REVIEW
ARTICLES

Toxic Damage to Motor Neurons

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Abstract—Amyotrophic lateral sclerosis (ALS) is a multifactor disease in the development of which both genetic and environmental factors play a role. Specifically, the effects of organic and inorganic toxic substances can result in an increased risk of ALS development and the acceleration of disease progression. It was described that some toxins can induce potentially curable ALS-like syndromes. In this case, the specific treatment for the prevention of the effects of the toxic factor may result in positive clinical dynamics. In this article, we review the main types of toxins that can damage motor neurons in the brain and spinal cord leading to the development of the clinical manifestation of ALS, briefly present historical data on studies on the role of toxic substances, and describe the main mechanisms of the pathogenesis of motor neuron disease associated with their action.

Key words: amyotrophic lateral sclerosis, motor neuron disease, toxic factors, lathyrism, konzo, cyanotoxins, heavy metals, branched-chain amino acids

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is one of the most common neurodegenerative diseases, and is characterized by relatively selective damage to motor neurons in the cerebral cortex and spinal cord [1, 2]. ALS is the most common cause of motor neuron lesion. The disease has a steadily progressive course and, in most cases, leads to the death of patients 3–5 years after the appearance of first clinical symptoms [3].

In recent years, significant progress has been achieved in studies on the molecular-genetic basis of the development and progression of the neurodegenerative process in ALS [4]. More than 20 loci associated with the development of familial and sporadic ALS cases have been described [5]. The main mechanisms of death of motor neurons in ALS, including excitotoxicity, oxidative stress, mitochondrial dysfunction, deficit of neurotrophic factors, impaired RNA metabolism, changes in protein conformation, and others were revealed [1, 6]. Data on the capability of two drugs, riluzole and edaravone, to slow down the progression of neurodegenerative process during ALS were reported [3].

At present, ALS is considered a multifactor disease with a complex of genetic and environmental factors involved in its development [7]. Over a long period of time, various toxins have been studied for their possible effects on the risk and progression of ALS [8–11]. The interest in this topic is due to several factors. On

the one hand, some variants of toxic relatively selective motor neuron damage, clinically different from ALS, but of considerable interest as a model of motor neuron damage, have been described [9]. On the other hand, a number of toxins, which act on the population level, may affect the risk of development and progression of ALS, including in genetically vulnerable persons [10]. The interest in this topic is supported by cases an increased incidence of reported ALS in a specific area, which is also very likely to be associated with the action of a number of environmental toxins, repeatedly described in the literature [11]. Finally, in some cases of intoxication, the development of ALS-like syndromes were described, which are curable when appropriate therapy is applied. Thus, the study on the role of toxic factors in the lesion of motor neurons is of interest for the investigation of the pathophysiology of the neurodegenerative process, for developing reasonable measures to reduce the population risk of ALS, and for identifying potentially curable cases of ALS-like syndromes.

LATHYRISM AND KONZO AS CLASSICAL TYPES OF TOXIC LESION OF MOTOR NEURONS

Lathyrism and konzo are variants of motor neuron damage, the association of which with the action of specific toxins is the most well proven. Both diseases have relatively selective damage of upper motor neurons, therefore, their main clinical manifestation is lower spastic paraparesis [9, 12].

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The development of lathyrism is based on the toxic effect of oxalyldiaminopropionic acid (β -ODAP, β -oxalylaminoalanine), which is contained in plants of the genus *Chin* (*Lathyrus*) of the Legume family [13, 14]. Lathyrism has been known since ancient times and was probably the first neurotoxic disease known to mankind. In 1671, the Duke of Württemberg prohibited the consumption of peas because of their ability to cause paralysis of the legs. In Europe, Africa, and Asia, outbreaks of this disease were repeatedly observed during lean years or during wars, when the consumption of peas increased sharply. Francisco Goya's famous engraving "Glory to the Peas," painted in 1808 during the famine in Madrid after the invasion of Napoleon's troops, depicts a group of people eating porridge from peas, and a woman with probable signs of lathyrism [15]. Kozhevnikov described more than 100 cases of disease similar to lathyrism during the epidemic in 1882 in the Saratov region [16]. Filimonov was probably the first in the world who, in the 1920s, performed a pathomorphological examination of the nervous system of a patient who suffered from lathyrism and died due to acute leukosis [15]. Large lathyrism outbreaks were observed in some European countries during World War II. In recent years, lathyrism outbreaks were observed in India, Bangladesh, and Ethiopia [17]. For example, a lathyrism outbreak with more than 2000 patients occurred in 1995–1997 in Ethiopia [18].

In most cases, lathyrism starts from the prodromal period with spasms in the leg muscles, paresthesia in the legs and frequent urination. Then, symmetrical lower spastic paraparesis develops relatively acutely, which is non-progressive but almost irreversible. Other impairments are absent in the delayed period of lathyrism. The disease more frequently develops in young men [9, 15].

