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HUMAN DISEASES ASSOCIATED WITH *NTE* GENE

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❀ Evolutionary conserved *NTE* gene is important for survival and functioning of nervous system cells, its dysfunction leads to various pathologies. Here we describe characteristics of different disorders induced by NTE protein activity inhibition (OPIDN) or by *NTE* gene mutations: hereditary spastic paraplegia (SPG39), Boucher – Neuhaüser, Gordon Holmes, Laurence – Moon, Oliver – McFarlane syndromes, Leber congenital amaurosis, pure cerebellar ataxia. Current review summarises accumulated data about clinical features of *NTE* associated diseases, presenting them in a historical way of biomedical studies, and observes molecular and genetic causes of these disorders.

❀ **Keywords:** NTE; PNPLA6; hSWS; neurodegeneration; nervous system disorders; hereditary diseases; spastic paraplegia; ataxia; organophosphates.

ЗАБОЛЕВАНИЯ ЧЕЛОВЕКА, АССОЦИИРОВАННЫЕ С ГЕНОМ *NTE*

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❀ Эволюционно консервативный ген *NTE* играет важную роль в поддержании жизнеспособности и функционирования клеток нервной системы, а нарушение его работы приводит к различным патологиям. В работе рассмотрены характерные черты различных болезней, как вызванных ингибированием активности белка NTE (OPIDN), так и обусловленных мутациями в гене *NTE*: наследственная спастическая параплегия (форма SPG39), синдромы Boucher – Neuhaüser, Gordon Holmes, Laurence – Moon, Oliver – McFarlane, врожденный амавроз Лебера, чистая мозжечковая атаксия. Обзор обобщает накопленные данные о клинической картине заболеваний человека, ассоциированных с геном *NTE*, представляя их в историческом аспекте медико-биологических исследований, и рассматривает молекулярно-генетические закономерности этиологии этих болезней.

❀ **Ключевые слова:** NTE; PNPLA6; hSWS; нейродегенерация; болезни нервной системы; наследственные заболевания; спастическая параплегия; атаксия; органофосфаты.

INTRODUCTION

The human Neuropathy Target Esterase *(NTE)* gene is now increasingly referred to as "*PNPLA6*" because of the patatin-like lysophospholipase (esterase) domain found in the corresponding protein. A family of PNPLA proteins contains such a domain, and at least eight representatives of this family have been found in humans [1]. Other names of PNPLA6 (hSWS, BNHS, LNMS, OMCS, SPG39, NTEMND, and iPLA2delta) are rarely used. However, since its discovery, the protein (and the corresponding gene) has been named "Neuropathy Target Esterase" for several decades. Thus, it will be used hereinafter. The NTE protein is evolutionarily conserved, and its orthologs are found in a wide range of organisms, from bacteria to mammals. The transmembrane region located at the N-terminus retains the protein on the membrane of the endoplasmic reticulum, and its long C-terminal fragment facing the cytoplasm serves not only as a lysophospholipase but also as a non-canonical regulatory subunit of protein

kinase A. In humans, the canonical isoform 4 of the protein is 1375 amino acids long. However, much research focused on isoform-2, which is 1327 amino acids long. The latter has three binding domains of cyclic nucleotide monophosphates, which occupy positions 163–262, 480–573, and 597–689, and the esterase domain occupies position 933–1099, where the nucleophilic active site is represented by Ser_{966} and the proton acceptor sites are represented by Asp_{960} and Asp_{1086}. The *NTE* gene is widely expressed in developing and adult nervous systems; however, with age, its expression becomes limited to large neurons, such as the pyramidal cells of the hippocampus and the Purkinje cells of the cerebellum [2, 3]. Knockout of the *NTE* ortholog of the same name in mice leads to the death of embryos on day 9 because of defects in placental development. Individuals carrying only one normal *NTE* allele are viable and develop normally, although they have a 50% reduced NTE activity [4]. Inactivation of *NTE* expression in mouse neurons leads to neurodegeneration, and cells of the hippocampus, thalamus, and Purkinje cells of the cerebellum die [5]. Dysfunction of *NTE* in humans causes severe autosomal recessive diseases with various clinical symptoms, such as hypogonadism, chorioretinal dystrophy, retinitis pigmentosa, ataxia, and spasticity.

