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CHARACTERIZATION OF TOXIC EFFECTS IN ACUTE POISONING WITH METHANOL AND ETHANOL

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✧ Toxic damage to the optic nerve is one of the causes of the development of degenerative processes in the fibers of the optic nerve, leading to its atrophy. Exposure to methanol and ethanol is associated with the damaging effects of metabolites, which lead to ATP deficiency. Knowledge and understanding of pathogenetic processes can help the doctor to make a timely diagnosis, which will allow the start of etiopathogenetic therapy as early as possible. The prognosis for acute poisoning with methanol and ethanol depends not only on the degree of intoxication, but also on the timeliness and accuracy of diagnostic and therapeutic tactics.

✧ ***Keywords:*** methanol poisoning; ethanol poisoning; optic atrophy; toxic optic neuropathy.

ХАРАКТЕРИСТИКА ТОКСИЧЕСКОГО ДЕЙСТВИЯ ПРИ ОСТРЫХ ОТРАВЛЕНИЯХ МЕТАНОЛОМ И ЭТАНОЛОМ

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✧ Токсические повреждения зрительного нерва являются одной из причин развития дегенеративных процессов в волокнах зрительного нерва, приводящей к его атрофии. Воздействие метанола и этанола связано с повреждающим действием метаболитов, которые приводят в дефициту аденозинтрифосфорной кислоты. Знание и понимание патогенетических процессов позволяет врачу поставить своевременно диагноз и начать этиопатогенетическую терапию как можно раньше. Прогноз при острых отравлениях метанолом и этанолом зависит не только от степени интоксикации, а также от своевременности и правильности диагностической и лечебной тактик.

✧ ***Ключевые слова:*** отравление метанолом; отравление этанолом; атрофия зрительного нерва; токсическая оптиконейропатия.

INTRODUCTION

Oftentimes, in the course of clinical practice, ophthalmologists – as well as neurologists – are required to deal with optic nerve pathological conditions. Understanding the pathogenesis of the damaging effect using the correct diagnostic approach of examination ensures the correct diagnosis of pathological condition, which, in turn, ensures timely etiological treatment.

One of the main causes of optic nerve damage is the neurotoxic effect of an exogenous substance – in particular, methanol, and ethanol. Acute poisoning is often accompanied by both neurological (such as tremor and impairment of consciousness) and ophthalmological symptoms (such as decreased visual acuity, impaired color vision, and scotomata). Of note, toxic neuritis as an acute and urgent condition typically requires early diagnosis and timely

treatment. Even with an adequate therapy, methanol, and ethanol poisoning can lead to optic nerve atrophy, that is, a persistent decrease in visual acuity or blindness [1].

BACKGROUND

According to statistics, the annual consumption of alcohol and its substitutes amounts to approximately 1 billion 28.3 million liters in Russian Federation. According to a survey conducted by the Federation Council Committee on Social Policy and Healthcare in 2010, the alcohol consumption increased from 9.3 liters to 10.5 liters of pure ethanol per capita over a period of five years. As a result, the number of cases of poisoning with alcohol and its surrogates also increased. Thus, the importance of studying the influence of this toxic effect on the optic nerve is beyond dispute [2].

ETIOLOGY

Methanol and ethanol poisoning occurs when alcohol and its substitutes are consumed orally [2].

However, it should be noted that methanol is used as an industrial solvent and vehicle antifreeze. Therefore, one of the common grounds for the development of toxic optic neuropathy is often related to the inhalation of methanol vapors [1].

