACID-BASE BALANCE

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Abstract

As a result of analysis of the available scientific data, a significant relationship between hyperkinetic syndromes and changes in the acid-base state has been revealed. The provoking effect of alkalosis on the occurrence and severity of hyperkinetic disorders was confirmed. An own example of effective treatment of patient with essential myoclonus with taking in account his acid-base state has been given. The addition of acetylsalicylic acid to the treatment with clonazepam caused a more significant decrease in the severity of hyperkinetic disorders and improved the patient's general condition and his quality of life. So that we suggest studying of acid-base balance in patients with hyperkinetic syndromes and syndrome of increased neuromuscular excitability in the outpatient setting and in hospital conditions at the making of initial diagnosis, and also recommend studying of acid-base balance in patients who already have neurological diagnoses, if such a study has not been made previously. Correction of acid-base status in the treatment of patients with hyperkinetic syndromes and the syndrome of increased neuromuscular excitability contributes to greater effectiveness of therapy than just symptomatic treatment of hyperkinetic disorders.

Key words: acid-base balance, alkalosis, essential myoclonus, hyperkinetic disorders

ВОЗМОЖНОСТИ ПАТОГЕНЕТИЧЕСКОЙ КОРРЕКЦИИ ГИПЕРКИНЕТИЧЕСКИХ НАРУШЕНИЙ С УЧЕТОМ СОСТОЯНИЯ КИСЛОТНО-ОСНОВНОГО БАЛАНСА

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В результате анализа имеющихся научных данных выявлена существенная взаимосвязь между гиперкинетическими синдромами и изменениями кислотно-основного состояния. Подтверждено провоцирующее действие алкалоза на возникновение и выраженность гиперкинетических нарушений. Приведен собственный пример эффективного лечения пациента с эссенциальной миоклонус с учетом его кислотно-основного состояния. Авторы предлагают изучать кислотно-основного баланс у пациентов с гиперкинетическими синдромами и синдромом повышенной нервно-мышечной возбудимости в амбулаторных и в стационарных условиях при постановке первоначального диагноза, а также рекомендуют такого рода диагностику для пациентов, уже имеющих неврологические диагнозы. Коррекция кислотно-основного состояния способствует большей эффективности терапии, чем просто симптоматическое лечение таких нарушений.

Ключевые слова: кислотно-щелочной баланс, алкалоз, эссенциальный миоклонус, гиперкинетические расстройства

Relevance of the topic. Hyperkinesias occupy a significant proportion of the neurological symptoms and syndromes that practicing neurologists reveal in their routine practice. One of these hyperkinesis is myoclonus. The term myoclonus is defined as sudden, rapid, shock-like movement. These movements can be “positive” or “negative”. Positive myoclonus leads to muscle contraction or muscle groups contaction. Asterixis or negative myoclonus is a short-term loss of muscle tone followed by contraction of other muscles, which leads to a nod type movement. These involuntary movements often have a

characteristic sawtooth pattern and they usually disappear during sleep. Typically, a myoclonus is a short (10–50 ms, rarely more than 100 ms), irregular muscle contractions, often without noticeable movement. Myoclonus amplitude can vary significantly. The lightning nature of a rectangular myoclonus wave helps in its differentiation from tremor (rhythmic oscillations), chorea (large, smooth movements), dystonia (reduction duration more than 100 ms, often with a twisting position), ticks (pulse duration> 100 ms, can be temporarily suppressed), or fasciculations (single muscles involved, minimal motor effect [1, 2].

Myoclonus can be physiological, familial, observed with progressive myoclonus epilepsy, lysosomal glycogen metabolism disorders, mitochondrial dysfunction, secondary due to congenital metabolic disturbances, injuries, neurodegenerative diseases, renal and hepatic insufficiency, non-ketone hyperglycemia and hypercapnia, alkalosis, alkalosis, alkalosis, alkalosis, alkalosis, alkalosis, alkalosis [3-6].