ORGANOPHOSPHORUS COMPOUND-INDUCED DELAYED NEUROPATHY

The first described syndrome associated with NTE dysfunction was organophosphorus compound-induced delayed neuropathy (OPIDN). The specific form of paralysis affected tens of thousands of people who consumed the falsified alcoholic drink Jamaica Ginger (Jake) during the prohibition law period in the United States. The first sign of the disease as leg muscle pain, sometimes accompanied by toe numbness, was noted 10–20 days after the intake of the beverage. After another 7–10 days, similar manifestations were registered in the upper limbs, but they were less pronounced. Patients with the moderate type of the disease could walk using crutches, whereas those with the severe type were bedridden [6]. Limb weakness developed over 2 months, and the only known highly severe case ended with bulbar syndrome and death. The patients' condition improved over time; muscle strength in the upper limbs recovered faster than that in the lower ones, but the patients did not achieve complete recovery. Histological analysis of postmortem material revealed destruction of the limb muscles, their replacement by connective tissue, a decrease in the lumen of small arteries approaching them, and angiogenesis. In the peripheral nerves, the number of axons decreased, and the nerve fiber demyelinated. In the spinal cord, the lower sections of the descending lateral pyramidal tract were affected, and gliosis (proliferation of astrocytes) and demyelination were registered. Moderate damage was noted in the upper sections of Goll's thin fascicle (afferent fibers extending from the lower extremities) but not in the wedge-shaped fascicle (afferent fibers extending from the upper extremities). Degeneration of the white matter (myelinated axonal bundles) was noted only in the spinal cord. Degeneration of the gray matter (bodies of nerve cells) was found mainly in the anterior horns of the spinal cord containing motor neurons and, to a lesser extent, in the lateral horns containing visceral motor neurons. The course of the disease did not depend on the age of the patients [7].

Chemical analysis of the adulterated Jamaica Ginger (Jake) and testing of the mixtures on rabbits, dogs, monkeys, chickens, and calves revealed that the toxic agent is represented by phenolic phosphoric acid esters, namely, triorthocresil phosphate (TOCP), added by bootleggers to the beverage instead of the bitter ginger extract. Tripparacresil phosphate did not cause similar effects but exerted a toxic effect similar to the action of phenols (in particular, cresols), which did not affect motor functions, probably due to its cleavage to paracresol in the body.

After the oral or intramuscular administration of TOCP sublethal doses to rabbits and the administration of a counterfeited beverage, the first symptoms appeared only after a few days. Thus, hyperexcitability of reflexes, spastic gait, developing tremor, and emprosthotonos (position of the body with the trunk bent forward due to muscle contraction) were registered, which progressed to flaccid paralysis with impaired heartbeat and weakened slow breathing and then to the death of

the animal. Small doses caused effects of a similar nature but less pronounced, and the animals recovered after some time.

Subsequent studies found that various organophosphates (OPs) have toxic effects. Organic esters of phosphoric acid are components of some neuroparalytic poisons, industrial chemicals, and medicinal drugs. Since the 1970s, OPs have become widely used in insecticides [8, 9]. When ingested, these substances cause severe neuropathy, the symptoms of which can be divided into three stages, namely, acute cholinergic syndrome, moderate intermediate syndrome, and OPIDN [10, 11].

The targets of organophosphate esters are serine hydrolases (they have a Ser residue in the active center), including acetylcholinesterase (AchE), butyrylcholinesterase (BchE, pseudocholinesterase), and neuropathy target esterase (NTE, neurotoxic esterase), which plays a major role in OPIDN pathogenesis, detected using the radioactively labeled irreversible inhibitor diisopropyl fluorophosphate [12, 13].

Organophosphate esters, such as mipafox, diisopropyl fluorophosphate, chlorophos, and dichlorvos, inhibit NTE, AchE, and BchE [14, 15]. Neuropathic OPs, phosphoramidates, and phosphonates interact with the active center of NTE (with a hydroxyl group of serine), forming phosphate ester as an intermediate product. The second stage of the reaction is called "NTE aging" because this process is progressive and irreversible, that is, nucleophilic agents cannot activate NTE again. During this reaction, one of the side radicals at the phosphorus atom is split off. Sulfonyl fluorides, phosphinates, carbamates, and thiocarbamates are not neurotoxic; they interact with NTE and phosphorylate it but do not cause aging of the latter, that is, they do not lead to NTE inhibition and OPIDN development [2].

The ability of NTE to bind OP determines the enzymatic (esterase) activity of a protein. NTE activity in a protein lysate can be evaluated by the hydrolysis of phenylvalerate (phenyl pentanoic acid ester) in the presence of paraoxon (a non-neurotoxic OP that does not inhibit NTE activity but inhibits AchE) but in the absence of mipafox (a neurotoxic OP that inhibits NTE and AchE activities) [16]. When testing various OPs for neurotoxicity, chicken is widely used as a model because the phenotypic manifestations of OPIDN in this animal are highly similar to those in humans. A latent phase lasting for 8–14 days after the injection of the OP solution into the esophagus is followed by rapid fatigue, unwillingness to move, and clumsy gait; over the next 4–5 days, weakness in the limbs progresses, and birds lose the ability to stand, the Achilles reflex weakens, and hypotension in the legs occurs. Weakness also gradually develops in the wings, which is much less pronounced than in that the legs. Often 3–4 weeks after severe poisoning, the birds die, but death can be avoided by reducing the dose of OP.