Lathyrism diagnostic criteria include: (1) consumption of *Lathyrus sativus* or other neurotoxic pea species at least two weeks prior to symptom development; (2) symmetrical lower spastic paraparesis with an increase in tendon reflexes and clonus and the Babinsky reflex can be detected from the legs; (3) absence of sensitivity disorders; (4) absence of signs of damage to the cranial nerves, damage to the cerebellum, and cognitive disorders [9].

The main mechanisms of the toxic effect of β -ODAP are excitotoxicity, induction of oxidative stress, and mitochondrial dysfunction [11, 19–22]. Excitotoxicity is considered as damage to neurons due to overstimulation or long-term stimulation of glutamate receptors leading to increased intracellular calcium concentration. At present, excitotoxicity is considered as one of the leading mechanisms of the pathogenesis of neurodegenerative diseases, including ALS [23–25]. Motor neurons are especially vulnerable to excitotoxic damage due to the high level of expression of AMPA (α -amino-3-hydroxy-5-methyl-4-

isoxazolepropionic acid) glutamate receptors and the low expression of calcium-binding proteins. Several mechanisms of excitotoxic effects of β -ODAP have been demonstrated [20]. Firstly, due to its structural similarity to glutamate this substance can be an agonist of AMPA receptors, and this has been demonstrated in various models in vitro and in vivo. Secondly, β -ODAP inhibits the Na^+ -dependent glutamate transporter leading to an additional increase in extracellular glutamate concentration, the so called glutamatergic loop. Thirdly, β -ODAP can serve as a substrate for the cystine/glutamate transporter, also leading to increased extracellular glutamate concentration [26]. It was shown that β -ODAP may increase the generation of reactive oxygen species and inhibit the activity of catalase, glutathione peroxidase, and cystathionine gamma-lyase [27, 28]. Moreover, β -ODAP inhibits the activity of the NADH-dehydrogenase complex, or, mitochondrial complex I [29]. The involvement of oxidative stress is supported by data on the protective effect of methionine and cysteine in a model of β -ODAP-induced lesion of motor neurons [20]. It is noteworthy that the risk of lathyrism decreases when food enriched with sulfur-containing amino acids is consumed simultaneously [30]. Impairments of mitochondrial calcium homeostasis may also be important for the pathogenesis of lathyrism [31].

Similarly to lathyrism, the main clinical symptom of konzo is lower spastic paraparesis [32, 33]. This disease was firstly observed in the Democratic Republic of the Congo (DRC). Konzo translates as "bound legs" (the word "konzo" is used by one of the tribes of the DRC to refer to an amulet used to weaken the legs of animals during hunting) [34]. In addition to the DRC, which remains the main center of konzo prevalence, outbreaks of this disease have been observed in many other countries in sub-Saharan Africa, including Mozambique, Tanzania, Angola, Cameroon, Zambia, the Central African Republic and others [34–38].

It is considered to be convincingly proven that the cause of konzo is the use of insufficiently processed cassava (*Mánihot esculénta*)—plants of the Euphorbiaceae family. Cassava is the main source of nutrition for the population of a number of African countries, and the role of this drought-resistant plant is especially significant when agroecological or social conditions worsen (drought, civil wars, etc.). This is the cause of the peculiarities of the epidemiology of konzo, such as occurrence in the form of outbreaks, although individual sporadic cases of the disease have also been observed [39–41]. A clear epidemiology of konzo remains unknown. It is believed that in total, hundreds of thousands of people suffer from this disease in different African countries, while in some rural areas the incidence of the disease may reach 5%. Adults (most often women of childbearing age) and children older than 3 years may become ill [9, 34].

The core of the clinical picture of konzo is an acute non-progressive and irreversible lower spastic paraparesis. At the onset of the disease, reversible disorders of sensitivity in the legs, such as paresthesia or pain, may occur. As a rule, within several days, the condition becomes stable without additional progression and finally, lower spastic paraparesis of various severity forms. The development of spastic tetraparesis in combination with signs of pseudobulbar syndrome is described in severe cases. For patients who retain the ability to move, cross legged, i.e. "scissor"-like gait, is very characteristic. In the mildest cases, the symptoms in the residual period are limited to spasticity in the legs when walking and running. In some cases, signs of bilateral optical neuropathy and oculomotor disorders, in particular, pendulum nystagmus, are described [34, 42, 43]. It should be noted that effective methods for treatment of konzo are still absent.

The diagnostic criteria of konzo were determined by the WHO and are as follows: (1) the presence of a temporary connection with the use of cassava as a main food product; (2) sudden onset with less than 1-week progression and non-progressive course of weakness in the legs in a previously healthy person; (3) symmetrical spasticity in the legs during walking or running; (4) bilateral increase of tendon reflexes in the legs without signs of backbone and spinal cord diseases [34].

