Clinical and Neurophysiological Features of Hereditary Motor sensory Neuropathy, Issues of Optimization of Diagnosis and Therapy

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ABSTRACT

Hereditary neuropathies are a group of severe genetic heterogeneous diseases of the peripheral nervous system, characterized by pronounced clinical polymorphism. Currently, it is customary to distinguish 4 groups of neuropathy depending on the combination of damage to the motor or sensory portions of the peripheral nerves, and the most common group is NMSN. They account for about 80% of all patients, which are divided into two main types: demyelinating (1) and axonal (2). All HMSN groups were characterized by a triad of clinical symptoms: atrophy of the distal parts of the hands and feet with their deformity, sensory disturbance in the area of atrophied muscles, hypo or areflexia of the muscles of the upper and lower extremities

Keywords: Hereditary neuropathies, Modern ideas about the etiology and pathogenesis, disease in sporadic cases, allergic and other exogenous polyneuropathies

Introduction

Relevance. Hereditary neuropathies are a group of severe genetic heterogeneous diseases of the peripheral nervous system, characterized by pronounced clinical polymorphism. Currently, it is customary to distinguish 4 groups of neuropathy depending on the combination of damage to the motor or sensory portions of the peripheral nerves, and the most common group is NMSN. They account for about 80% of all patients, which are divided into two main types: demyelinating (1) and axonal (2). All HMSN groups were characterized by a triad of clinical symptoms: atrophy of the distal parts of the hands and feet with their deformity, sensory disturbance in the area of atrophied muscles, hypo or areflexia of the muscles of the upper and lower extremities. As a rule, HMSN had a moderately progressive course that did not lead to severe disability of patients. When diagnosing the disease in sporadic cases, endocrine, infectious-allergic and other exogenous polyneuropathies were excluded. (Yudina G.K., Sirko E.A., 2004).

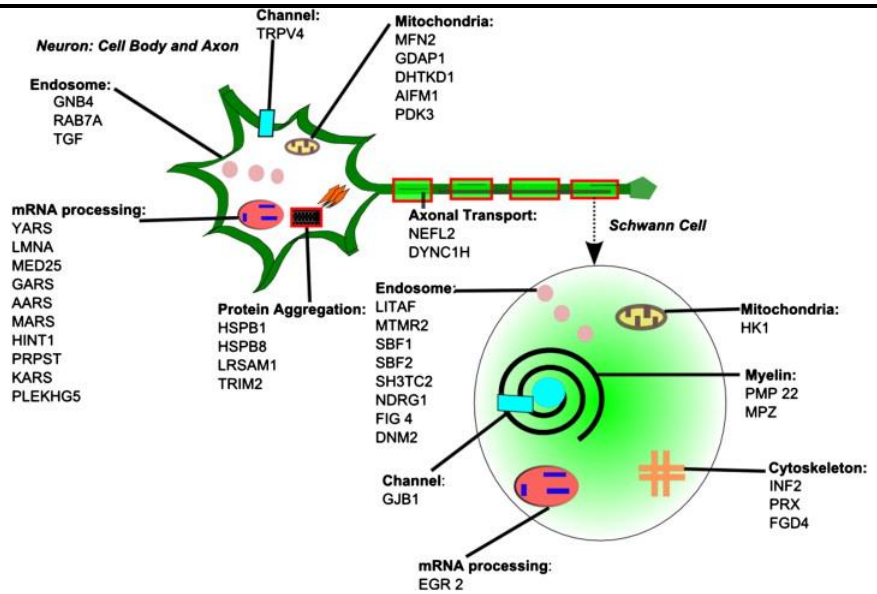
Small heat shock proteins (sHsp) are a widespread family of ATP-independent chaperones that play an important role in maintaining cellular homeostasis. Representatives of this family are united by the presence of an Ig-like highly conserved α-crystallin domain (ACD) in the central part of the molecule, which is flanked by a variable and, as a rule, random N-terminal domain (NTD) and a short C-terminal domain (CTD). Several sHsp genes have been found in the genome of most organisms (for example, 10 genes have been identified in humans). Small heat shock proteins are characterized by a small (from 12 to 43 kDa) molecular weight of monomers. The presence of the α crystallin domain ensures the formation of stable dimers of small heat shock proteins that can associate and form larger oligomers. sHsp are involved in the regulation of numerous processes occurring in the cell, such as protecting the cell from the accumulation of

aggregates of misfolded proteins, apoptosis, reorganization of the contractile apparatus and cytoskeleton, and proliferation. This is probably why mutations in the sHsp genes often lead to the development of various diseases. To date, more than 20 mutations in the human small heat shock protein HspB1 gene are known, the expression of which correlates with the occurrence of distal congenital motor neuropathy (DCMN) and Charcot-Marie-Tooth type 2 disease (CMT2) - diseases characterized by progressive damage to the axons of the motor and / or sensory neurons. Studies on the effect of amino acid substitutions, correlated with the development of neuropathies, on the structure and functions of HspB1 have been conducted for a long time, however, many questions remain unresolved. In addition, it remains unclear how point substitutions in HspB1 lead to the development of neuropathies. It is generally accepted that the development of neuropathies may be associated with impaired axonal transport and damage to the axon cytoskeleton. It is assumed that amino acid substitutions in HspB1, which correlate with the development of neuropathies, may somehow affect its interaction with the main component of neuronal intermediate filaments, the neurofilament light chain.