Histological studies of poisoned birds revealed disorganization of the myelin layer of peripheral nerves, formation of myelin globules, and fragmentation and nodularity of axons resembling Wallerian degeneration, directed from the primary site of injury to the distal parts of the axon. Such pathological changes appear not earlier than a week after poisoning. In the spinal cord, the ventral spinocerebellar tract in the lower regions (sacral, lumbar, and thoracic), which is responsible for motor function, and the dorsolateral spinocerebellar tract in the cervical region are affected. The predominant degeneration of nerve fibers of large diameter and the greatest length, which consist of the processes of motor neurons, and pathological changes occurring mostly in the distal neurons, are consistent with the clinical phenotype of the primary damage to the motor activity of the distal lower extremities. Axonal degeneration occurs independently of demyelination, which indicates that OP exerts a toxic effect on the neurons and glial cells. In addition, lipid droplets are occasionally detected in Schwann cells [17].

Later, NTE activity was found in chicken [18], human [19], and mouse [20] lymphocytes, which greatly simplifies the screening of OPs for toxicity.

The action of neurotoxic OPs, in addition to the irreversible inhibition of NTE, leads to disorders in calcium homeostasis; this phenomenon leads to the activation of the calcium-induced neutral protease, which cleaves proteins in the synaptic terminals of axons [21, 22]. Examination

of chicken tissues exposed to OPs revealed increased levels of calcium/calmodulin-dependent kinase II (Ca^{2+}/CaMKII) mRNA in the cerebellum and spinal cord. In the same tissues, atypical phosphorylation of cytoskeletal proteins was noted. Thus, one study hypothesized that Ca^{2+}/CaMKII is involved in the pathogenesis of OPIDN [23]. However, another study did not confirm this assumption [15].

OPIDN studies revealed that NTE participates in the development of neuropathy in mammals and birds. The pathological consequences of intoxication were described in detail, a wide range of neurotoxic OP, NTE inhibitors, was found, a method for measuring NTE activity was proposed, and the NTE activity in the nervous and lymphoid tissues in mammals and birds was revealed.

HEREDITARY SPASTIC PARAPLEGIA

NTE dysfunction can be caused not only by inhibition by toxic OPs but also by mutations in the corresponding gene, as observed in one form of hereditary spastic paraplegia (HSP).

HSP is a syndrome that unites a group of human diseases characterized by progressive spastic (spasmodic) paraparesis (paralysis of a pair of limbs). The predominant lesion of the lower limbs distinguishes HSP from ataxia, in which coordination in both pairs of limbs is impaired [24]. The incidence of the disease is estimated at 1.8–9.8 cases per 100,000 people [25].

The first cases of such a disease were described in 1876, and the term "spastic paraplegia" was first used in 1880 by the German physician Adolf Strümpell, who described several cases of "pure" spastic paralysis [26, 27]. The disease progresses with age, and it starts with weakness of the lower extremities. Patients complain of "stiffness," a feeling of instability, and "unsteadiness" in the legs, especially when climbing up the stairs, as well as toe numbness. A significant distinguishing aspect of the pathogenesis is a spastic gait caused by increased muscle tone. The patient moves with small steps, with difficulty raising feet, and makes a semicircle with his foot when taking a step [28–30].

Examination of the material after autopsy revealed degeneration of the distal part of the axons of long myelinated fibers in the lateral corticospinal (pyramidal) tracts. This degeneration expands from the cervical to the lumbar region of spinal cord. In addition, pathological changes occur in the anterior corticospinal tract, Goll's fascicle, but not in the brain [31]. Ascending sensory fibers can be affected in the upper spinal cord [32]. In some cases, relatives with different clinical manifestations show a similar profile of neurodegeneration, and only the intensity of pathological changes in different parts of the central nervous system differs [33]. In many cases, spastic paraplegia does not affect life expectancy. Such patients die for various other reasons; therefore, histological studies of the brain in such patients are not performed, or the results are unpublished. For almost 100 years of studying the disease, by 1974, only 11 cases were described in which the pathomorphology of the nervous system was investigated. Data collected from various publications indicated the lesion of neurons with long processes, primarily in the corticospinal (pyramidal) tract [34].

The hypothesis about the mechanism of the pathology occurrence was first introduced in 1954 by Greenfield. He suggested that neurodegeneration is caused by an esterase deficiency [34, 35]. By this time, cases of OPIDN were well known, and its clinical manifestations were highly similar to those of HSP.

To date, more than 55 genes associated with HSP have been identified, which determines the heterogeneity of cases described from the early stages of the study of this disease. The classification of forms of spastic paraplegia was divided into 74 main (SPG1–74, spastic paraplegia gene) and 23 "unclassified" HSP-associated types. Most forms are monogenic diseases, but genes have not yet been found in some loci linked to HSP. Mutations in genes lead to disruption of various cellular processes, such as axon transport, myelination, growth of nerve cell processes, vesicular transport, intracellular signaling, mitochondrial function, lipid metabolism, and DNA repair [25].