METABOLISM OF ETHANOL AND METHANOL

Once ethanol enters into the gastrointestinal tract, it is absorbed rapidly and revealed in the blood within 5 min. Ethanol metabolism occurs in the liver and is divided in several stages. The first stage represents the oxidation of ethanol to acetaldehyde using alcohol dehydrogenase. In the second stage, the acetaldehyde, in turn, is oxidized to acetic acid with the involvement of the enzyme acetaldehyde dehydrogenase. The third stage comprises of the formation of acetyl coenzyme A (acetyl-CoA; which is oxidized in the Krebs cycle to water and carbon dioxide) from acetate [2, 3]. As a result, oxidation of ethanol generates large amounts of acetaldehyde, acetate, and reduced nicotinamide-adenine dinucleotide (NAD). Acetate interacts with the formation of acetyl-CoA, which is one of the substrates for intermediary metabolism. While most of the acetyl-CoA formed is metabolized in the Krebs cycle under normal conditions, in cases of ethanol poisoning, the tricarboxylic acid cycle is blocked by acetaldehyde and cannot dispose all the acetyl-CoA, which leads to its use in the synthesis of fatty acids and the formation of ketone bodies. The formation of ketone bodies not only binds the excessively formed acetyl-CoA, but also promotes the reoxidation of NAD and oxidized NAD in the acetoacetate to β-hydroxybutyrate reaction, which thereby leads to the accumulation of the latter. Besides, glycolysis disorders developing in the course of it (accumulation of glycerol 3-phosphate with a rapid decrease in 1,3-diphosphoglycerate) are associated with hyper-reduction of the NAD pool and are manifested by excessive formation of lactate from pyruvate. However, the increase in lactic acid levels is usually insignificant. Moreover, excessive formation and accumulation of acetate, ketone bodies and, to a lesser extent, lactate in the cell results in the natural development of metabolic acidosis [2]. A special aspect of ethanol is its ability to form hydrogen bonds with the lipids of the cell membrane, thus, making the cell membrane more permeable. The presence of ethanol near the cell membrane is suggested to cause its dehydration [4].

The oxidation of methanol in human body generally proceeds three–six times slower than that of ethanol. The main oxidation products are formaldehyde and formic acid. A part of formaldehyde binds to proteins, while the other part is oxidized to formic acid. At the same time, the oxidation of formaldehyde to formic acid proceeds rather quickly, and it is metabolized much slower. The toxic effect of methanol is primarily associated with formic acid and formaldehyde, which suppress the cytochrome system, inhibit oxidative phosphorylation, thereby causing adenosine triphosphoric (ATP) acid deficiency that mainly occurs in the brain tissue and retina [2]. Further, during the formate accumulation, tissue respiration is impaired, which leads to severe tissue hypoxia. As a result, metabolic acidosis is formed, and the pH is shifted to the acidic side [2, 3]. Hence, the tissue hypoxia typically occurs in the first hours due to the action of formic acid on the chain of respiratory enzymes at the level of cytochrome C reductase. The synthesis of ATP terminates, and consequently, tissue hypoxia develops. With the presence of hypoxia and a decrease in energy supply, biological oxidation is impaired, which implies the accumulation of underoxidized products such as lactic acid. This leads to systemic acidosis [3]. In addition, methanol is a strong protoplasmic poison that disrupts oxidative phosphorylation in the cytochrome oxidase system [5]. It has been revealed that at the cellular level, the methanol molecule, in contrast to the ethanol molecule, is not able to penetrate the cell membrane [4].

All these processes lead to demyelination and, subsequently, optic nerve atrophy [5].

General toxic and ocular symptoms of ethanol and methanol poisoning

For early diagnostics, as well as solving the issue of the presence and nature of exogenous intoxication, history data are as significant as external examination of the patient, results of ophthalmological and neurological examinations, and laboratory data. The neuro-ophthalmological symptoms often contribute to differentiation of the causes of exogenous intoxication and poisoning. It should be borne in mind that an assessment of clinical manifestations, in particular, neuro-ophthalmological symptoms, depends not only on the nature of the toxic substance, but also on the degree of intoxication, including the stage of the pathological process development [6].

Besides, ethanol has a specific effect on the adrenergic system. Under its influence, norepinephrine is released intensely, which accompanies mental and autonomic arousal, as well as motor restlessness. Subsequently, the labile fractions of norepinephrine are destructed, which is accompanied by mental and motor inhibition [6].

Generally, acute ethanol poisoning is accompanied by alcohol intoxication. While a concentration of ethyl alcohol of 0.28–1.0 g/l in the blood serum can cause euphoria, talkativeness, slowness of reactions, nystagmus, mild coordination disorders, and hypoalgesia, a concentration of 1–2 g/l of plasma often leads to disinhibition, exaggeration of facial expressions and movement, inadequate behavioral reactions (which often leads to breaking of ethical standards), conjunctival hyperemia, nystagmus, ataxia, dysarthria, and hypoalgesia. In addition, a concentration of 2–3 g/l of plasma causes irritability, resentfulness, depression, and affective reactions prominently, as well as impulsive actions, pale or hyperemic face, tachycardia, low blood pressure, nausea, vomiting, and drowsiness. The pupils are miotic, but sometimes moderately mydriatic (in response to pain stimulation, with manifestations of respiratory failure). Nystagmus, diplopia, conjunctival congestion are also revealed. At a dose of 4–5 g/l, diplopia, dilated pupils reacting sluggishly to light, severe ataxia, and uncoordinated movements are noted. Subsequently, amnesia of the intoxication period occurs. At a concentration of >5–6 g/l, pallor of the face, hypokinesia, impaired consciousness of the type of moderate somnolentia, dilated pupils with sluggish reaction to light, strabismus, diplopia, as well as hypothermia, cold sweat, severe dysarthria or anarthria, general anesthesia, tachycardia, coarse breathing, hyperventilation, somnolentia, and semisomnus likely to pass into a coma are reported. A dose exceeding 7 g/l of blood plasma is, however, extremely lethal [7].

