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CLINICAL AND NEUROPHYSIOLOGICAL FEATURES OF HEREDITARY MOTOROSENSORY NEUROPATHY, ISSUES OF OPTIMIZATION OF DIAGNOSIS, MATERIALS AND METHODS OF INVESTIGATION

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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 and axonal . 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, Collection of anamnesis, disease in sporadic cases, Neurophysiological research methods, Assessment of neurological status.

INTRODUCTION

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 and axonal . 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

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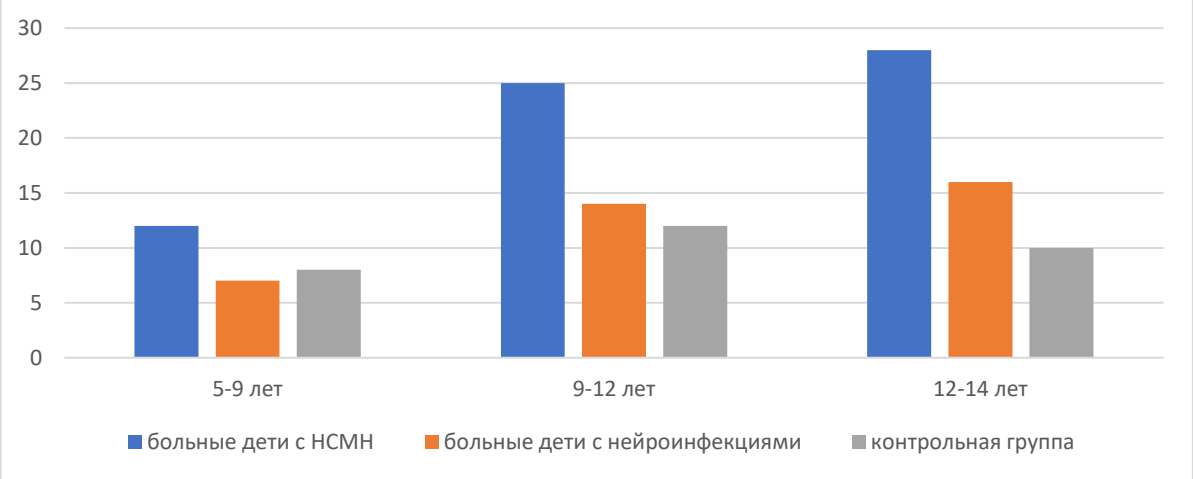
substitutions in HspB1, which correlate with the development of neuropathies, may somehow affect its interaction with the main component of neuronal intermediate filaments, the neurofilament light chain.

The main group was divided into 2 subgroups: 30 children with hereditary motosensory neuropathy and 30 children with spastic-diplegic cerebral palsy. The age of sick children ranged from 5 to 14 years. The average age was 9.0±4.5 years. The observation groups were comparable in terms of sex and age characteristics and the number of people (p≤0.05).



Rice. 2.1.2. Distribution of children by age characteristics

Inclusion criteria: the presence of acute and progressive weakness in the arms or legs, accompanied by normal or reduced tone, compliance with the GMFCS and FMS criteria, the presence of hereditary motosensory neuropathy proven by molecular genetic methods.

Exclusion criteria: HMSN associated with diabetes mellitus, systemic connective tissue diseases, genetically untyped forms of HMSN, metabolic polyneuropathy against the background of diabetes mellitus, thyroid lesions, chronic liver and kidney diseases, polyneuropathy as a complication of Lyme Borreliosis, Leprosy, paraneoplastic lesions, polyneuropathy critical states.

RESEARCH METHODS.

1. Collection of anamnesis - collection of complaints, anamnestic data, an analysis of the course of concomitant somatic pathology was carried out. Information was taken from interviews with the patients themselves and their relatives, as well as from epicrises from the medical history and outpatient cards.