Thus, the primary disorders of various processes of maintaining the vital activity and functioning of cells of the nervous system, caused by mutations in different genes, lead to a similar clinical phenotype, manifested as HSP. Mutations in the

NTE gene lead to similar consequences, contributing to the development of one of the HSP forms, SPG39.

In 2008, two families whose members suffered from motor neuron disease were studied because they showed symptoms similar to those of OPIDN or Troyer syndrome (a HSP form, SPG20, caused by mutations in the spartin gene) and progressive spastic weakness of the lower extremities. However, in Troyer syndrome, developmental retardation, impaired cognitive functions, emotional lability, abnormal skeletal structure, ataxia, dysarthria, and dysphagia are noted in addition to progressive spastic paraplegia and atrophy of distal muscles.

Electrophysiological studies confirmed motor neuropathy of the lower and upper extremities. Magnetic resonance imaging (MRI) revealed spinal cord atrophy in the thoracic region. The disease was inherited as an autosomal recessive trait. One of the families studied was a representative of Jewish Ashkenazi, that is, the studied patients were characterized by a high coefficient of inbreeding. Patients from this family were homozygous for the *c.[3034G/A]* missense mutation of the *NTE* gene (resulting in the Met1012Val substitution). Patients from another studied European family were heterozygous compounds carrying two mutations in the *NTE* gene, *c.[2669G/A]* (leading to the replacement of Arg890His) and *c.[2946_2947insCAGC]* (leading to a frame shift and the formation of a truncated protein with a changed sequence after amino acids at position 1019). All mutations detected affect the esterase domain within the region of the NTE protein from amino acids 727 to 1216. The control group comprising 105 healthy people did not have any of the mutations identified [36].

The first signs of the disease appeared in childhood up to 7 years of age in the form of weak, slowly progressive gait disturbances. Increasing hand weakness and atrophy developed between the ages of 12 and 21 years. No cognitive impairment was noted in the patients. Significant weakness was due to muscle atrophy, which was detected in the distal regions of the upper and lower extremities. A 82-year-old patient was unable to walk due to weakness and severe muscle spasticity in the upper and lower extremities. Another patient (38 years old) had a spastic gait. Patient 3 (38 years old) and patient 4 (48 years old) could move independently using a cane, although they had severe spastic paraparesis [37].

Mutations in the *NTE* gene and other genes lead to disruption of various cellular functions, inhibiting the vital activity of similar cells of the nervous system, which manifests itself as HSP. A similar sign of the pathogenesis of various forms of HSP is motor neuropathy of the pyramidal tracts. Thus, various initiating mechanisms lead to a general HSP phenotype, which can be supplemented by other signs specific to each form. Molecular mechanisms that cause a defective NTE function (in the case of mutation or inactivation with organic phosphates) lead to neurodegeneration, characterized by the death of central or peripheral motor neurons or their axons.

BOUCHER–NEUHAÜSER AND GORDON HOLMES SYNDROMES

In 2014, two more diseases (Boucher–Neuhaüser and Gordon Holmes syndromes) were associated with mutations in the *NTE* gene. The results of exome sequencing of two patients with Boucher–Neuhaüser syndrome and one patient with Gordon Holmes syndrome revealed, mutations in the *NTE* gene. Analysis of the genealogic tree showed an autosomal recessive inheritance pattern. One patient was a carrier of homozygous missense mutation *c.[3173C>T]*, which resulted in the Thr1058Ile substitution. The second patient was a carrier of a heterozygous compound with mutation *c.[2212–1G> C]*, leading to exon 20 skipping, a shift in the reading frame, a change in the sequence of the *p.[Val738Glnfs*98]* protein, and a missense mutation of *c.[3328G>A]*, leading to the substitution of p.[Val1110Met]. A third patient with Gordon Holmes syndrome was a carrier of the heterozygous compound *c.[3084_3085insGCCA]//[4084C>G]*, which led to the synthesis of defective proteins p.[Arg1031Glufs*38]/[Arg1362Gly]. Through Sanger sequencing, the *NTE* gene sequence was studied in four patients of other families with Boucher–Neuhaüser syndrome, and other mutations were identified (*c.[3134C>T]//[3365C>T]*, p.[Ser1045Leu]/[Pro1122Leu] and *c.[1732G>T]/*