The stabilization of the acid-base state of the human body is provided by phosphate (1% of the buffer capacity of blood, its role in the tissues, especially in the kidneys, is very significant), bicarbonate (10% of the buffer capacity of blood), protein and hemoglobin (about 70% of the buffer blood capacity) buffer systems and the functioning of specific physiological mechanisms of compensation in some organs (lungs, kidneys, liver, gastrointestinal tract, bone tissue) [7-9].

Phosphate buffer system provides regulation of acid-base balance within cells, mainly kidney tubules. Phosphate buffer consists of two components: - Na2HPO4 (alkali) and NaH2PO4 (acid).

Bicarbonate buffer system is a buffer of blood and intercellular fluid, it maintains the balance of HCO3 / CO2. Where:

$$H + HCO3 <----> H2CO3 <----> CO2 + H2O$$

HCO3 functions as a base. CO2 (carbon dioxide) - as an acidic substance. Thus, an increase in HCO3 (bicarbonate) or a decrease in CO2 will make the blood more alkaline. Reducing HCO3 or increasing CO2 makes the environment more acidic. CO2 levels are physiologically regulated by the pulmonary system through respiration, while HCO3 levels are regulated by the kidneys through reabsorption. Thus, respiratory alkalosis is a decrease in the CO2 content in serum. Although it is theoretically possible to reduce the production of

CO2, this condition is mainly the result of hyperventilation, when CO2 is exhaled through the lungs [10].

Protein buffer system - the main intracellular buffer. It accounts for about 75% of the buffer capacity of the intracellular fluid. The components of the protein buffer are an acid weakly dissociating protein (protein COOH) and salts of a strong base (protein COONa).

Hemoglobin buffer system is the most capacious blood buffer. It consists of the acidic component - oxygenated HbO2 and alkaline - non-oxygenated Hb.

Bone carbonates are a depot for buffer systems of the whole body. They contain deposited a significant amount of salts of carbonic acid. With a rapid increase in the acid content, this system provides up to 30-40% of the buffer capacity.

Changes in the acid-base state are possible both in the direction of alkalosis and in the direction of acidosis. At the same time, as a rule, more attention is paid to the development of acidosis in the pathogenesis of diseases, including neurological ones, although both of these conditions have a negative effect on the functional state of the nervous system.

Alkalosis might be compensated and uncompensated. With compensated alkalosis, the indicators of the acid-base status of the blood are within the normal range and only changes in buffer systems and regulatory mechanisms are observed. With uncompensated alkalosis, the pH exceeds the upper limit of normal, which is caused by an excess of bases and a violation of the physiological mechanisms of regulation of acid-base balance.

The main causes of metabolic alkalosis are listed below [11]:

Chloride depletion:

gastric diseases: vomiting, mechanical drainage, bulimia

chloruretic diuretics: bumetanide, chlorothiazide, metalazone, etc.

diarrhea: villous adenoma, congenital chloride diarrhea, posthypercapnic state

reduction of chlorides in food with a base load: chloride-deficient infant formula

gastrocystoplasty

cystic fibrosis (cystic fibrosis) - a high content of chloride in sweat

excess potassium / excess mineralocorticoid

primary aldosteronism: adenoma, idiopathic, hyperplasia, renin-sensitive, glucocorticoid-suppressed, carcinoma

mineralocorticoid excess

primary excess of deoxycorticosterone: deficiency of 11β- and 17α-hydroxylase

drugs: licorice (glycyrrhizic acid) in the form of confectionery or flavoring, carbenoxolone