In addition to konzo, the use of cassava may also lead to the development of tropical ataxic neuropathy, which is expressed as slowly progressive sensory polyneuropathy, sensitive ataxia, bilateral optical neuropathy, and sensorineural hearing loss that are observed in old age [41, 44].

According to the predominate hypothesis the development of konzo is related to the toxicity of cyanides that are contained in cassava [9, 34, 36, 44, 45]. Data from toxicological studies show that metabolites of linamarin, cassava cyanogenic glycoside, specifically, the mitochondrial toxin cyanide, the AMPA chaotropic agent thiocyanate, and the motor system toxin cyanate, are very important in konzo pathogenesis [36]. An elevated concentration of thiocyanate ($\text{SCN}(-)$), the main metabolite of cyanides, was revealed in the blood serum and urine of konzo patients [46]. In konzo, the main mechanism of damage to motor neurons is probably induction of oxidative stress and protein carbamylation [34, 47]. The toxic effects of linamarin and cyanate were reproduced in experiments with various animals [36, 48]. The most interesting study was performed using a model of chronic cyanate intoxication in rhesus macaques, in which the development of a clinical picture similar to konzo, with symptoms such as sudden development of tetraparesis, was shown, and during a pathomorphological examination, structural changes in Betz cells, the anterior horns of the spinal cord and basal ganglia were revealed [49]. The other notable hypothesis indi-

cates that both lathyrism and konzo may be caused by cyano group-containing nitrils, which are contained in peas and cassava [50]. The risk of developing the disease increases with insufficient intake of sulfur-containing amino acids from food, which participate in rodenase-mediated conversion of cyanide into a water-soluble and less toxic thiocyanate excreted with the urine [9].

L-BMAA

In 1945, Zimmerman, who served as a military physician in the US Navy, described a cluster with a high prevalence of motor neuron disease among the indigenous Chamorro population of Guam [51]. The first epidemiological study of 1954 performed in the island population supported that the distribution of the disease with the clinical symptoms, which were similar to ALS, among the indigenous Chamorro population of Guam was 100 times higher compared to the global average indices [52]. The highest prevalence of the disease was observed in some village settlements. For example, in Umatac, it was 273 patients per 100 thousand [53]. At the same time, a large number of cases of Parkinsonian syndrome were noted among Chamorros, which developed in adulthood and was often accompanied by distinct cognitive impairments reaching the degree of dementia. Cases of Parkinsonian syndrome with dementia were often found in the same families where cases of ALS had already been observed; sometimes both syndromes developed in the same patients. In 1961, Hirano et al. named this disease as "ALS-parkinsonism-dementia" [54]. The disease was also called lytiko-bodig disease. In the local dialect, "lytiko" corresponded to a phenotype with progressive muscle weakness, the clinical picture of which was similar to the classic form of ALS, and "bodig" reflected the development of subcortical degeneration with Parkinsonian syndrome [55].

At the onset of the disease, the clinical picture in most cases started from the development of progressive muscular weakness, which is more expressed in the distal parts of the hands and legs, and an increase in tendon and periosteal reflexes. Later on, widespread hypotrophy of the limb muscles, bulbar disorders and pseudobulbar syndrome, increased tone in the limbs mainly of the plastic type, hypokinesia, rest tremor, a bent posture, and a slow gait were formed. The fatal outcome was most often caused by progressive respiratory failure due to skeletal muscle hypotrophy [56].

Despite the substantial prevalence of males among the patients, the medical-genetic study of patients and members of their families in a short time allowed exclusion of genetics as the leading etiological factor of disease development. In addition, the disease developed not only among the Chamorro people but also among residents of the island who came from outside, although the incidence rates among immigrants were

slightly lower. Plato et al. studied all the observed cases of ALS and/or “parkinsonism–dementia” among the residents of Guam island within the period 1958–1999 ($n = 135$) and found that the risk of the disease was slightly higher in the patients’ relatives than in the population who had clinically healthy relatives [57].

The consumption of a large amount of flour prepared from the fruits of cycad palms (*Cycas micronesica*) has been proposed as a key etiological factor in the development of the “ALS–parkinsonism–dementia” complex [58]. It was hypothesized that despite a multistep process of treatment of cycad seeds, they retain neurotoxic factors, which may be accumulated in the human body due to the regular use of flour in food. In the 1950s, it was shown that cycad seeds contain the strong poison cicasin, but studies of its biological effects in animal models did not lead to the establishment of any connection between its toxicity and lytico-bodig disease [52].