[3197T>C], p.[Gly578Trp];[Phe1066Ser]). New cases of the syndrome were later described, which were also characterized by mutations in the *NTE* gene (*c.[2944_2947dub]/[3932G>A]*, p.[Leu983fs*86]/[Arg1311Gln]). In addition, the exomes of 538 patients with various neurodegenerative diseases, but not with the syndromes described above, were studied; 67 patients had early ataxia with onset before the age of 30, 144 patients with "complex" forms of HSP, 192 patients with "pure" HSP, and 135 patients with recessive Charcot–Marie–Tooth disease type 2. Analysis of exome sequencing data revealed that one patient with spastic ataxia carried a heterozygous compound for mutations in the *NTE* gene *c.[3084_3085insGCCA]/[3299T>G]*, leading to the synthesis of defective proteins *p.[Arg1031Glufs*38]/[Val1100Gly]*. Another HSP patient had a heterozygous compound for mutations *c.[787G>A]/[2519G>A]* in the *NTE* gene, which led to p.[Val263Ile]/[Gly840Glu] substitutions. The mutated loci were highly conserved in different species (from yeast to mammals) and affected either the esterase domain of NTE or domains of interaction with cyclic nucleotide monophosphates or regions adjacent to them. The detected mutant alleles were absent or had a low frequency in the databases GEM.app (2175 exomes), dbSNP137, and NHLBI ESP (6500 exomes). In the control group of 1637 patients with neurodegenerative diseases, with the exclusion of all the above diseases, no homozygotes or heterozygous compounds for mutations in the *NTE* gene were detected (based on the results of exome DNA sequencing analysis). These results indicate that mutations in the *NTE* gene can result in various hereditary diseases [38].

Boucher–Neuhaüser syndrome can be caused exclusively by mutations in the *NTE* gene [39, 40]. This monogenic disease, inherited by an autosomal recessive type, combines a triad of symptoms, such as spinal ataxia (disorder of movement coordination), hypogonadotropic hypogonadism (hormone level reduction of the pituitary–hypothalamic system (luteinizing and follicle-stimulating hormones) that decreases sex hormones, inhibits gametogenesis, and manifests itself in adolescence in the form of sexual development retardation), and chorioretinal dystrophy (irreversible degenerative changes in the choriocapillary layer of the eye vascular membrane, affecting the retinal pigment layer and Bruch's membrane, resulting in visual impairment) [41–43].

To date, 40 cases of Boucher–Neuhaüser syndrome have been described in the literature. Symptoms manifest at different ages, from the first year of life to the age of 40 years, and the first symptom may be one of the above triad (ataxia, visual impairment, and sexual development retardation). As a rule, one of them necessarily manifests itself before the age of 15 years. In patients, ataxia manifests itself in the form of impaired coordination of movements of the upper and lower extremities and dysarthria (speech impairment) develops. In a significant proportion of patients, the clinical phenotype indicated the involvement of the pyramidal pathway in the disease pathogenesis. In some patients, slight impairments in cognitive functions (decreased attention, impairment of immediate, and short-term memory) may be found. In some cases, MRI examination of patients reveals cerebellar atrophy (in the hemispheres and in the vermis) and an increased signal in the brainstem region in T2-weighted images. Visual defects in all patients are expressed as paracentral scotoma (a blind spot in the field of view near the point of regard) or decreased visual acuity. In all patients, motor disorders of the eye were described, namely, nystagmus (frequent oscillatory eye movement) and impaired vestibulo-ocular reflex (staring on an object when turning the head). Blood test reveals a significant decrease in the levels of testosterone, luteinizing hormone, and follicle-stimulating hormone. The patients' genitals are underdeveloped. Patients are infertile, but timely hormone therapy restores fertility [39, 44].

Gordon Holmes syndrome is similar to Boucher–Neuhaüser syndrome. The classic clinical features of this disease are spinal ataxia and hypogonadotropic hypogonadism, but the syndrome is not accompanied by chorioretinal dystrophy. The syndrome was first described in 1908 by the English neurologist Gordon Holmes [45] as progressive spinal ataxia with the onset after the age of 35 years, accompanied by hypogonadism and nystagmus. A study of the cerebellum of one of

the patients on postmortem material revealed a threefold decrease in its weight compared with the weight of a normal cerebellum; the greatest changes were observed in the vermis and flocculus. Significant degenerative changes accompanied by gliosis were found in olives involved in the control of motor functions. Degeneration of the molecular and granular layers, Purkinje cells, and myelinated fibers was found in the cerebellum. In the spinal cord, a slight clearing of the pyramidal tract in the thoracic and lumbar regions was noted, consistent with a slight increase in the excitability of the knee reflex [46].

Gordon Holmes syndrome can be caused by mutations in different genes, namely, *NTE, RNF216* (encodes ubiquitin E3 ligase), *OTUD4* (encodes OTU deubiquitinase 4), and *STUB1* (encodes a protein that has ubiquitin E3 ligase activity, which is also capable of inhibiting the ATPase activity of family HSP70 chaperons).