Liddle syndrome

secondary aldosteronism

excess adrenal corticosteroids: primary, secondary, exogenous

severe hypertension: malignant, accelerated, renovascular

hemangiopericytoma, nephroblastoma, renal cell carcinoma

Bartter syndrome and Gitelman syndrome and their variants

laxative abuse, clay consumption

Hypercalcemic condition

hypercalcemia in malignant tumors

acute or chronic milk alkaline syndrome

Other

carbenicillin, ampicillin, penicillin

bicarbonate intake: massive or in the presence of renal failure

way out of starvation

hypoalbuminemia

Acid-alkaline imbalance in various metabolic disorders naturally leads to disruption of the functioning of the brain and spinal cord. Compared with acidosis, patients with alkalosis have more severe neurological symptoms that are difficult to correct [12-16]. This is due, in particular, to the greater sensitivity of GABA-ergic neurons to alkalosis than to acidosis [12]. Alkalosis can provoke the development of many neurological symptoms, in particular, myoclonus. With a sharp change in pH above 7.55, a significant decrease in cerebral blood flow is observed with the development of seizures and coma [17].

Photo-myoclonus and myoclonus-like hyperkinesis have been described in metabolic alkalosis [18, 19].

In 2003, the first case of myoclonus caused by metabolic alkalosis due to vomiting associated with drug intake was described, in which severe hyponatremia, bipocalemia and alkalosis were also observed [20]. A case of metabolic alkalosis and myoclonus caused by the use of antacids containing sodium bicarbonate in a person with a pre-existing cerebrovascular disease was described in Japan [21]. Also described is the case of the occurrence of myoclonus in a 90-year-old patient on the background of long-term use of licorice contained in the antacid preparation [22]

Neuromuscular symptoms of metabolic alkalosis include, in addition to myocloni, also paresthesias and fasciculations, which may be associated with a decrease in the content of ionized calcium in serum. At the same time, Chvostek’s symptom is usually negative.

Fasciculations and tetany are generally more common than myoclonus. It is assumed that tetany is caused not only by a decrease in the concentration of ionized calcium in serum, but is also associated with an increase in pH-dependent myofibrillary sensitivity to calcium [23, 24].

In addition to metabolic alkalosis, respiratory alkalosis is also isolated. It is the most common acid-base imbalance, with the same frequency occurring in men and women. The frequency and prevalence of the disease depends on the etiology. Accordingly, the level of morbidity and mortality also depends on the etiology of the disease. In almost all cases, respiratory alkalosis is induced by hyperventilation, leading to central mechanisms, hypoxemia, pulmonary pathology and iatrogeny [10]. The central causes are head injuries, strokes, hyperthyroidism, anxiety disorders, pain, stress, the effects of certain drugs, drugs such as salicylates and various intoxications [10]. Hypoxic stimulation leads to hyperventilation in an attempt to correct hypoxia due to the loss of CO2. Pulmonary causes include pulmonary emboli, pneumothorax, pneumonia, and acute asthma or COPD exacerbations. Iatrogenic causes are primarily associated with hyperventilation in intubated patients with mechanical ventilation [10].

There are the following pathogenetic aspects of the development of respiratory alkalosis in various somatic diseases [25]:

Hyperthyroidism: hyperthyroidism increases the severity of ventilation chemoreflexes, thereby causing hyperventilation. The severity of chemoreflexes normalized in the treatment of hyperthyroidism.

Pregnancy: Progesterone levels increase during pregnancy. Progesterone stimulates the respiratory center, which can lead to respiratory alkalosis, which is common in pregnant women. [26].

Congestive heart failure: in patients with congestive heart failure (and other diseases with a decrease in cardiac output) hyperventilation is observed at rest, during exercise and during sleep. This is due to the fact that pulmonary vascular and interstitial receptors are stimulated due to pulmonary stagnation. In addition, low cardiac output and hypotension stimulate respiration by acting on the arterial baroreceptors.

Chronic / severe liver disease. Several mechanisms have been proposed to explain hyperventilation associated with liver disease. Elevated levels of progesterone, ammonia, vasoactive intestinal peptide and glutamine can stimulate respiration. Patients with severe liver disease or portal hypertension may have pulmonary arteriovenous anastomoses in the lungs or portal pulmonary shunts, leading to hypoxemia. This stimulates peripheral

chemoreceptors and leads to hyperventilation, and the degree of respiratory alkalosis correlates with the severity of liver failure. [26]

Salicylate overdose: Respiratory alkalosis initially develops, followed by metabolic acidosis, which causes secondary hyperventilation.

