УДК 616.74-009.55-02:616.832.21
DOI: https://doi.org/10.17816/PAVLOVJ100672

Комплексная нейропсихиатрическая и лабораторно-инструментальная диагностика в определении тактики терапевтического ведения пациентов со спинальной мышечной атрофией: региональный опыт

А. Я. Гайдук[1, 2]✉, П. Камминг[3], В. В. Черникова[4], Я. В. Власов[4], Д. А. Смирнова[1, 5]

[1] Международный научно-образовательный центр нейропсихиатрии, Самара, Российская Федерация;
[2] Научно-исследовательский институт организации здравоохранения и медицинского менеджмента Департамента здравоохранения города Москвы, Москва, Российкая Федерация;
[3] Университет Берна, Берн, Швейцария;
[4] Самарский государственный медицинский университет, Самара, Российская Федерация;
[5] Национальный медицинский исследовательский центр психиатрии и неврологии имени В. М. Бехтерева, Санкт-Петербург, Российская Федерация

АННОТАЦИЯ

Введение. Спинальная мышечная атрофия (СМА) — редкое наследственное инвалидизирующее заболевание и наиболее частая наследственная причина смертей младенцев. Своевременная комплексная диагностика СМА позволяет планировать терапевтическую тактику и сохранять качество жизни пациентов. Одной из задач этой работы явился обзор актуальных данных литературы на тему этиопатогенеза, клинической картины, валидной диагностики и современной эффективной тактики ведения СМА.

Цель. Оценить тактики ведения пациентов со СМА с учётом нейропсихиатрической симптоматики, проанализировать проблемы организации и предложение мероприятий, направленных на повышение качества оказания медицинской помощи, на основании практического опыта Самарской области и с учетом современного состояния проблемы.

Материалы и методы. В работе проанализированы данные архива Самарской областной клинической больницы имени В. Д. Середавина, обработано 132 истории болезни 77 пациентов с датами выписки с января 2008 г. по февраль 2022 г. с диагнозами (по шифру Международной классификации болезней и проблем, связанных со здоровьем, 10-го пересмотра (МКБ-10)): G12.0 (детская СМА, I тип [Верднига–Гоффмана]), G12.1 (другие наследственные СМА), G12.8 (другие СМА и родственные синдромы) и G12.9 (СМА неуточненная). Проведен анализ результатов клинических, лабораторных, инструментальных и нейропсихологических диагностических методов в сопоставлении с тактикой терапевтического ведения этих пациентов. Для статистической обработки данных применялись методы дескриптивной статистики.

Результаты. *Социодемографические данные.* На февраль 2022 г. зарегистрировано 58 пациентов (средний возраст — 38,4 (41,3) года), из них 32 (55,2%) человека — лица женского пола, в том числе 21 ребёнок (средний возраст — 12,3 (7,4) года, 14 (24,1%) девочек), с диагнозами по МКБ-10: G12.0 (n = 7; 12,0%; только дети), G12.1 (дети: n = 14; 24,1%; взрослые: n = 29; 50,0%), G12.8 (n = 6; 10,3%; только взрослые), G12.9 (n = 2; 3,4%; только взрослые). *Клинические данные.* Моторные нарушения от лёгкого проксимального нижнего парапареза (n = 13; 22,4%) до выраженного тетрапареза (n = 7; 12,0%). Исследование психического статуса ограничивалось оценкой состояния сознания и продуктивности контакта. *Данные о терапии.* До 2021 г. в регионе поводилась симптоматическая терапия СМА, с марта 2021 г. нусинерсен получали 8 детей (13,8% от общей выборки) в возрасте 7,3 (8,8) года, рисдиплам — также 8 детей (13,8%) в возрасте 9,5 (6,9) года; родители еще 3-х детей (5,2%) возрастом 7,5 (2,4) года отказались от приема препаратов. Из числа взрослых пациентов (n = 37; 63,8%; 35,3 (23,6) года) с подтверждённой СМА 5q (n = 10; 17,2%, 35,3 (19,0) года) нусинерсен получал 1 пациент, остальные 9 взрослых (15,5%) не получали терапию, 3 (5,2%) добивались права (на момент поведения анализа) получать препараты.

Заключение. Анализ данных выявил дефицит ранней диагностики СМА (все диагнозы поставлены пациентам с уже выраженной симптоматикой), оценки аффективных и когнитивных нарушений, мониторинга эффективности лечения (отсутствие валидизированных шкал оценки моторных навыков), а также показал низкую доступность терапии для взрослых пациентов, что требует реорганизации в регионе помощи пациентам со СМА с учетом выявленных факторов.

Ключевые слова: *спинальная мышечная атрофия; наследственные нервно-мышечные заболевания; нейропсихологическое исследование; биомаркеры; патогенетическая терапия; нусинерсен; рисдиплам*

Для цитирования:
Гайдук А.Я., Камминг П., Черникова В.В., Власов Я.В., Смирнова Д.А. Комплексная нейро-психиатрическая и лабораторно-инструментальная диагностика в определении тактики терапевтического ведения пациентов со спинальной мышечной атрофией: региональный опыт // Российский медико-биологический вестник имени академика И.П. Павлова. 2022. Т. 30, № 3. С. 323–334. DOI: https://doi.org/10.17816/PAVLOVJ100672

Рукопись получена: 14.02.2022 **Рукопись одобрена:** 17.05.2022 **Опубликована:** 30.09.2022

DOI: https://doi.org/10.17816/PAVLOVJ100672

Complex Neuropsychiatric and Laboratory-Instrumental Diagnostics in Determination of Tactics of Therapeutic Management of Patients with Spinal Muscular Atrophy: Regional Experience