In 2014, two studies revealed the relationship between the development of Gordon Holmes syndrome and mutations in the *NTE* gene through exome sequencing. The first study, in which the *c.[3084_3085insGCCA]//[4084C>G]* mutation was found, has already been mentioned above [38]. In another work, new mutations were found in six patients from three families, whose genotypes (and the resulting substitutions in the protein product) were as follows: homozygote *c.[C3380G]* (p.[Ser1127Cys]); compound *c.[C3931T]//[ins2494TGTGGGCCTGGGG]* (p.[Arg1311Trp]/[Gly832fs*13]); and compound *c.[1127insG]//[C3295T]* (p.Asp376Glyfs*18/Arg1099Cys). Gordon Holmes syndrome was noted in patients from the first two families, and Boucher–Neuhaüser syndrome was found in patients from the third family [47].

Apparently, hypogonadotropic hypogonadism accompanying these syndromes is caused by dysfunction of the neuroendocrine cells of the pituitary gland. An experiment using an immortalized culture of mouse pituitary cells (LβT2) showed a decrease in the secretion of luteinizing hormone in response to the treatment of the culture with gonadotropin releasing hormone in the presence of an NTE inhibitor, organic phosphate chlorpyrifos oxone, which reduced the esterase activity of NTE by 70%. In addition, the level of luteinizing hormone mRNA did not decrease, but the intensity of exocytosis decreased rapidly. An attempt to influence hypogonadotropic hypogonadism using gonadotropin-releasing factor therapy was unsuccessful, and the level of luteinizing hormone in the blood of patients did not increase. The supposed cause of the vesicular transport defect is phosphatidylcholine metabolism disruption due to a decrease in NTE activity [47].

Thus, analysis of the distribution of pathogenic mutation loci in the *NTE* gene shows that they can be located not only in functional domains (nucleotide binding and esterase) but also in other parts of the gene [38, 39]. This result means that the functional structure of the protein is still not fully understood. Amino acid substitutions resulting from mutations can lead to altered protein folding or altered functions of known domains. The facts described do not exclude the hypothesis of the presence of other functional domains in the protein structure, the role of which is not known to date. The clinical significance of this phenomenon is expressed in the need for sequencing of the entire gene to confirm the carriage of the pathogenic allele in the genetic description of *NTE*-associated diseases.

OLIVER–MCFARLANE SYNDROME, LAURENCE–MOON SYNDROME, AND LEBER CONGENITAL AMAUROSIS

In 2015, the list of diseases associated with mutations in the *NTE* gene expanded because of modern omic technologies, namely, exome sequencing. In eight patients with Oliver–McFarlane syndrome in five families, new mutations in the *NTE* gene were registered (genotypes and corresponding changes in the protein are indicated):

- *c.[1571T>C]//[3373G>A]*, p.[Leu524Pro]/[Asp1125Asn];
- *c.[2116C>T]//[3385G>C]*, p.[Gln706*]/[Gly1129Arg];
- *c.[343-2A>T]//[3373G>A]*, p.[ivs-42A>T]/[Asp1125Asn];
- *c.[3322C>T]//[3385G>C]*, p.[Arg1108Trp]/[Gly1129Arg];
- *c.[1238_1239insC]//[3385G>C]*, p.[Pro413fs*28]/[Gly1129Arg];
- homozygote *c.[2763G>A]*, p.[Trp921*].

Another group of 10 patients from six families with Oliver–McFarlane and Laurence–Moon syndromes also had new pathogenic mutations in the *NTE* gene, leading to the following changes in the primary structure of the gene and the corresponding protein in heterozygous compounds:

- *c.[3296G>A]//[3526G>A]*, p.[Arg1099Gln]/[Gly1176Ser];
- *c.[3091_3092insAGCC]//[3385G>A]*, p.[Arg1031fs*38]/[Gly1129Arg];
- *c.[2176G>C]//[3091_3092insAGCC]*, p.[Gly726Arg]/[Arg1031fs*38].

Mutation resulting in splicing impairment of *c.[1973+2T>G]* and missense mutation of *c.[3644T>G]* resulting in p.[Val1215Ala] substitution were also found. Moreover, another variant with a duplication of the fragment containing exons 14–20 and missense mutation of *c.[3644T>G]* resulting in substitution of p.[Val1215Ala] were detected. Only one of the mutations described was previously known and associated with Boucher–Neuhaüser syndrome (*c.[3091_3092insAGCC]* leading to a shift in the reading frame and the synthesis of the truncated protein p.[Arg1031fs*38]) [38]. Most of these mutations result in changes in the known functional domains of the NTE protein (esterase and nucleotide binding); evolutionary conservation of all variable residues (sometimes impaired in some species) has been demonstrated [48, 49]. Experiments to restore embryogenesis in *Danio rerio* with knockdown of the *NTE* ortholog, the *pnpla6* gene, induced by the injection of morpholine oligonucleotides, showed that human wild-type *NTE* mRNA almost completely restores the morphology of larvae, in contrast to mutant mRNAs containing the above-mentioned substitutions. The phenomena under study confirm the negative effect of these mutations on the NTE protein functioning [48]. Oliver–McFarlane syndrome was named after the authors who first described in 1965 a case of congenital trichomegaly, which is an increase in the length of the eyelashes and eyebrows (up to 4 cm), manifested in a child at birth. Patient monitoring for 2 years has shown that he developed mentally and physically much more slowly than normal children. Hypothyroidism, retinal degeneration, and uneven distribution of pigment in the fundus have been noted [50]. Later, other similar cases were described, accompanied by alopecia (partial or complete baldness), congenital hypogonadotropic hypogonadism, growth hormone deficiency, progressive ataxia, nystagmus, peripheral polyneuropathy, and cerebellar atrophy detected on computed tomography [51]. To date, 22 cases of the disease have been described [48, 49]; for all of them, an autosomal recessive mode of inheritance was revealed. Common signs of the syndrome are congenital trichomegaly and hypogonadism, mental and physical retardation, pituitary hormone deficiency, childhood chorioretinal dystrophy or retinitis pigmentosa (degeneration of light-sensitive cells with fibrosis and gliosis replacing them, deposition of pigment in the fundus), and neuropathy (peripheral sensory polyneuropathy, ataxia, or spastic paraplegia) [48].