In 1967, shortly after establishing the link between another ALS-like syndrome lathyrism and the consumption of neurotoxic compounds (L-BOAA) contained in leguminous plants from the genus *Chin*, biochemist Arthur Bell et al. found in cycad seeds another toxin, specifically, beta-*N*-methylamino-L-alanine (L-BMAA) [52]. However, the initial experimental studies demonstrated that the content of free L-BMAA in cycad flour is not comparable with concentrations that have a toxic effect, and therefore the hypothesis about the etiological role of L-BMAA was rejected [52]. Other studies showed that cycad flour contains high concentrations of protein-bound L-BMAA. Moreover, in the areas with high incidence of ALS–parkinsonism–dementia the L-BMAA concentrations in flour are also high [59]. Controversial data on the content of L-BMAA in the tissues of biological organisms are mostly related to the use of different analytical methods for the assessment of concentrations of L-BMAA and its metabolites [60, 61].

Another possible way of getting L-BCAA into the human body is the consumption by the Chamorro people of the meat of flying foxes fed on cycad seeds. The concentration of L-BMAA mostly in the adipose tissue of flying foxes could be significantly higher than in flour because of the mechanism of accumulation in the food chain. The consumption of flying fox meat for food was an integral part of the cultural traditions of the indigenous population, which even led to the extinction of one of species (*Pteropus tokudae*) and a sharp decline in the populations of others. A further decrease in the frequency of eating flying foxes by the indigenous population most likely led to a significant decline in the incidence of the “ALS–parkinsonism–dementia” complex [61]. With a high probability, L-BMAA accumulated in the organisms of other animals that feed on cycad seeds, whose meat was consumed by the indigenous population [62, 63].

The following epidemiological studies demonstrated that the incidence of the ALS–parkinsonism–dementia complex is gradually decreasing [64]. Nevertheless, cases of the disease continue to be observed until now, however the prevalence of the isolated ALS phenotype has significantly decreased, and the average age of the disease onset has become higher [65]. A study on the entire population of the Guam in the 2000s revealed a high prevalence of dementia among people over 65 years of age but in the overwhelming majority of cases, patients had classic Alzheimer’s type dementia [66].

The initial pathomorphological studies supported the presence of clusters of neurofibrillary tangles in the brain tissue of patients that were similar to those observed in Alzheimer’s disease. Moreover, in patients with the isolated ALS phenotype, i.e. without Parkinsonian syndrome and strong cognitive impairments, their number was less to some extent [67]. In addition, a lot of deposits of (TAR)-DNA-binding protein 43 (TDP-43) were revealed in neurons and glial cells of the brain of patients. The functions of this protein are the inhibition of transcription and the regulation of splicing. TDP-43-positive inclusions are described in neurons in various types of fronto-temporal dementia and in classical ALS [68]. The hypothesis about the etiological role of L-BMAA was confirmed by the detection of this neurotoxin in the brain tissue of patients with ALS–Parkinsonism syndrome and classical ALS who lived on the island of Guam and in Canada; this observation also confirms the phenomenon of accumulation (biomagnification) of the toxin in the food chain, leading to a significant increase in the concentration of L-BMAA entering the human body by the alimentary route [69, 70].

In 2003, it was found that cyanobacteria of the genus *Nostoc*, living as symbionts on cycad roots, can release L-BMAA. Additional studies showed that practically all known free-living and symbiont cyanobacteria species can produce L-BMAA [69, 71]. The concentration of L-BMAA produced by bacteria is very low, but L-BMAA accumulates in the bodies in the higher levels of the food chain starting from zooplankton [71]. This discovery led to the hypothesis that the other local ALS outbreaks around the planet may also have been induced by a high concentration of cyanobacteria, producing L-BMAA in drinking water and/or food [52, 72]. Eutrophication and a number of other processes caused by climate changes lead to an increase in the population of cyanobacteria in natural reservoirs, which in turn may cause an increase in the global incidence of ALS [60, 63, 70].

The discovery of the production of L-BMAA by cyanobacteria was followed by a number of studies aimed at studying the concentrations of L-BMAA in reservoirs densely populated with various types of cyanobacteria around the world. Thus, loci of increased L-BMAA content were described in natural reservoirs of

Great Britain, Denmark, in the Gulf of Florida in the United States, and in the Gobi Desert in Mongolia [52].

Attempts have been repeatedly made to link the increased level of L-BMAA in drinking water sources with the high prevalence of ALS among the population of the respective geographical area. Thus, a cluster with more than 25-fold higher ALS prevalence was described near the Mascoma lake in New Hampshire in the United States compared to the other states. High concentrations of L-BMAA were found in the lake water and the in tissues of the fish that live there [73].