Fever and sepsis: Fever and sepsis can manifest as hyperventilation, even before the development of hypotension. The exact pathogenetic mechanism of this condition is unknown, but it is believed that it is due to the stimulation of the carotid sinus or hypothalamus with increasing body temperature.

Gram-negative sepsis: before the development of fever, hypoxia or hypotension, acute respiratory alkalosis develops, which may be the only early symptom. [26].

Pain: Hyperventilation can be caused by stimulation of peripheral and central chemoreceptors, as well as behavior control systems.

Hyperventilation syndrome, which is also known as psychogenic hyperventilation, was first described in 1935 [27]. Hyperventilation is triggered by stress and anxiety, both of which act on the behavioral control of breathing. Hyperventilation stops during sleep, when the behavioral control system is inactive, and only the metabolic system controls respiration. The diagnosis of hyperventilation syndrome is a diagnosis of exclusion, it is necessary to exclude all organic diseases, including, above all, life-threatening conditions, such as: pulmonary embolism, myocardial ischemia, hyperthyroidism, before making this diagnosis [28].

Respiratory alkalosis, in turn, can be acute and chronic. This is determined based on the level of metabolic compensation for respiratory disease. Excessive levels of HCO3 are buffered to maintain physiological pH through renal reduction of H secretion and increased secretion of HCO3, however, this metabolic process takes several days, while respiratory disease can alter CO2 levels in minutes or hours. Thus, acute respiratory alkalosis is associated with high bicarbonate levels, since there was not enough time to reduce HCO3 levels, and chronic respiratory alkalosis was associated with low and normal HCO3 levels [10].

The symptoms of respiratory alkalosis depend on its duration, severity and underlying disease causing hyperventilation. Hyperventilation syndrome can mimic many other serious diseases and includes weakness, cardiac arrhythmias, increased neuromuscular excitability, tingling in the fingers and toes and around the lips (paresthesia), chest pain, with pronounced alkalosis, tetany can develop [29, 30]. Acute onset of hypocapnia can cause cerebral vasoconstriction with a decrease in cerebral blood flow and such neurological symptoms as

dizziness, confusion, syncope and convulsions. The first cases of spontaneous hyperventilation with the development of dizziness and tingling, followed by the development of tetany, were described in 1922 in patients with cholecystitis, abdominal distension and hysteria. [31]. Haldane JS, Poulton EP. (1908) described painful tingling in the hands and feet, numbness and sweating of the hands, and cerebral symptoms that occurred after experimental hyperventilation. [32].

Treatment of respiratory alkalosis is aimed at treating the underlying pathology. In patients with anxiety disorders, anxiolytics are used. Beta-adrenergic blockers can help control sympathicotonia, which can lead to hyperventilation syndrome in some patients. [28]. Determining the presence of sympathicotonia in the cardiovascular system in clinical practice is most appropriate, from our point of view, using the Kerdo index or cardiointervalometry.

Treatment of respiratory alkalosis primarily depends on the cause of it. Antibiotics are effective for infectious diseases. For embolic diseases, anticoagulant therapy is necessary. Support for lung ventilation may be required in patients with acute respiratory failure, asthma, acute or chronic obstructive pulmonary disease. In patients who are on artificial ventilation, it may be necessary to regulate the ventilation parameters with a decrease in the respiratory rate. In this group of patients, it is also necessary to control the content of arterial and venous gases. In severe cases, the pH can be directly restored using acidifying agents [10].

Generally accepted in clinical practice is the provision of the mandatory control of acid-base balance in intensive care units and intensive care units. In other cases, much less attention is paid to the study of acid-base balance, which primarily applies to outpatient patients, in particular, to patients with a neurological profile. This situation is explained in particular by the fact that the indicators of acid-base balance are in fairly tight boundaries and their significant changes in most cases cause serious violations of the patient's health, leading to their hospitalization in the intensive care unit and intensive care unit. It has been established that with metabolic alkalosis with pH 7.55, the risk of death is 45%, with indicators above 7.65 the risk increases significantly and reaches 80% [33,34].