The main complaints about the visual system also depend on the degree of intoxication and include impaired visual acuity, concentric narrowing of visual fields, impaired color vision, and the presence of paracentral scotomata. At the initial stages, patients often complain of blurred vision, vision dim-out, muscae volitantes, and diplopia. Color vision impairment is characterized by the difficulty of distinguishing primarily between red, green, and blue. An impairment of dark adaptation is also possible. With prolonged consumption of alcohol and the development of chronic alcoholism, amblyopia occurs. At that, visual acuity decreases gradually, a change in refraction toward its increase is possible, which leads to the onset or increase of myopia [7].

Moreover, methanol poisoning generally occurs when a suicide is attempted or it is mistakenly taken instead of ethanol. The symptoms of methanol poisoning can appear as early as 12–18 h after the ingestion of the toxin. During this time, it is oxidized to formate, and acidosis occurs [1]. At that, signs of intoxication are noted, which are usually combined with impaired visual acuity, sometimes up to blindness ("blind drunk"). This is due to the toxic effect of methanol oxidation products on retinal ganglion cells [7]. The degree of intoxication is characterized by the degree of acidosis. The most common symptoms of methanol and ethanol poisoning are headache, dizziness, nausea, vomiting, and drowsiness. A severe degree of intoxication can be accompanied by coma and cardiac arrest [1]. A gradual painless bilateral impairment of visual acuity occurs, which may be accompanied by blurred vision [8]. An exception is possible when a large amount of methanol is taken when attempting suicide which causes rapid bilateral blindness [9]. Also, patients complain of impaired color vision, which is disproportionate to impairment of visual acuity [8]. In addition, central defects are noted, which include central, paracentral, and centrocecal scotomata which at first may be relative, but later become absolute. These three types of visual field lesion imply the involvement of the central part of the optic nerve in the process [1, 10]. Some patients may also complain of dyschromatopsia [1].

E.Zh. Tron [7] identified the following four variants of visual impairment in cases of methanol poisoning.

1. Severe vision deterioration or complete blindness in the acute poisoning stage. In such cases, vision is not restored later.

2. After the vision deterioration in the peracute period of poisoning, a noticeable improvement — sometimes up to full recovery — occurs occurs later.

3. The initial rapid deterioration of vision is replaced by a temporary improvement. The vision, however, deteriorates again, and this time the loss is persistent.

4. Vision impairment has a remitting course. It is characterized by alternating periods of improvement and deterioration of visual functions.

In the early stages, ophthalmoscopy may reveal the edematous, hyperemic optic discs with peripapillary retinal edema. It is worth paying attention to the reaction of the pupil; as a rule, the reaction to light is sluggish, and the lack of reaction to light indicates a poor prognosis. The optic discs gradually turn pale, and the retinal arteriostenosis is registered. The outcomes of methanol poisoning are quite diverse. Patients may complain of transient or permanent visual impairment. Blurred or impaired visual acuity may improve within two weeks of treatment. However, it is worth remembering that subsequently a persistent decrease in visual acuity and the presence of scotomata is possible in view of the development of optic nerve atrophy [1].

Diagnostics

Properly taken history is relevant in the diagnosis of toxic neuritis. It is necessary to ask the patient what kind of alcohol he or she has been taking, the amount of it, and the time from consumption. It is also necessary to clarify who else has consumed this type of alcoholic beverage, and whether they have any complaints and symptoms [7, 10].

Among the laboratory testing methods, the determination of osmolality, and blood gas level is used. The pathognomonic sign of methanol poisoning is acidosis [10].

Moreover, acute changes in fundus appearance have been described and include peripapillary dilated vessels and hemorrhages [11]. Histopathological evaluation showed significant loss of both nerve fibers of the papillomacular bundle and of diffuse nerve fibers [11].

One of the methods for diagnosing the optic nerve pathology is electrophysiological testing methods. These include the pattern electroretinography. A decrease in the amplitude and number of oscillatory potentials is characteristic, and so is a decreased response with an increase in time to the peak of *b*-wave (a positive wave on the electroretinogram, indicating the electrical activity of bipolar and Mueller cells) [12].

