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Therapeutic Stimulation Electroneuromyographic Therapy for Muscle Atrophy in Patients with Hemophilia

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Abstract: ***The last decades have been marked by a breakthrough in the study of the molecular genetic basis of spinal muscular atrophy, which has significantly improved the diagnosis and treatment of these diseases and served as a platform for the development of innovative therapeutic approaches with the ability to modulate a genetic defect. Given the limited availability of etiotropic methods for the treatment of spinal muscular atrophy, traditional approaches to therapy aimed at the pathophysiological mechanisms of the development and course of the disease retain their proven effectiveness, which, in turn, dictate the need for their improvement and increase in effectiveness.***
Keywords: spinal muscular atrophy, RHS and MHS scales, electromyography, therapy

I. INTRODUCTION

It is well known that progressive neuromuscular pathology of childhood is a difficult to treat group of hereditary degenerative diseases with severe statomotor dysfunction leading to disability. A special category in the structure of such diseases are patients with spinal muscular atrophy (SMA), which is characterized by progressive degeneration of motor neurons of the spinal cord as a manifestation of a homozygous mutation (deletion/conversion) of SMN1, the “survival motor neuron gene 1” [2]. Increased attention to SMA is due to a steady increase in the number of patients with this disease [3]. The prevalence of proximal SMA is on average 5.5 per 100 thousand of the population, in newborns it is 1 per 6–10 thousand The frequency of heterozygous carriage is 1 per 40–60 people. The incidence of SMA type 1 (Werdnig-Hoffmann disease) is 6 per 100,000, with a prevalence in the range of 0.04–0.28 per 100,000. The incidence of SMA type 2 (intermediate form) and type 3 (Kugelberg-Welander disease) is calculated on average as 10.6 per 100 thousand, with a prevalence of 1.5 per 100 thousand. And the main reason for the indicated neuroepidemiological situation is the medical and social aspects of survival and adaptation of previously difficult-to-treat patients with severe variants of SMA [8]. The successes of modern molecular genetic diagnostics, additional methods of highly informative instrumental studies have served as a platform for the creation of large-scale clinical trials. One of these areas is targeted therapy using “small molecules” aimed at replacing the SMN1 gene with viral vectors and other disease-modifying agents. According to current data, in this therapeutic segment, the method of using a self-complementing adeno-associated virus type 9 (scAAV-9) as a vector for the SMN1 transgene is promising. According to literature data, a patented drug of this type is AVXS-101. Based on the preliminary positive results of multicenter placebo-controlled studies, relatively recently in the Russian Federation, the USA and in a number of European countries, the antisense oligonucleotide "Spinraza" was proposed and recommended as an etiotropic therapy as an effective means of modulating the alternative splicing of the SMN2 gene, functionally modifying it in SMN1, which in aggregate, according to preliminary results, restores the functioning of motoneurons, preventing their degeneration [3]. Despite promising achievements in the field of etiotropic treatment, the targets have not been fully achieved, and given the peculiarities of intrathecal drug administration, the mechanisms of infrastructural organization have not been finalized, which limits the usefulness of measures in this segment of long-term therapy. But at the same time, taking into account the trajectory of the natural course of the disease, characterized by degeneration of motor neurons of the spinal cord, atrophy of skeletal muscles, and generalized weakness, the control and prescription of pathogenetically targeted proactive personalized palliative treatment of SMA are relevant in the context of early detection of pathological symptoms and preservation of the functional capabilities of patients. Purpose of the study is to determine the effectiveness of proactive tactics for the treatment of patients with SMA, based on the analysis of electromyographic (EMG) data using verified scales for assessing the functional capabilities of patients, in comparison with traditional approaches to the management of children with this pathology.

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II. METHODS

The design of the work is based on a prospective cohort study conducted on the basis of the Republican Clinical Center for Neurorehabilitation of the Ministry of Health of the Donetsk People's Republic, which is a state institution and has been engaged in the rehabilitation of children with organic pathology of the nervous system for more than 30 years. Under our supervision for 15 years were 95 children (66 boys and 29 girls) with a genetically confirmed diagnosis of proximal SMA from the Donetsk region and other regions of Ukraine, as well as neighboring countries. The diagnosis of SMA was based on typical clinical symptoms, electromyography data and was necessarily confirmed by the results of a molecular genetic study, which was carried out at the Federal State Budgetary Scientific Institution “Medical Genetic Research Center named after academician N.P. Bochkov” and the Medical Genetic Center "Genomed".