2. Assessment of neurological status. Clinical and neurological research method included the assessment of movement on the scales GMFCS (GrossMotorFuncionClassificationSystem) - System for assessing large motor functions, FMS (FunctionalMotorScale) - Functional motor activity scale. The dynamics of improvement for sick children was carried out after 3,6, 12 months.

The standard neurological examination included: the study of muscle tone, muscle strength,

The research method is retrospective with a series of prospective observations. The subject of the study is medical documentation (case histories, extracts from the medical history), the results of anamnesis, clinical assessment, neurophysiological and biochemical studies.A prospective cross-sectional study of patients with NSMI receiving pathogenetic therapy was carried out according to the established protocol with an examination after 1, 3, 6 months from the start of therapy. Then after 1 and 2 years, while maintaining residual effects.The observation protocol included an assessment of the neurological status, an assessment of the cross-sectional area, electrophysiological and biochemical parameters.

including standing and walking on toes and heels, the study of tendon reflexes using a neurological hammer. The treatment was considered effective if, already during therapy or immediately after, an improvement in neurological status was recorded with a short plateau period or its absence. Therapy was considered ineffective if the patient's condition continued to deteriorate despite treatment.

3. Neurophysiological research methods. An electroneurophysiological study was performed using a Neurosoft device (Russia). The technique for studying motor fibers consisted in stimulating the motor points of peripheral nerves (the areas where the nerve is located closest to the skin surface) with rectangular pulses of 0.05-0.5 ms duration with a bipolar stimulating electrode, where the cathode is located distal to the anode (antidromic method of electrical stimulation).

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The stimulation frequency did not exceed 0.5-1/s. Above-threshold stimulation led to the appearance of a muscle response (M-response), which was recorded by cutaneous cup silver-chloride electrodes filled with contact paste. When examining the tibial nerve, the recording electrodes were located as follows: active - on m. abductor hallucis, reference - 2 cm distal, a grounding tape electrode was attached around the lower third of the leg. The study included an assessment of the conduction and characteristics of the evoked motor response during abduction from the standard muscles of the hand and foot during stimulation of the motor fibers of the main nerves - the median, ulnar, peroneal, tibial nerves from both sides, the sensory action potential from the median and gastrocnemius nerves, F-wave. 4. Biochemical research methods. Biochemical research was carried out on the equipment DiruiCS-300B, which is characterized by a capacity of up to 300 tests per hour. The examination included the study of calcium, magnesium and phosphorus, as well as the content of ALT (alanine transferase), AST (aspartate transferase), CPK (creatine phosphokinase), LDH (lactate dehydrogenase) and alkaline phosphatase in sick children before and after the therapy and compared with healthy children.

5. Statistical research methods. All mathematical calculations necessary for writing this work were carried out by the author independently on a personal computer using the Microsoft Office Excel 2003, Biostat software package and the STATISTICA applied medical statistical program. Quantitative parameters in the work are presented as a mean value, standard deviation, median, 5th and 95th percentiles and minimum (Min) and maximum (Max) values, the Spearman and Pearson correlation coefficient was calculated depending on the nature of the sample distribution. Significant differences between two independent variables were determined for parametric methods using the Student's t-test, for non-parametric data using the Mann-Whitney test (U-test). Compliance with the criteria for the normal distribution of the sample was assessed using the Kolmogorov-Smirnov and Shapiro-Wilke test. For samples with a normal distribution, a one-way analysis of variance was performed to assess the relationship between several independent variables and one orthogonal factor. To search for the reproducibility of the obtained data, the intraclass correlation method was applied. When conducting a statistical analysis of the results obtained, digital materials were combined into time series, which were analyzed according to their main indicators. The differences were considered significant at the 95% probability threshold ($p < 0.05$).When conducting statistical data processing and interpreting the results, we took into account modern international requirements for the provision of statistical analysis results in articles and dissertations for a degree.

Statistical processing was supplemented by using the Student-Fisher test, taking into account the parameter of equality of variances. As a characteristic of the boundaries of expected deviations, a 95% confidence interval was calculated.