Methanol poisoning treatment

In methanol poisoning, gastric lavage is usually not recommended, as methanol is rapidly absorbed, thereby rendering the procedure ineffective. However, if accidental ingestion of antifreeze or other household solvents is identified early, gastric lavage, and induction of vomiting may be considered. In the early stages of methanol intoxication, two antidotes — ethanol and fomepizole — can help reduce the conversion of methanol to formaldehyde. Ethanol is a competitive substrate for alcohol dehydrogenase, and fomepizole is an inhibitor of alcohol dehydrogenase. Any antidote can be used to reduce toxic metabolites accumulated in such patients. In addition, it is important to control the patient's general state. Sodium bicarbonate is used to eliminate metabolic acidosis, and hemodialysis should be considered in critical clinical conditions such as severe acidosis, methanol concentration over 50 mg/dL, deterioration of vital signs, and renal failure [11].

If possible, it is necessary to check with the patient if someone else had consumed alcohol, as intoxication may develop in them as well. This is important for timely diagnostics and, accordingly, early therapy [11]. The patient should be kept under medical supervision, and the blood gas level and electrolyte composition should be monitored every 1–2 h for at least 8 h. Following the therapy, the patient should be kept under medical supervision for the timely detection of late complications, such as optic nerve atrophy [11].

Ethanol poisoning treatment

The treatment for ethanol poisoning depends on the degree and stage of intoxication. A gastric lavage is required in cases of mild degree of intoxication. Pyridoxine has antidote properties; it prevents the formation of acetaldehyde — 10 ml of 5% pyridoxine solution is injected intramuscularly. Pentylenetetrazol at a dose of 0.2 ml, phenocoll 0.01 g or sydnocarb 0.002 g, and nicotinic acid 0.1 g are administered orally. In severe degrees of poisoning, the therapy should first begin with the restoration of breathing and eliminating oxygen deprivation. The critical level of arterial hypotension (blood pressure <80 mm Hg) is an indication for intravenous transfusion of Polyglucin or Hemodez at a dose of 500 ml, isotonic sodium chloride solution 500 ml, heparin 10,000–20,000 units, and hydrocortisone 125–250 mg. In order to accelerate detoxification, the oxidative processes are stimulated in order to convert acetaldehyde into the end products of metabolism. While vitamin B1 5% solution at a dose of 5 ml and nico-

tinic acid 1% solution at a dose of 5 ml promote the oxidation of acetaldehyde, pyridoxine 5% solution at a dose of 5 ml and ascorbic acid 5% solution at a dose of 10 ml delay the conversion of ethanol into acetaldehydes. Of note, at the time of retrieval from coma, it is advisable to administer sodium oxybutyrate, phenazepam, and mebicar. The use of neuropeptides is also beneficial [2, 14].

Prognosis

Since the neuro-ophthalmological manifestations of intoxication and poisoning in the clinical presentation are characterized by a certain sequence, monitoring such cases can contribute to determining not only the cause of intoxication or poisoning, but also the degree of their severity, which can be important when deciding on the most rational therapeutic approach, the efficiency of the treatment, as well as the likely prognosis. It should be noted that prognosis for visual functions depends directly on the amount and dose of alcohol or its surrogate consumed [7].

The prognosis of visual functions also depends on the degree and stage of intoxication. With an early visit to the hospital and low intoxication, as well as timely therapy, visual acuity is gradually restored. However, color impairment recovers slower than visual acuity. In severe cases of poisoning, the visual acuity is not restored [8]. In addition, when methanol is consumed in large amounts for the purpose of suicide, a complete loss of visual acuity and the development of blindness are possible due to demyelination of the optic nerve fibers and, as a consequence, optic nerve atrophy develops [11].

CONCLUSIONS

Toxic neuritis belongs to the category of optic nerve pathological conditions with damage to cell mitochondria. At the initial stage, patients may complain of blurred vision. In case of poisoning with methanol or ethanol, the optic nerve is damaged, which is characterized by rapid decrease in visual acuity, which can subsequently develop into atrophy of the optic nerve with a persistent decrease in visual acuity, sometimes up to blindness. There is a change in visual fields in the form of central and paracentral scotomata. Ophthalmoscopy reveals the edematous and hyperemic optic disk [10].

Toxic damage to the organ of vision is a disease that can result in atrophy of the optic nerve and, as a result, loss of vision. Therefore, timely diagnostics and the choice of the most effective treatment regimen at the onset of the disease represent a priority solution to this problem [14].