According to the developed model, patients were divided into 2 groups. Patients of the main group, which included 65 children (68.4%), regularly, at the established time intervals, underwent clinical diagnostic examination. The concept of treatment was based on the principles of a personalized approach using proactive complex step-by-step therapy with the determination of the leading pathological pattern that determines the severity of motor disorders and the level of functionality based on the results obtained during clinical and electromyographic monitoring. Children from the comparison group (30 children (31.6%)) received conventional symptomatic therapy, including medications that improve the course of metabolic processes in muscles in age-specific dosages (group B vitamins, neuropeptides, carnitine-containing compounds), cholinotropic agents, classical massage, physiotherapy treatment. The dynamics of the course of the pathological process was also assessed according to the results of clinical and electromyographic monitoring at time intervals similar to the main group. The number of patients included in the study was determined by the number of children hospitalized in the neurorehabilitation department. The smaller sample size in the comparison groups is due to the intention to provide effective care to a larger number of patients due to the orphan nature of the disease.

According to the developed design of the study, the level of evaluation of functional capabilities and EMG data was carried out through standardized time ranges with a control mark (“Initial data”, “1 year”, “3 years”, “5 years”). In the early stages of the disease, the treatment regimen for children from the main group included microdoses of compounds with a metabolic effect (meldonium, acetyl-L-carnitine - 0.5–1 ml Nos. 10–15). A progressive decrease in functional capabilities in the motor sphere was the basis for an additional reflex effect on the zones of cervical and lumbar anatomical thickenings using mesopuncture methods containing doses of neuropeptides (1 ml No. 500 mg/day. When a concomitant axonal lesion was detected, drugs containing the active substance ipidacrine (5–20 mg/day) were prescribed. In cases of progression of the identified changes in peripheral nerve fibers, a course of actovegin (50–200 mg/day) was recommended along with thioctic acid compounds (40–80 mg/day) for up to 50–70 days. The electromyographic pattern of myogenic lesions dictated the need to include in the treatment regimen therapy with combined metabolic properties (citrulline malate: 0.5-1 mg/day - up to 1 month; ubiquinone: 2 mg/kg/day - up to 3 months). With the progression of such changes, a course of parenteral administration of phosphocreatine at age-specific dosages of 50–100 mg/day was carried out. The rehabilitation treatment scheme included an adapted massage with elements of stretch gymnastics with an emphasis on the development of less affected areas of the muscular apparatus of the limbs with the recommended quarterly course. With the initial symptoms of scoliosis, it was recommended to use soft orthotics, physiotherapeutic methods of influence, including a mechanized manual bed, vacuum stimulation, point injection of microdoses (0.5–2 ml No. 10–15) of neuropeptides (Cerebrolysin, Cortexin). When the degree of scoliosis worsened for a long period, an individualized rigid orthosis for the back was prescribed, additional courses of soft manual therapy were carried out, a course of paravertebral electrophoresis with B vitamins (thiamine chloride - 1–2 ml every other day No. 5 in combination with pyridoxine - 1– 2 ml No. 5 every other day) in combination with oral intake of cholecalciferol (500–1000 IU/day) [6].

The proposed concept of a personalized approach to the management of children with SMA made it possible to slow down the rate of progression of the disease and maintain a higher level of patients' motor abilities. A deep analysis of the EMG data made it possible to timely detect secondary neurogenic and myogenic lesions, which made it possible to correct them in different directions.

III. RESULTS

On the basis of phenotypic variation, the compared groups were differentiated into SMA type 2 (54 children: 40 (74.1%) patients were the main group, 14 (25.9%) patients were the comparison group) and SMA type 3 (41 patients: 25 (61.0%) - main group, 16 (39.0%) - comparison group). The time interval from the onset of SMA to admission of the patient to the study in the main groups of SMA type 2 was 3.50 ± 0.64 months, SMA type 3 — 6.12 ± 3.03 months, in the comparison group SMA 2 type - 3.86 ± 0.66 months. ($p = 0.7968$), type 3 SMA — 6.12 ± 1.75 months. ($p = 0.8517$). The age range of the study participants was: 1–3 years old — 68 children (71.6%), over 3 years old — 27 patients (28.4%).

The follow-up period was 5.3 ± 0.4 years. Inclusion criteria for the study were age from 1 to 12 years, a genetically determined form of proximal SMA with an autosomal recessive type of inheritance, compliance with the clinical phenotype of SMA type 2 and SMA type 3. The exclusion criteria were the presence of severe somatic pathology, the refusal of parents or legal representatives from the study. According to the consensus reached by international experts from SMA Europe, the European Neuromuscular Consortium, SMN1/SMN2 genetic testing is a highly reliable method and belongs to the first-line examinations for suspected SMA. As part of a genetic examination, the patients underwent a study of the locus of the short arm of the 5th chromosome of the SMN gene. The greatest differences between the studied groups were revealed when studying the type of genetic mutation. The 0/SMN1 genotype, indicating a deletion on one allele and an intragenic mutation on the other allele, was identified in two children with type 2 SMA. In the SMA type 3 group, no such mutation was detected during the entire period of the study. Homozygous deletion (conversion) of exon 7 and/or exon 8 of SMN1 (genotype 0/0) was detected significantly more often in patients: this type of mutation in children of the SMA type 2 group was 96.3%, in patients with SMA 3 -th type - 100%. Of interest are the results of the genetic analysis of the parents of patients with type 2 and 3 SMA, in which the deletion of the heterozygous exon 7 of SMN1 prevailed, accounting for 94.3% of all studies. The cis-configuration, which indicates the presence of two or more copies of the 7th exon on one chromosome, was diagnosed much less frequently.