Laurence–Moon syndrome has also been named after the authors who first described in 1866 four children from the same family with early chorioretinal dystrophy and retinitis pigmentosa, severely reduced visual acuity, and hemeralopia (night blindness, which is poor sight in twilight and darkness) but normal field of vision. In addition, the authors drew attention to retardation in the development of patients, short stature, underdevelopment of the genitals, difficulties in motor activity, and oscillation of the eyes (apparently, corresponding to nystagmus) [52, 53]. Various phenotypic manifestations over the next century and a half were associated with the syndrome, including cases with polydactyly, Klinefelter syndrome, and mental retardation. The unifying symptoms of the syndrome were autosomal recessive inheritance mode, chorioretinal dystrophy in combination with retinitis pigmentosa, complete blindness, defects in the pituitary gland (pituitary hormone deficiency, mental retardation, growth retardation, hypogonadotropic hypogonadism, underdevelopment of the genital organs, and secondary sexual characteristics) [54]. In some cases, neuropathy (peripheral sensory polyneuropathy, ataxia, or spastic paraplegia) appears. Thus, Laurence–Moon syndrome is highly similar to the pathogenesis of Oliver–McFarlane syndrome, differing primarily in the absence of trichomegaly, and is similar to the development of Boucher–Neuhaüser

disease, being supplemented by some other signs in the absence of sensorimotor neuropathy [48]. To date, only mutations in the *NTE* gene are known to cause these three syndromes.

In addition, Leber congenital amaurosis may be associated with mutations in the *NTE* gene. Among 200 patients with this pathology, one was revealed to have the genotype (and corresponding changes in the primary structure of the NTE protein) of *c.[3084_3085insGCCA]//[1076C>T]*, p.[Ser1028fs*40]/[Thr359Ile]. The patient was born blind due to retinal destruction and suffered from severe autism [49]. This is the only case described in the literature that requires careful verification and confirmation of the connection between *NTE* and Leber amaurosis. Attention is drawn to the complication of the syndrome with autism, previously not associated with mutations in the *NTE* gene. The pathology itself is heterogeneous from a genetic and symptomatic point of view. Mutations in at least 25 genes have been associated with Leber congenital amaurosis [55]. Nevertheless, NTE defect undoubtedly plays a role in visual dysfunction.

The discovery of the association of *NTE* mutations with visual dysfunction prompted the study of the expression of *NTE* orthologs in animal models. Thus, the expression of *sws*, the *NTE* ortholog in *Drosophila melanogaster*, can be identified in the photoreceptor cells of flies, and the effect of *sws* dysfunction on age-dependent ommatidia degeneration can be revealed. Such experiments confirmed the evolutionary conservative role of *sws/NTE* in maintaining the viability of photoreceptor cells [49].

PURE CEREBELLAR ATAXIA

The syndromes described above do not limit the possible clinical presentation of *NTE* gene dysfunction due to mutations. A study in 2017 showed for the first time that mutations in this gene lead to pure cerebellar autosomal ataxia not aggravated by any other symptom. In the Indian population of Zoroastrian Parses, two relatives who were descendants of children born from closely related marriages were found to have two new mutations in the *NTE* gene simultaneously because both patients were homozygous. The *c.[3847G>A]* mutation resulted in the p.[V1283M] substitution, and the *c.[3929A>T]* mutation had the p.[D1310V] missense effect. The first symptoms appeared in patients around the age of 12 years in the form of staggering gait and difficulty in writing. With age, the disease progressed, nystagmus appeared, brisk tendon reflexes occurred, and dysarthria developed. As a result of ataxia, the patients needed to use a wheelchair, but they lived to at least 70 years. No other disorders characteristic of the syndromes listed in this section have been identified [56].