Conflict of interest. The authors declare no conflict of interest.

Authors' contributions:

Aigul Maratovna Barieva processed and analyzed the literature under study and wrote the text.

Alexander Nikolaevich Samoilov created the text design, selected the literature, and wrote the text.

REFERENCES

1. Chane JW. Optic nerve disorders: diagnosis and management. Springer-Verlag New York; 2014. P. 185-186. https://doi.org/10.1007/978-1-4614-0691-4.
2. Бонитенко Е.Ю., Бонитенко Ю.Ю., Бушуев Е.С., и др. Клиника, диагностика, лечение, судебно-медицинская экспертиза отравлений алкоголем и его суррогатами. – СПб.: ЭЛБИ-СПб, 2013. – С. 14–79. [Bonitenko EYu, Bonitenko YuYu, Bushuyev ES, et al. Klinika, diagnostika, lecheniye, sudebno-meditsinskaya ekspertiza otravleniy alkogolem i ego surrogatami. Saint Petersburg: ELBI-SPb; 2013. P. 14-79. (In Russ.)]
3. Софронов Г.А., Александров М.Б. Экстремальная токсикология. – Санкт-Петербург: ЭЛБИ-СПб, 2012. – 254 с. [Sofronov GA, Aleksandrov MB. Ekstremal'naya toksikologiya. Saint Petersburg: ELBI-SPb; 2012. 254 p. (In Russ.)]
4. Patra M, Salonen E, Terama E, et al. Under the influence of alcohol: the effect of ethanol and methanol on lipid bilayers. *Biophys J*. 2006;90(4):1121-1135. https://doi.org/10.1529/biophysj.105.062364.
5. Малютина Н.Н., Тараненко Л.А. Патофизиологические и клинические аспекты воздействия метанола и формальдегида на организм человека // Современные проблемы науки и образования. – 2014. – № 2. – С. 367. [Malyutina NN, Taranenko LA. Pathophysiological and clinical aspects of exposure to methanol and formaldehyde on human body. *Sovremennye problemy nauki i obrazovaniia*. 2014;(2):367. (In Russ.)]
6. Яскевич В.П., Динмухаметова А.Г., Апечкин Н.Н. Военная токсикология: учебник. – Казань: КГМУ, 2000. – 325 с. [Yaskevich VP, Dinmukhametova AG, Apechkin NN. Voyennaya toksikologiya: uchebnik. Kazan': Kazanskiy gosudarstvennyy meditsinskiy universitet; 2000. 325 p. (In Russ.)]
7. Никифоров А.С., Гусева М.Р. Офтальмоневрология. – М.: ГЭОТАР-Медиа, 2014. – 647 с. (Серия: Библиотека врача-специалиста. Неврология, офтальмология). [Nikiforov AS, Guseva MR. Oftal'monevrologiya. Moscow: GEOTAR-Media; 2014. 647 p. (Series: Biblioteka vracha-spetsialista. Nevrologiya, oftal'mologiya) (In Russ.)]
8. Bowling B. Kanski's clinical ophthalmology: a systematic approach. Elsevier, Saunders Ltd.; 2015. P. 792-793.
9. Pane A, Miller NR, Burdon M. The neuro-ophthalmology survival guide, 2nd ed. Elsevier, Saunders Ltd.; 2018. P. 76-77.
10. Wang AG. Emergency neuro-ophthalmology. Rapid case demonstration. Springer Singapore; 2018. P. 27-30.
11. Somlai J, Kovács T, ed. Neuro-ophthalmology. Springer International Publishing; 2016. 728 p.

12. Шамшинова А.М. Электроретинография в офтальмологии. – М.: Научно-медицинская фирма «МБН», 2009. – 150 с. [Shamshinova AM. Elektroretinografiya v oftal'mologii. Moscow: Nauchno-meditsinskaya firma "MBN"; 2009. 150 p. (In Russ.)]
13. Bhatti MT, Schmalfuss I. Handbook of neuroimaging for the ophthalmologist. Taylor&Francis; 2014. 416 p.
14. Березников А.И., Филиппенко Н.Г. Особенности терапии токсических поражений зрительного нерва // Научные ведомости Белгородского государственного университета. Серия: Медицина. Фармация. – 2014. – № 11–1. – С. 25–28. [Bereznikov AI, Filippenko N.G. Osobennosti terapii toksicheskikh porazheniy zritel'nogo nerva. *Belgorod State University scientific bulletin. Medicine, pharmacy*. 2014;(11-1):25-28. (In Russ.)]

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