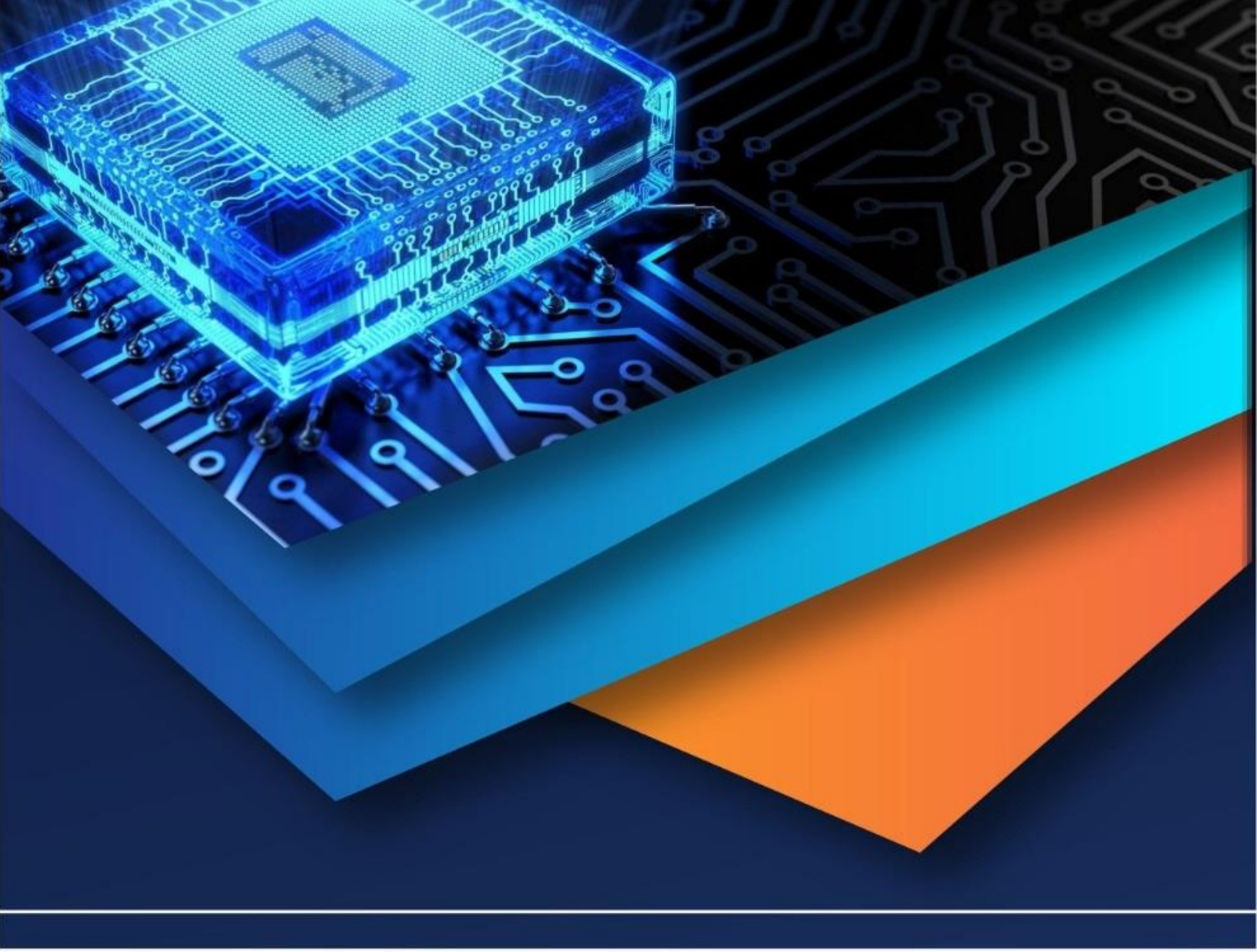
IV. CONCLUSION

A combinatorial personalized clinical and electromyographic approach to choosing a treatment strategy and evaluating the effectiveness of therapy for statomotor disorders, taking into account the staging of the disease and the progression trajectory, active and systematic monitoring contribute to a pathogenetically substantiated differentiated selection of therapy. Dynamic monitoring of the course of SMA, taking into account the characteristics of the clinical pattern, adequate management tactics at various stages of the disease, helps to slow down the rate of progression of the disease and the development of complications, which positively affects the motor abilities of patients. In this regard, the problem of early diagnosis of SMA is of paramount importance, which makes it possible to determine in a timely manner the strategy of therapeutic measures, including modern possibilities of gene therapy.

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