Modern ideas about the etiology and pathogenesis of hereditary motosensory neuropathies.

Hereditary motor sensory neuropathies represent a large diagnostic category of neurological diseases with an incidence of 1 in 2500 patients. Understanding the clinical diagnostic criteria within hereditary motor sensory neuropathies is essential for understanding the broader category of hereditary motor, sensory, and autonomic neuropathies.Thus, Reilly makes recommendations to simplify the classification of hereditary motor-sensory neuropathies in the light of recent molecular genetic advances.

Over the past 25 years, there have been revolutionary changes in the molecular genetics of hereditary neuropathies. More than 40 genes have been identified that cause hereditary motor sensory neuropathies with many different types of mutations. These mutations provide clues to the cellular pathways of inherited neuropathies, and knowledge of cellular pathways may help provide information for therapeutic purposes. Although 4 genes account for the majority (over 90%) of all molecular diagnoses of hereditary motor sensory neuropathy: myelin peripheral protein 22 (PMP 22), gap protein β1 (GJβ1), myelin null protein (MPZ), and MFN2, it has recently been found that new genes are associated with hereditary motor sensory neuropathies, including PDK3, GNB4, INF2, FBLN5.Hereditary motor sensory neuropathies are caused by a duplication on chromosome 17p11.2 containing the peripheral myelin protein 22 (PMP 22) gene. A distinctive feature of axons in the central and peripheral nervous system is the myelin sheath, which increases the speed of propagation of electrical impulses. Myelin is a multi-layered helical structure that envelops axons with a thickness of more than 1 micron; Schwann cells form the myelin sheath in the peripheral nervous system, and oligodendrocytes do the same in the central nervous system. A single Schwann cell myelinates one axon, in contrast to oligodendrocytes, which myelinate multiple axons. These often dramatic individual mononeuropathies (usually painless) are superimposed on pre-existing diffuse, length-dependent, sensory-predominant large-fiber neuropathies, relieving heat pain associated with small fibers. Macrodeletions of 17p11.2, which includes the entire PMP22 gene, are the most common cause of HNPP. Microinsertions, microdeletions and point mutations in PMP22 leading to frameshifts and nonsense mutations (stop codons) are also responsible for HNPP.



Rice. 1. Genes that cause hereditary motor sensory neuropathies associated with various structures of neurons and Schwann cells: the localizations of genes associated with the neuron cell body, axon and Schwann cell are listed.

A distinctive feature of axons in the central and peripheral nervous system is the myelin sheath, which increases the speed of propagation of electrical impulses. Myelin is a multi-layered helical structure that envelops axons with a thickness of more than 1 micron; Schwann cells form the myelin sheath in the peripheral nervous system, and oligodendrocytes do the same in the central nervous system. A single Schwann cell myelinates one axon, in contrast to oligodendrocytes, which myelinate multiple axons. Myelin allows you to increase the speed of conduction along axons without increasing the diameter of the axons through the process of salutary conduction, in which nerve impulses jump between the nodes of Ranvier, which are the gaps between two segments of myelin. Although myelinating Schwann cells are responsible for demyelinating neuropathy, neurons expressing the mutant protein may also contribute to demyelinating neuropathy.The myelin sheath has two regions, compact and non-compact, which contain unique proteins (Fig. 2) [14]. The compact region contains the myelin structural proteins PMP22, P0 (encoded by MPZ) and myelin basic protein . Most myelin is compact and contains cholesterol, sphingolipids, galactocerebroside, and sulfatide. The non-compact region is partly formed due to the large distances between the cell nucleus and the Schwann cells; non-compact myelin contains gap junctions that provide a radial path to the myelin sheath for the passage of water, Schmidt-Lanterman cuts, ions, and small molecules. Non-compacted myelin can be divided into the paranode immediately adjacent to the node of Ranvier and the area of the juxtaparanode. The paranodal region contains loops of the Schwann cell membrane, which contain Schwann cell proteins such as Cx32, the major gap junction protein in myelin. It also contains myelin-associated glycoprotein (MAG), neurofascin 155, and the axonal proteins Caspr and Contactin. The juxtaparanodal region contains potassium channels and Caspr2, both expressed by axons. Schwann cells and axons also interact along the internodes of peripheral nerves, providing mutual benefit to both cells, including trophic support. Disorders that occur in Schwann cells lead to loss of axons, the ultimate path of all diseases of hereditary motor sensory neuropathies. Thus, Schwann cells serve as a source of neuroprotection [15]. The interaction of Schwann cells and axons is disrupted in almost all demyelinating hereditary neuropathies, since significant changes occur in the physiology of axons. This relationship is evidenced by secondary degeneration of axons, which are clinically observed as muscle atrophy,

and physiologically as reduced amplitudes when testing nerve conduction.

