DIAGNOSTIC AND TREATMENT METHODS

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INITIAL CLINICAL MANIFESTATIONS AND PREMORBID FEATURES OF VARIOUS PHENOTYPIC VARIANTS (II, III) OF SPINAL MUSCULAR ATROPHY

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Relevance. Spinal muscular atrophy (SMA) is one of the important problems of practical public health due to diagnostic errors and late verification of the initial symptoms of the disease. Insufficient attention is paid to the study of various aspects of the early clinical diagnosis of SMA. An unqualified approach to the interpretation of normal and abnormal neurological status, unidirectional and “stereotyped” actions of a doctor lead to an erroneous interpretation of semiotics and syndromology of motor disorders.

Purpose. To study the initial symptoms and premorbid background in children with SMA II and III types.

Material and methods. On the basis of the Republican Neurorehabilitation Clinical Center (Donetsk), 95 children with SMA were examined, including 66 boys (69.4%) and 29 girls (30.6%). In order to study the possibility of early diagnosis and taking into account the importance, we retrospectively studied the features of the SMA onset in children. In studying life and disease anamnesis, attention was paid to the premorbid features in the clinical and neurological status of early childhood. The concomitant neurological symptoms were studied.

Conclusions. Careful assessment of family history, clarification of manifestations, rate of progression and interpretation of motor disorders in the disease onset are leading factors in early clinical diagnosis of SMA.

Keywords: spinal muscular atrophy, children, initial symptoms, premorbid features.

Introduction. Spinal muscular atrophy is a severe progressive disease developing in the early childhood, the leading etiological factor of which is homozygous deletion of the telomere copy of the SMN gene [1]. The disease is characterized by progressive degeneration and irreversible loss of the spinal cord motor neurons, associated with severe motor disorders and disability [5]. Over the past two decades, significant progress has been made in the study of the molecular-genetic foundations of SMA, which has significantly improved the diagnosis and treatment of these diseases and served as a platform for the development of innovative therapeutic approaches to SMA with the ability to modulate the genetic defect [4]. Nevertheless, there is a great heterogeneity in terms of clinical response to currently available treatment methods, ranging from lack of response to impressive results [6]. There is the generally accepted point of view, that efficacy is improved when treatment is initiated before symptom onset [9]. Thus, research on the problems of hereditary neuromuscular diseases in the leading European centers, including the Department of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium; MDUK Neuromuscular Center, Department of Pediatrics, University of Oxford, Oxford, UK, show that innovative therapeutic approaches, regardless of the pathogenetic routes of action, are more effective when patients are treated before or shortly after symptoms rather than later in the disease [3, 4]. It has been suggested that this concept is relevant for all types of treatment, including a variety of drug and non-medical interventions [8]. Therefore, early identification of basic clinical and neurological symptoms, the study of potential factors that inspire the debut of the disease from the perspective of proactive measures aimed at preventing accelerated progression and development of disability is one of the priorities in the segment of SMA.

Research Objective: to study early symptoms and premorbid features of the clinical and neurological status of SMA types II and III children.

Research material and methods. Study was conducted at Republican Neurorehabilitation Clinical Center (Donetsk), 95 children with SMA were examined, including 66 boys (69.4%) and 29 girls (30.6%). Clinical and neurological (anamnesis of the disease, study of neurological status), molecular genetic, functional (electroneuromyography) and statistical methods of study were used.

Inclusion criteria - age from 1 to 12 years, genetically verified form of proximal SMA with autosomal recessive type of inheritance, compliance with clinical phenotype of intermediate SMA (II) or Kugelberg-Welander disease (III), absence of severe concomitant somatic pathology. Exclusion criteria - age under 1 year and over 12 years, absence of molecular genetic testing or genetically non-verified proximal form of SMA with autosomal recessive type of inheritance, patients with SMA of Werdnig-Hoffmann (I) and SMA IV, presence of severe somatic pathology, refusal by the child's parent or legal representative to participate in study.

According to modern recommendations for verification of the SMA phenotype [4, 5] SMA type II was found in 54 (56.8%) children and type III - in 41 (43.2%) patient.

We also reviewed current literature on features of SMA onset in children to establish possible methods of early diagnosis.

According to the consensus statement by international experts from SMA Europe, the European Neuro-Muscular Consortium, the genotype of mutation and the number of copies of SMN2 must be studied in patients as part of genetic screening. Furthermore, parents of patients must also be screened for carrying SMN1 deletion mutation. Molecular and genetic studies were carried out at the "Medico-Genetic Scientific Center" (Moscow), Medico-Genetic Centre "Genomed" (Rostov), Institute of Molecular Biology and Genetics of NASU (Kyiv, Ukraine).

Electromyographic study, including surface, stimulating, needle electromyography ("Neuro-MVP-micro", "Neurosoft", Russia) was conducted to clarify the pathophysiological mechanisms of the

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formation of motor disorders in patients with SMA.

The statistical analysis was carried out by methods of variation statistics on PC using Statistica 10.0 application package (Statsoft Inc., USA). For quantitative indicators the average value (M) and its standard error (±m) were calculated, for qualitative values relative shares (P, %) were calculated.

The study was approved by the local ethical committee of Republican Neurorehabilitation Clinical Center (Protocol № 3-9/19 dated 13.04.2011). Parents or legal representatives of patients were acquainted and informed about the aims, nature, diagnostic procedures and gave voluntary informed consent.

RESULTS AND DISCUSSION. The results of molecular genetic studies are presented in Tables 1-3.