We also used the criterion Wilconson for intergroup comparisons of significance and the Mann-Winney test for unrelated samples. The critical level of significance of the tests was determined at $p \leq 0.05$. To achieve the set goal and objectives, 60 patients with various types of peripheral neuropathies were examined. The control group consisted of 30 perfectly healthy children without hereditary pathology.The main group was divided into 2 subgroups: 30 children with hereditary motosensory neuropathy and 30 children with spastic-diplegic cerebral palsy. The age of sick children ranged from 5 to 14 years. All subjects underwent a thorough preliminary anamnestic and clinical selection, which was carried out using the method of stratified randomization using inclusion / exclusion criteria.The sample size for analyzing the reasons for refusal of treatment by patients was approved according to WHO recommendations (2019).

To conduct an exploratory study and identify possible refusals of patients from treatment, a special questionnaire was developed, which includes, along with passport data (name, age, gender, place of residence, profession), questions about past and concomitant diseases, eating habits, bad habits).As a result of the studies, it was found that most often patients complained of progressive muscle weakness in the distal parts of the arms and legs (85%), deformity of the feet (74%), impaired sensitivity (dysergia) - 78%.

As a result of the anamnesis, the following parameters were established: the duration of the disease in the main group and the comparison group averaged 6.3±2.4, 5.3±1.8, respectively; the social level averaged 1.8±0.7, 2.1±0.9 at a rate of 2.1±1.0; physical activity averaged 0.52±0.46, 0.64±0.35 at a rate of 0.61±0.37.

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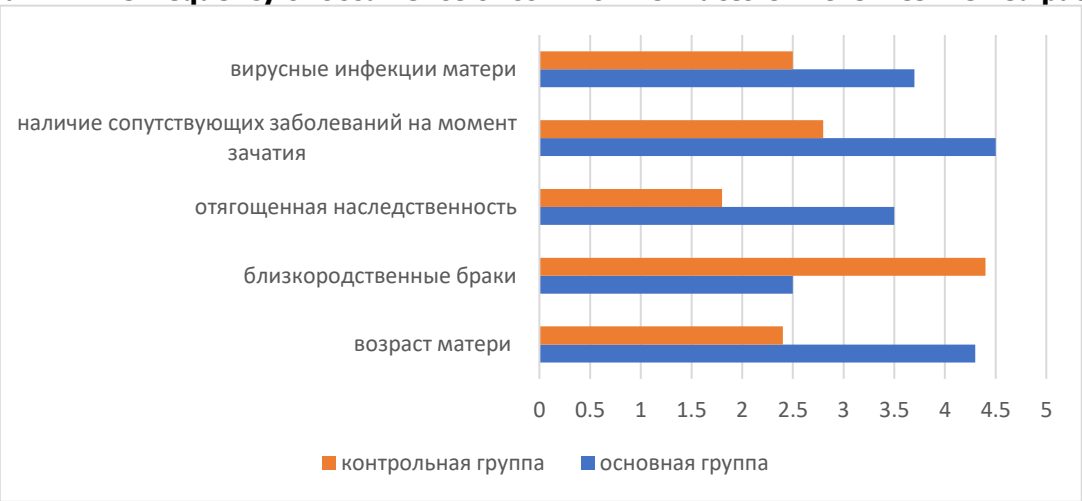
Diagram 1. The frequency of occurrence of common risk factors in the interviewed patients



After analyzing the results of treatment, it can be revealed that the reasons for refusing treatment in many cases were due to insufficiently accurately collected anamnesis (86.7%), which led to the absence of repeated electroneuromyographic studies (76.9%), proving the remission of the disease and due to this and the lack of control over treatment (81.2%).

In this diagram, it is noted that hereditary motor-sensory neuropathies and the consequences of neuroinfection have an average frequency of distribution, on average occupying 54.37% of the most common nosological diagnoses. Moreover, multifocal motor neuropathy ranks last according to the case histories that we studied for 2011-2021.

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