1.2. Length-dependent pattern, tau proteins, chaperone proteins, beta-amyloid.

NMSN consists of many types of neuropathy and is estimated to have a prevalence rate of 17 to 40 per 10,000 people. Patients usually have length-dependent neuropathy of large diameter motor and sensory nerves. The current application of electrophysiology, prior pathological descriptions, and genetic data provide the basis for a detailed classification. Inheritance patterns and details of the primary localization of neurons are complemented by a combination of genetic and modern electrophysiological studies.

HMSN is classified into 5 groups: (1) HMSN 1 is a dominantly inherited demyelinating form with low nerve conduction velocity (≤38 m/s at the elbow joint of the forearm) showing gross nerve hypertrophy and diffuse myelin sheaths separated by longitudinally directed collagen fibrils (bulbs onion) on nerve biopsy. HMSN 2 is a dominantly inherited axon-dominated neuropathy demonstrating normal to borderline slow nerve conduction velocity (>38 m/s at the ulnar forearm) with axonal atrophy on nerve biopsy. HMSN 3 (also called Dejerine-Sottas disease) usually occurs in infancy or childhood with ambulatory milestone loss and more general neurological deficits. It is often dominantly inherited and has an extremely low nerve conduction velocity (usually from solitary fingers to low ulnar motor nerve values). The HMSN 3 category, however, has been overshadowed by the genetic classification because many patients with HMSN 3 have mutations that also occur in HMSN 1. This HMSN 3 category clarifies the spectrum of clinical severity and does not expand on genetic causes. (4) HMSN 4 is autosomal recessive, usually with childhood onset and demyelinating nerve conduction velocity Many patients in this group have blood relatives; they may also have extraneural features, including facial dysmorphism and scoliosis, especially with HMSN 4C, the most common form of HMSN 4. Those familiar with the earliest classifications will remember that HMSN 4 was originally used to describe patients with impaired phytanic acid metabolism (t e., Refsum's disease); this earlier formulation was abandoned because these neuropathic patients were recognized to have systemic damage to many organs, including the skin (ichthyosis), retina (retinitis pigmentosa), and cerebellum (ataxia). (5) HMSN 5 was originally described with spasticity. It was considered a "difficult HSP" due to spasticity and neuropathy. Within each of these 5 HMSN categories, each group has additional subclasses based on a specific genetic cause. HNPP is a dominantly inherited neuropathy characterized by recurrent episodic focal numbness, tingling, and weakness in response to nerve injury from pressure or strain. These often dramatic individual mononeuropathies (usually painless) are superimposed on pre-existing diffuse, length-dependent, sensory-predominant large-fiber neuropathies, relieving heat pain associated with small fibers. Macrodeletions of 17p11.2, which includes the entire PMP22 gene, are the most common cause of HNPP. Microinsertions, microdeletions and point mutations in PMP22 leading to frameshifts and nonsense mutations (stop codons) are also responsible for HNPP. The same PMP22 gene, when duplicated or missense mutations are present, causes HSMN 1A. HNPP is less common than HMSN 1A. Families of nerve conduction studies confirm clinical heterogeneity with varying degrees of generalized sensory neuropathy, prolongation of the motor distal latency, and conduction block at pressure sites. Attacks of focal weakness and loss of sensation improve over time, but the underlying generalized neuropathy usually worsens. Biopsy of the sural nerve reveals folded myelin loops that form characteristic thickenings of the nerve. They differ from bulbs in which folded myelin loops are not observed. In addition to swelling, there is a general thinness of myelin in all other myelinated nerve fibers.

References:

1. Aleksandrov A.V. [and etc.]. Neurodegenerative diseases: fundamental and applied aspects / Aleksandrov A.V., Voronina T.A.,

Bachurin S.O., Gavrilova S.I., Alesenko A.V., [et al.], Moscow: Nauka, 2010 .
2. Aniol V.A., Tishkina A.O., Gulyaeva N.V. Neurogenesis and neuroinflammation: the role of WNT family proteins // Neurochemistry. 2016. No. 1 (33). C. 5–11.
3. Akhmadeeva L.R. Hereditary neuromuscular diseases in the Republic of Bashkortostan (issues of pathogenesis, clinic and prognosis): diss. ... doc. honey. Sciences. Ufa, 2001. 295 p.