The features of SMA onset in children were retrospectively studied in order to study the possibility of early diagnosis and taking into account the importance. The first symptoms occurred in the age range from 7 months to 7 years. In our studies the development of SMA at the age under 1 year (8.4±1.1 months) was noted in 22 children (23.2%), from 1 to 3 years (20.1±7.5 months) - 53 (55.8%), over 3 years (41.9±4.0) - 20 children (21%). Thus, the first symptoms of the disease more often occurred at the age of 1 to 3 years.

Parents associated the development of clinical manifestations of the disease with recent acute respiratory viral infection, in 28 children (29.5%), with DPT vaccination in 19 patients (20%), in 3 (3.2%) the first symptoms were preceded by anxiety, stressful situations in kindergartens or at home. In the remaining 45 children (47.4%), the onset could not be linked to any external cause.

Thus, the immune response dysregulation factor played a role in the disease onset, which necessitated further research in this direction for preventive purposes in order to delay the SMA onset, thus determining a higher level of functionality before the onset of the disease.

The study of life and disease anamnesis focused on pre-morbid features of clinical and neurological status (Table 4).

According to the draft of the study, early clinical and neurological manifestations of various phenotypic SMA variants were specified (Table 5).

At present, doctors have quite a wide range of diagnostic possibilities [2, 7], but unfortunately, the frequency of diagnostic errors and late verification of initial symptoms of the disease remains high. These problems are determined by a lack of awareness among primary-care practitioners, which in turn is attributed to absence of definite clinical pattern specifically developed for primary care environment that would lead to suspecting early manifestations of SMA and identifying leading symptoms [4]. Children are often observed for a long time at home for perinatal encephalopathy with motor disorders or muscle hypotension syndrome, hip

Таблица 1

Mutation genotypes in patients with SMA type II and III

SMA type, number of patients	Gene mutation type	
	genotype 0/0	genotype 0 / SMN1^{m}
SMA type II (n=54)	51 (94.4 %)	3 (5.6 %)
SMA type III (n=41)	40 (97.6%)	1 (2.4%)

Note: Genotype 0/0 - homozygous deletion (conversion) of exon 7 and/or 8 exon SMN1; genotype 0 / SMN1^{m}- deletion on one allele and intragenic mutation on the other allele.

Table 2

Number of SMN2 copies in children with SMA II and III types

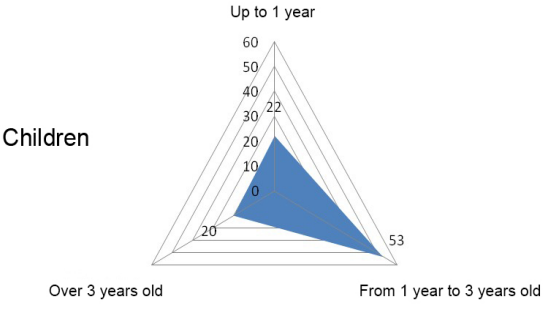
SMA type, number of patients	Число копий SMN2, n (%)		
	2	3	4
SMA type II (n=54)	3 (3.9 %)	46 (85.2 %)	5 (10.9 %)
SMA type III (n=41)	-	15 (36.6 %)	26 (63.4 %)

Table 3

Genetic analysis of parents of type II and III SMA patients

Number of surveyed parents of SMA patients	Вариант носительства делеции SMN1, n (%)	
	Heterozygous exon 7 SMN1 deletion	Presence of two or more copies of exon 7 SMN1 on one chromosome (cis configuration)*
122	115 (94.3 %)	7 (5.7 %)

Note: * Diagnosed using multiplex probe amplification.



The dependence of the incidence of SMA on age

Table 4

Clinical and neurological symptoms before the initial manifestations of SMA (n=95)

Clinical manifestations	Number	%
Hip dysplasia	90	94.7
Hypermobile joint syndrome	88	92.6
Valgus/varus foot	75	78.9
Early speech development	56	58.9
Poor weight gain	45	47.3
Slowly starting child	36	37.9
Slumped when seated	44	46.3

Table 5

Initial manifestations of SMA different variants in children (n=95)

Symptoms	SMA II type (n=54)		SMA III type (n=41)	
	абс.	%	абс.	%
Limited range of active movements in the extremities	50	92.6	18	43.9
Restrictions and movement disorders, frequent falls, tripping, fatigue	23	42.6	41	100
Hard to go up and down the stairs	6	11.1	32	78
Tongue fasciulation + intention tremor	48	88.9	7	17.1
Reduced hand agility	49	90.7	6	14.6
Weakness and hypotrophy of shoulder belt and upper torso muscles	49	90.7	3	7.3
Weakness and hypotrophy of thigh and pelvic belt muscles	11	20.4	34	82.9
Muscle cramps	3	5.6	27	65.9
Spinal column deformity	47	87	22	53.4

dysplasia, flatfoot or valgus foot deformity [1]. Such mistakes in diagnostics, on the one hand, can be explained by untimely examination, absence of dynamic follow-up, wrong differentiation of normal and abnormal neurological status, insufficient knowledge of primary semiotics and SMA syndromology by primary care neurologists, erroneous interpretation of anamnesis data, and on the other hand - unidirectionality and cliché actions of doctors are also associated with erroneous interpretation of semiotics and syndromology of motor disorders.

Conclusions. Careful assessment of family history, clarification of manifestations, rate of progression and interpretation of motor disorders in the disease onset are the leading factors of early clinical diagnosis of SMA, that allow consider the further development of motor symptoms and complications that aggravate condition of a sick child and affect the vital prognosis.

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