The discovery of cases of pure ataxia associated with mutations in the *NTE* gene is an undoubted argument for revising the existing phenomenology in the classification of motor diseases. The classical algorithm for the clinical diagnosis of hereditary motor diseases has long been based on the mutual exclusion of ataxia/spasticity. However, in the last decade, in connection with the introduction of omic technologies in clinical research, a number of examples of the influence of mutations of the same gene on the development of a whole spectrum of diseases have been found. These findings lead to the conclusion that ataxia and spastic paraplegia represent a continuum. This pleiotropy has already been found for at least 69 genes. Interestingly, their functional analysis reveals three main biological processes that control these genes, namely, lipid metabolism, carboxylic acid metabolism, and cytoskeleton organization. Such a revision of the classification can be productive for identifying the mechanisms of pathogenesis and for searching the optimal personalized therapy methods based on compensation of defective function and not on a symptomatic approach [57].

The above reasoning is also valid for the entire range of diseases caused by mutations in the *NTE* gene. If OPIDN and HSP are extreme manifestations of spasticity in a continuum of degenerative phenotypes, then pure ataxia is completely opposite. In this case, Boucher–Neuhaüser, Gordon Holmes, Laurence–Moon, and Oliver–McFarlane syndromes become intermediate variants shifted to one side or the other. An exception is the only described case of Leber congenital amaurosis that does not exhibit motor neuropathy. Such a "unifying" classification is important for

the four intermediate syndromes, which are highly similar in clinical presentation and are sometimes diagnosed conventionally.

CONCLUSION

The discovery of a whole range of diseases caused by mutations in the *NTE* gene enables to draw important conclusions about its role in various cells and at the general physiological level. With the development of spasticity, the long and large neurons of the corticospinal (pyramidal) tracts are affected, accompanied by classic "pyramidal signs," including brisk tendon reflexes and Babinski reflex. Ataxia is primarily associated with damage to the cerebellum, which was found in Boucher–Neuhaüser, Gordon Holmes, and Oliver–McFarlane syndromes and in pure cerebellar ataxia [39, 43, 46–48, 56]. Spasticity and ataxia can occur in Laurence–Moon syndrome, but there are no studies to date that visually confirm the type of motor degeneration in this syndrome. In the only known case, in which the structure of the brain was studied using MRI, the patient suffered from spasticity; therefore, no noticeable changes in the cerebellum were found [48]. However, MRI or autopsy studies of relevant patients are expected to reveal the degeneration of either the pyramidal tracts or the cerebellum, depending on the clinical phenotype (spasticity or ataxia).

Boucher–Neuhaüser, Gordon Holmes, Laurence–Moon, and Oliver–McFarlane syndromes are associated with pituitary dysfunction, leading to a decrease in the level of one or more hormones (thyroid-stimulating, somatotropic, and gonadotropic) in the blood of patients. This phenomenon results in the retardation of growth, mental development, and puberty; impaired gonadal development and sterility; trichomegaly; and alopecia. The MRI study of the brain of several patients revealed a decrease in the volume of the pituitary gland.

Furthermore, mutations in the *NTE* gene can lead to degeneration of the eye vascular layer underlying the retina and/or to degeneration of the retina pigment cell layer (rods and cones). Chorioretinal atrophy is registered in Boucher–Neuhaüser, Laurence–Moon, and Oliver–McFarlane syndromes. Retinitis pigmentosa is a characteristic sign of the last two syndromes, the course of which is much more severe than that of other diseases considered in this section. The lesion of the retina manifests itself in the first years of life, progresses, and leads to complete blindness. The same is true for Leber amaurosis.

The hereditary diseases under consideration (excluding OPIDN) are extremely rare. Today, only a few dozen cases of such diseases are known. According to genomic studies, the vast majority of patients are heterozygous compounds carrying two *NTE* mutations in homologous chromosomes. This finding means that mutations in *NTE* occur *de novo* randomly and rarely in different paternal and maternal ancestors who are healthy heterozygous carriers. The most serious diseases are the congenital Laurence–Moon and Oliver–McFarlane syndromes, as well as the considered case of Leber congenital amaurosis. Patients with these diseases are assumed to carry both mutations that disrupt the activity of the esterase and nucleotide-binding domains. In other syndromes, dysfunction affects only one domain. Therefore, they are milder and manifest themselves after the first decade, and some symptoms sometimes appear even at the fourth decade of life [49]. Analysis of the esterase activity of NTE in the fibroblasts of patients with different mutations and different diseases showed the presence of four groups of activity levels, indicating differences in the effect of certain mutations on protein function [48]. The symptoms almost never cause lethal consequences, with the exception of a single case of severe poisoning with triorthocresyl phosphate, but lead to patient disability.

Although the relationship between mutations in the *NTE* gene and the development of various diseases has been revealed, the specific mechanisms of pathogenesis remain unclear. Therefore, additional studies of the relationship of specific mutations, functions of the *NTE* gene, and the clinical manifestation of diseases associated with it remain relevant.

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