Special attention should be paid to the planned large-scale epidemiological study covering the population of three regions of France within the so-called French BMAALS program. During this study, geographical areas with an increased incidence of ALS will be analyzed with the use of a questionnaire among the population, including features of food intake, drinking water sources used and water for irrigation. The levels of L-BMAA will be measured in the biological samples of vegetables and fruits growing in this area, drinking water and water used for watering plants. Additionally, a histochemical examination of the brain tissue of patients with sporadic ALS, who lived in this area, will be performed in order to study the contents of L-BMAA and its metabolites [60].

There are several theories concerning the mechanisms of L-BMAA neurotoxicity. Firstly, L-BMAA is not only an agonist of glutamate NMDA receptors, but at low concentrations it selectively damages motor neurons due to activation of AMPA and kainate receptors [70, 71, 74]. Secondly, L-BMAA affects functioning of the cystine-glutamate antiporter, the so called the xc-transport system, leading to induction of oxidative stress and elevation of the concentration of extracellular glutamate [75]. Thirdly, L-BMAA can be incorporated into protein structure due to L-serine substitution which results in impaired folding and subsequent protein aggregation, a well-known mechanism in the pathogenesis of some neurodegenerative pathologies [76, 77]. Additionally, L-BMAA may lead to accumulation of insoluble TDP-43 protein, the aggregation of which in the tissues of the central nervous system is observed in ALS patients [78]. One more mechanism of neurotoxic action of L-BMAA is probably stimulation of secretion of proinflammatory cytokines due to activation of nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3)-inflammasome [79].

It was shown that after the entering into the gastrointestinal tract L-BMAA has a double negative impact. Firstly, it goes into neurons of the enteric nervous system and induces mitochondrial dysfunction. Secondly, when L-BMAA enters the organized lymphoid tissue of the mucous coats of the digestive tract it provides hyperactivation of the structures of the immune system and, thus, maintains chronic inflam-

mation in the cavity of the gut that can also evoke neurodegeneration along the gut-brain axis [80].

It has been shown that L-BMAA is involved in the pathogenesis of other neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and retinopathy pigmentosa [60]. It was suggested that L-BMAA penetrates the blood-brain barrier and interacts with neuromelanin in the substantia nigra and locus coeruleus that may underly the development of parkinsonian syndrome [81]. Interestingly, specific retinal pigment epitheliopathy, which sometimes preceded the main symptoms of the disease, developed in some patients from the island of Guam with the "ALS-parkinsonism-dementia" complex, which may also be due to the direct effect of L-BMAA on the neuromelanin of the retinal pigment epithelium [55].

L-BMAA neurotoxicity has been demonstrated in neuronal cell cultures where it induced degeneration and cell death [82]. The direct effect of L-BMAA on the structures of the central nervous system also resulted in neuronal death in the hippocampus [83]. In animal models, L-BMAA administration was followed by the formation of various anatomic anomalies of the development of the structures of the central nervous system and impairment of their normal functioning, including hyperexcitability, which manifest as myoclonia and seizures. In birds, the development of vacuolar myelinopathy was described whereas in rodents, a classical pattern of motor neuron diseases was found [84–86]. Long-term 30-day intrathecal administration of L-BMAA to rats resulted in degeneration of motor neurons of the ventral horns of the spinal cord, astrogliosis, and accumulation of TDP-43 protein aggregates [87]. In general, the effect of L-BMAA, even at the early stages of animal development, has long-term effects not only on the development and normal functioning of the structures of the nervous system but also on systemic energy metabolism, leading to the development of mitochondrial dysfunction in many tissues [88]. Thus, due to the long latency period between the first ingestion of L-BMAA into the body and the onset of symptoms of the disease, it can be considered a so-called "slow toxin": the development of the clinical picture of the ALS-parkinsonism-dementia syndrome is most likely possible only if the body is exposed to L-BMAA for a long time [77, 89].

HEAVY METALS

For a long time, the possible role of heavy metals in the pathogenesis of ALS and other neurodegenerative diseases has been intensely studied [10, 90, 91]. Studies in this area can be divided into three groups. In some studies, in large samples the association between the action of heavy metals as environmental factors and the risk of development of ALS was analyzed at the population level. These studies are directed to the examination of the role of heavy metals as risk factors

of the development and progress of ALS as a multifactor disease. The second group of studies is directed to the description of distinct clinical cases, in which the development of ALS symptoms coincided with confirmed intoxication. Though these observations are rare and often have no evident causal relationship of the metal action with the development of the disease, they are very interesting from the practical point of view, especially, when it is possible to achieve regression or stabilization of symptoms. Finally, the third group of studies is directed to the investigation of the mechanisms of neurotoxic effects of heavy metals in vitro or in vivo in various models. Among heavy metals, most studies were focused on the possible relationship between the development of ALS and the action of lead and mercury.