The results of our own observations: Under our observation was the patient, who was sent to us for a consultation with myoclonic hyperkineses. In the study of indicators of acid-base status of the blood, a pronounced alkalosis with a pH of 7.75 was detected. In connection with the naturally arising doubts about the reliability of the analysis, a repeated study was performed. With repeated analysis, the pH was at the level of 7.65.

Data from laboratory and instrumental methods of research of a patient:

TSH - 1.24 μMO / ml

Free thyroxin T4 - 1,5ng / dl

Triiodothyronine free T3 - 4.26 pg / ml

Antibodies to thyroglobulin less than 10 MO / ml

Antibodies to thyroperoxidase - 0.66 IU / ml

Tireoglobulin - 20,4 ng / ml

Parathyroid hormone - 41 pg / ml

Calcitonin - less than 2 pg / ml

Potassium - 4.25 mmol / l

Sodium - 144.0 mmol / l

Calcium ionized - 1.16 mmmol / l

Bicarbonate - 30.6 mmol / l, the norm - 22.0 - 29.0 mmol / l

Ceruloplasmin venous blood - 0.369 g / l

The blood pH 06.14.18 - 7.75, 06.30.18 - 7.605, 10.17.18 - 7.42.

PCO2 - 51.6 mmHg, PO2 - 22 mmHg.

Urine: straw yellow, clear, specific gravity 1014, pH - 6.0, protein - no, glucose - no

Leukocytes - 2-3 in the field of view, epithelium flat 1-2 in the field of view.

MRI of the brain: MR signs of moderate expansion of convective cerebrospinal fluid spaces in the frontal regions, uneven expansion of perivascular spaces. Volume and focal formations of the brain was not detected. EEG showed no signs of epileptic activity.

The fundus of the eye: the optic nerve discs are pale pink, clear boundaries, narrowed arteries, dilated veins. Diagnosis: OI Angiopathy of the retina.

Myoclonic hyperkinesis was observed in neurological status. Meningeal and focal signs were not found. Chvostek's and Trousseau's signs were absent. For the purpose of differential diagnosis between metabolic and gas alkalosis, a study was made to determine the content of bicarbonate levels in blood serum, the level of which, as is known, increases with metabolic alkalosis. An increase in serum bicarbonate levels above normal was found, indicating metabolic alkalosis. The content of ionized calcium in the patient's blood was within the normal range. Serum potassium and magnesium levels were also within the normal range, which made it possible to exclude the presence of Bartter and Gitelman syndrome.

In order to conduct pathogenetic and symptomatic therapy, the patient was prescribed acetylsalicylic acid at a dosage of 75 mg 1 time per day and clonazepam at the standard dosage, which led to a pH shift to 7.45 after 1 month and a significant reduction in the severity of myoclonic hyperkineses.

Conclusions:

1. As a result of our analysis of the available scientific data, a significant relationship has been revealed between hyperkinetic syndromes and changes in the acid-base state.

2. The provoking effect of alkalosis on the occurrence and severity of hyperkinetic disorders was revealed.

3. In connection with the above, we consider it expedient to study acid-base balance in patients with hyperkinetic syndromes and syndrome of increased neuromuscular excitability in the outpatient setting and in hospital conditions at the initial diagnosis, and we also recommend the study of indicators of acid-base balance in patients with hyperkinetic syndromes and syndrome of increased neuromuscular excitability, already having neurological diagnoses, if such a study has not been performed previously.

4. Correction of the acid-base state in the treatment of patients with hyperkinetic syndromes and the syndrome of increased neuromuscular excitability contributes to a greater effectiveness of the therapy given than the symptomatic treatment of hyperkineses only.

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