Lead. In contrast to many other metals, lead has no natural biological functions in the human body; however, it easily accumulates after acute or chronic exposure [92]. Even at low doses, it damages many organs and systems, including bone tissue, skeletal muscles, the heart, liver, kidneys, and the immune and nervous systems [93–96]. In addition to this, lead is a relatively well-studied carcinogen. Lead is widely used in many industries, leading to the risk of development of acute intoxication or chronic effects of lead, which is contained in air, water or soil [92].

The relationship between the effect of lead and the risk of ALS has been revealed in many studies (see, for example [97–101]) and is also supported by several meta-analyses [102–104]. In one meta-analysis [102], it was shown that the risk of ALS development increases by approximately two times if the profession-associated effect of lead was in anamnesis and near 5% of ALS cases may be related to lead. It is important to note that lead is of the greatest importance as a professional (production) factor [92].

Lead easily penetrates the blood-brain barrier and accumulates in neurons and glial cells. In ALS patients, a statistically significant increase in lead concentration was observed in the blood serum and cerebrospinal fluid [92, 98]. Lead has a pleiotropic toxic effect. The enzymopathic effect of lead determined by its binding to sulfhydryl groups and inhibition of activity of some key enzymes is very important [94, 105]. Specifically, lead inhibits the activity of 5-amino-levulinic acid dehydratase, which is followed by the impairment of heme formation [96]. Moreover, lead can substitute bivalent cations, including Ca^{2+} , Mg^{2+} , Fe^{2+} , and Zn^{2+} , in protein molecules [106]. One more well-studied mechanism of lead toxicity is the induction of oxidative stress [107].

The capability of lead intoxication to evoke degeneration of motor neurons in the spinal cord and to damage axons of peripheral motor neurons and skeletal muscles has been demonstrated in several experimental studies [108]. The data reported by Ash et al. [109] are very important in the context of studies on

the role of lead in the development of ALS. In this study, the capabilities of 91 potential neurotoxins to induce the formation of TDP-43-positive deposits, one of the key pathomorphological signs of ALS, were examined. Among all the tested molecules, only lead acetate and methylmercury chloride had these capabilities [109].

Among the potential mechanisms of the toxic effect of lead on motor neurons, the possibility of its influence on the folding of metal-containing proteins is also discussed. Lead can increase the expression of *SOD1* mRNA [110], and thus, it can potentially affect the accumulation of this protein with anomalous conformation. This is probably one of the mechanisms of the effect of lead on the development of ALS in genetically predisposed individuals [103].

It should be noted that lead in ALS can also have a paradoxical effect. Specifically, it has been shown that during the development of the disease, the content of lead in the blood and bone tissue positively correlates with survival [111, 112]. This may be related to the capability of lead to increase the expression of vascular endothelium growth factor, although the role of other factors is also discussed [10, 103, 111].

The most well-studied type of damage to the nervous system after lead intoxication is peripheral neuropathy. Its typical feature is the asymmetry and predominant lesion of the motor fibers, and the extensors of the fingers and the extensors of the wrist are most often involved. In severe cases, tetraplegia may develop. According to electroneuromyography (ENMG) data, axonal motor or more rarely, sensory neuropathy are observed. Signs of systemic damage may be observed, such as microcytic hypochromic anemia with normal serum iron levels and basophilic granularity of red blood cells, cramping abdominal pain, signs of kidney damage, arterial hypertension, as well as signs of so-called lead encephalopathy, i.e. cognitive and behavioral disorders, epileptic seizures, and ataxia [113]. In the literature, there are several clinical observations of the development of ALS-like syndromes with confirmed lead intoxication. A case of ALS-like syndrome with clinical features of mixed tetraparesis and regress of symptoms after chelation therapy was reported in 1968 [114]. A case of the development of lead intoxication due to inhalation of molten lead vapors for a ritual purpose was described, in which upper atrophic paraparesis with preserved tendon reflexes progressed for one year. It should be noted that in this case, cognitive impairments and signs of systemic damage, such as basophilic granularity of red blood cells and abdominal pain were revealed in a female patient. The restoration of hand strength and regress of cognitive impairments were observed four months after the termination of the ritual [115]. In another observation, a female patient developed two generalized tonic-clonic epileptic seizures along with systemic manifestations, including general weakness,

vomiting, abdominal pain, anemia, and arterial hypertension, and a few months later, progressive slow tetraparesis and bulbar syndrome with neuronal changes on ENMG. Increased lead concentrations were observed in the blood and urine. After a course of therapy with EDTA IV and DMPS, the symptoms regressed almost completely; however, after some time, the patient developed bilateral paralysis of the radial nerves and the lead content increased again. Then the source of lead intake into the body was determined; it was a lip cream containing 13.4% Pb [116]. The clinical features of the presented observations are isolated lesion of the lower motor neurons, and the presence of systemic manifestations that play the most important role in making an accurate diagnosis.

MERCURY AND ITS DERIVATIVES

Methylmercury is one of the most well-known and well-studied neurotoxins. The first cases of methylmercury intoxication, including fatal ones, were described in 1866 in chemists, just a few years after the first synthesis of this compound. In the 20th century, methylmercury was used as a fungicide leading to an increase in the industrial production of this compound. In the 1930s, the first reports of clinical and pathomorphological pictures of methylmercury intoxication in plant workers were presented [117]. It should be noted that from the toxicological point of view methylmercury is a special problem because of its capability to be accumulated in the food chain. In nature, mercury is methylated mainly in water due to biochemical, chemical, and photochemical processes. Then methylmercury is accumulated in mollusks and fishes, which may result in intoxication of humans and animals that consume them [118].

There are two known major disasters associated with the poisoning of a large number of people with methylmercury. In 1956, on the coast of Minamata Bay, Japan, more than 2000 cases of severe damage to the nervous system due to methylmercury intoxication were recorded. This disaster was caused by release of a large amount of inorganic mercury into the water of the bay by a local "Chisso" plant. Inorganic mercury was processed by bottom microorganisms into methylmercury, which accumulated along the food chain and entered the human body with fish and shellfish. The main symptoms of the disease called Minamata disease included sensory impairments, such as polyneuritic paresthesia and hypesthesia, concentric narrowing of the visual fields, hearing loss, ataxia, epileptic seizures, speech disorders, mental disorders, among others. Strong prenatal effects, including severe delay of mental development, motor impairments, among others, were also described. The official death toll from this disaster was 1043 people [117, 119, 120]. The second case of massive intoxication with methylmercury took place in Iraq in 1973 and it was related to the consumption of a batch of grain poisoned with meth-

ylmercury that was not intended for sale. Due to this, more than 6000 people fell ill and 452 individuals died [121]. After this, several smaller and less severe cases of methylmercury intoxication were reported; for example, in Brazilian residents engaged in fishing [122].

Methylmercury has a complex and multicomponent neurotoxic effect. It seems that three components of toxic influence of methylmercury are of most importance: (1) an increase in intracellular calcium concentration; (2) induction of oxidative stress; , and (3) interaction with sulfhydryl groups with the formation of thiol-containing complexes [117]. It has been shown in a series of experimental studies that the intracellular calcium concentration increases after the action of methylmercury due to its release from intracellular depots or input from the extracellular medium [123–125]. The later mechanism may be mediated by methylmercury-induced activation of NMDA glutamate receptors due to the interaction of methylmercury with receptor sulfhydryl groups [117]. Induction of oxidative stress is one of the consequences of increased intracellular calcium concentration [126, 127]. The increased formation of superoxide, hydrogen peroxide and peroxynitrite was reported in models of methylmercury intoxication [128, 129]. For the development of oxidative stress, it is also important that the binding of methylmercury to its sulfhydryl groups reduces the availability of glutathione [130, 131]. The decreased severity of the toxic effect of methylmercury after application of calcium chelators, blockers of calcium channels or various antioxidants, such as vitamin E, selenium, lipoic acid, and others, supports the importance of the above described mechanisms [132, 133]. After its binding with sulfhydryl groups, methylmercury can affect the structure and functions of some proteins, including tubulin and Na⁺/K⁺-ATPase [134]. Finally, one more very important mechanism of the neurotoxic action of methylmercury is the induction of apoptosis via different mechanisms [117].

From the point of view of the potential involvement of methylmercury in the pathogenesis of ALS, the data on the ability of methylmercury to selectively accumulate in the motor neurons of the spinal cord and cause degenerative changes under experimental conditions are of particular interest [135]. Moreover, in transgenic mice, chronic administration of methylmercury accelerates the onset of ALS [136]. The above described ability of methylmercury to induce the formation of TDP-43-containing deposits in the motor neurons under experimental conditions should also be noted [109]. In addition to methylmercury, metallic mercury vapor inhalation can also damage motor neurons of the spinal cord [137].

Despite all these data, at present there are no convincing data on the connection between methylmercury intoxication and damage to motor neurons. It should be noted that there are controversial data from population studies concerning the relationship

between the exposure to various mercury derivatives and the risk of ALS development [10]. Moreover, analysis of cases of Minamata disease shows that motor disorders are not of leading importance in methylmercury intoxication.

In the literature, there are several observations demonstrating the onset of the clinical picture of ALS after confirmed mercury intoxication with gradual progress of the disease leading to the death of patients despite the chelation therapy [138–140]. In these cases, the causal role of methylmercury is controversial, since it is impossible to exclude the chance of coincidence at the time of poisoning and the onset of ALS. It is noteworthy that in these observations the clinical picture was not completely typical for ALS. Furthermore, the inefficiency of chelation therapy may be due to its late start after mercury entered the body. Several reported cases of spontaneous or chelation therapy-evoked regress of symptoms are of particular importance because this allows exclusion of ALS. Thus, Adams et al. [141] reported a case of ALS-like syndrome after short-term intoxication with mercury in a plant worker with spontaneous regress of symptoms after the normalization of mercury content in the urine. The clinical pattern of the disease included clear asthenia, a 9-kg decrease in the body weight, atrophy of the deltoid and biceps muscles on the arms and thigh muscles with fasciculations; however, convincing evidence of damage to upper motor neurons was absent. Barber [142] also described the development of clinical features of ALS-like syndrome with spontaneous regress of symptoms in two workers of a plant producing inorganic mercury. Another study reports a case of the development of a clinical picture of progressive muscular atrophy, an ALS-like variant, which the authors associated with the presence of previously installed amalgam fillings. After the removal of the fillings and chelation treatment in combination with selenium and lipoic acid the state of the patient improved and was maintained over three years of additional observation [143]. However, in this case, mercury intoxication was not confirmed by laboratory tests. Three additional observations should be noted because of the development of a clinical-neurophysiological pattern of motor neuron hyperexcitability with regress of symptoms after the chelation treatment [144].

General analysis of the results of studies performed in this area shows that neurotoxicity of heavy metals, primarily lead and mercury derivatives, was relatively evident in experiments. Data from epidemiological studies on the relationship between exposure to heavy metals and the risk of ALS are controversial; however, in most studies this relationship was revealed and the data were mostly evident for lead. Specific cases of the development of ALS-like syndromes were reported after intoxication with heavy metals; however, it is difficult to establish the causal relationship in each case. It should be noted that the observations that show the possibility to delay progression of the disease or

regress of symptoms after the eliminating treatment are rare. We believe that in most described observations, the clinical patterns are not quite typical of ALS. In general, intoxication with heavy metals should be considered as one of multiple mechanisms of the development and progression of a neurodegenerative process in ALS. Moreover, a possible role of heavy metals in acceleration of the development of a neurodegenerative process in genetically predisposed individuals is discussed.

BRANCHED-CHAIN AMINO ACIDS

Branched-chain amino acids (BCAA) are a group of essential amino acids, such as leucine, isoleucine, and valine, which have a branched side aliphatic chain [145]. BCAA are actively used in sport and fitness as food additives for stimulation of muscle growth and recovery after training [146, 147]. Initially, BCAA were studied as a possible drug for the treatment of ALS; however, in one small randomized trial, it was shown that their application results in a more statistically significant decrease in vital capacity of the lungs compared to the placebo group [148]. To date, data of several experimental studies were published demonstrating a possible role of BCAA in the development and progress of ALS. An experimental study in cell culture showed that high concentrations of BCAA have a neurotoxic effect and enhance excitotoxicity. It has been shown that this effect of BCAA could be observed in cortical but not in hippocampal neurons, and is associated with the enhanced stimulation of NMDA glutamate receptors [149]. It was revealed that, in C57Bl/6J mice, the addition of BCAA to their diet at doses which were equivalent to those used in humans was followed by decreased expression of genes encoding some antioxidant enzymes and increased expression of genes encoding some oxygen transporters [150]. Another study demonstrated that BCAA induced hyperactivity and decreased the pain threshold in wild type mice but aggravated the motor deficit, and impaired synaptic plasticity in mice with the G93A *SOD1* mutation [151]. Carunchio et al. [152] demonstrated that a BCAA-enriched diet led to the development of hyperexcitation of cortical neurons in mice, an ALS-like phenomenon, and this effect is probably related to an increased persisting sodium current (INaP). Similar neurophysiological data were observed in mice with the G93A *SOD1* mutation. In this study, the mentioned neurophysiological effect was specific for BCAA because it was not observed after the use of non-branched-chain amino acids, such as phenylalanine or alanine. It was additionally shown that hyperexcitation of cortical neurons evoked by the G93A *SOD1* mutation or administration of BCAA might be prevented by rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR) protein kinase, activity of which is regulated by various nutrients, including BCAA [152]. Taken together the

current data are not sufficient to make a conclusion concerning a possible role of BCAA in the development and progress of ALS. These data attract serious attention, taking into account the distribution of BCAA intake as a food additive. It was hypothesized that the use of BCAA may be one factor in the high frequency of ALS development among professional American football players or football players in Italy [147]. The involvement of BCAA in the development of ALS needs careful analysis in future studies.

OTHER TOXINS

In recent years, the list of potential toxins that can serve as etiological factors or factors of risk or progression of ALS has significantly expanded. In addition to the toxins described above, the possible role of selenium [153], cadmium [154], aluminum [155], various pesticides [156], organic solvents and formaldehyde [10], some fungal neurotoxins [157], and a number of other toxins in the development of ALS is discussed.

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COMPLIANCE WITH ETHICAL STANDARDS

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

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