Arseniy Ya. Gayduk[1, 2✉], Paul Cumming[3], Viktoriya V. Chernikova[4], Yan V. Vlasov[4], Dar'ya A. Smirnova[1, 5]

[1] International Centre for Education and Research in Neuropsychiatry, Samara, Russian Federation;
[2] Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department, Moscow, Russian Federation;
[3] University of Bern, Bern, Switzerland;
[4] Samara State Medical University, Samara, Russian Federation;
[5] V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, Saint-Petersburg, Russian Federation

ABSTRACT

INTRODUCTION: Spinal muscular atrophy (SMA) is a rare hereditary disabling disease and the most common hereditary cause of infant deaths. The timely comprehensive diagnosis of SMA permits to plan therapeutic tactics and preserve the quality of patients' life. One of the objectives of the given work is a review of the actual literature data on etiopathogenesis, clinical presentation, valid diagnosis and modern effective tactics of SMA management.

AIM: To evaluate the management tactics of patients with SMA taking into account neuropsychiatric symptoms, to analyze problems of proposal and organization of measures aimed at improvement of the quality of medical care, on the basis of the practical experience of the Samara region and with consideration of the current state of the problem.

MATERIALS AND METHODS: In the work, the data of the archive of Seredavin Samara Regional Clinical Hospital were analyzed, 132 medical histories of 77 patients were processed with discharge dates from January 2008 to February 2022 with the following diagnoses (according to the code of the International Classification of Diseases and Health Related Problem, 10th revision (ICD-10)): G12.0 (spinal muscular atrophy, type I [Werdnig–Hoffmann disease], G12.1 (other hereditary SMA), G12.8 (other SMA and related syndromes) and G12.9 (unspecified SMA). The analysis of the results of clinical, laboratory, instrumental and neuropsychiatric diagnostic methods was performed in comparison with the tactics of therapeutic management of these patients. For statistical processing of the data, methods of descriptive statistics were used.

RESULTS: *Socio-demographic data.* As of February 2022, 58 patients were registered (mean age 38.4 (41.3) years, of them 32 (55.2%) were individuals of female gender including 21 children (mean age 12.3 (7.4) years, 14 (24.1%) girls), with the following diagnoses according to ICD-10: G12.0 (n = 7; 12.0%; only children), G12.1 (children: n = 14; 24.1%; adults: n = 29; 50.0%), G12.8 (n = 6; 10.3%; only adults), G12.9 (n = 2; 3.4%; only adults). *Clinical data.* Motor disorders from a mild proximal lower paraparesis (n = 13; 22.4%) to pronounced tetraparesis (n = 7; 12.0%). The study of mental status was limited to evaluation of the state of consciousness and effectiveness of contact. *Data on therapy.* Until 2021, symptomatic therapy of SMA was conducted in the region, since March 2021, 8 children (13.8% of the total sample) aged 7.3 (8.8) years received nusinersen, another 8 children (13.8%) aged 9.5 (6.9) years received risdiplam; parents of 3 more children (5.2%) refused taking drugs. Of adult patients (n = 37; 63.8%; 35.3 (23.6) years) with confirmed SMA 5q (n = 10; 17.2%, 35.3 (19.0) years), 1 patient received nusinersen, the rest 9 patients (15.5%) did not receive therapy, 3 (5.2%) were achieving the right to receive drugs (at the moment of the analysis).

CONCLUSION: The data analysis revealed deficit of early SMA diagnosis (at the moment of the diagnosis, all the patients were already having pronounced symptoms), of assessment of affective and cognitive disorders, monitoring of treatment effectiveness (absence of validated scales for motor skills assessment), and also showed low availability of treatment for adult patients, which requires reorganization of care of patients with SMA in the region taking into account the revealed factors).

Keywords: *spinal muscular atrophy; hereditary neuromuscular diseases; neuropsychiatric study; biomarkers; pathogenetic treatment; nusinersen; risdiplam*

For citation:
Gayduk AYa, Cumming P, Chernikova VV, Vlasov YaV, Smirnova DA. Complex Neuropsychiatric and Laboratory-Instrumental Diagnostics in Determination of Tactics of Therapeutic Management of Patients with Spinal Muscular Atrophy: Regional Experience. *I.P. Pavlov Russian Medical Biological Herald.* 2022;30(3):323–334. DOI: https://doi.org/10.17816/PAVLOVJ100672

Received: 14.02.2022 **Accepted:** 17.05.2022 **Published:** 30.09.2022

ECO•VECTOR

LIST OF ABBREVIATIONS

ALAT — alanine aminotransferase
ASAT — aspartate aminotransferase
CHOP-INTEND — the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CPK — creatine phosphokinase
ENMG — electroneuromyography
HFMSE — the Hammersmith Functional Motor Scale Expanded
HINE — the Hammersmith infant neurological examination
ICD-10 — International Classification of Diseases and Related Health Problems of 10th edition
LDG — lactate dehydrogenase
MFM — Motor Function Measure
MLPA — Multiplex Ligation-dependent Probe Amplification
MRI — magnetic resonance imaging
NF — neurofilaments
NGS — Next generation sequencing
qMRI— quantitative magnetic resonance imaging
RF — Russian Federation
RULM — Revised Upper Limb Module
SMA — spinal muscular atrophy
SMN — survival of motor neuron protein
SMA 5q — spinal muscular atrophy induced by mutation in SMN1 gene on the long arm of the 5th chromosome
TIMP — the Test of Infant Motor Performance Screening Items
US — ultrasound examination
VEM – vital and essential medicines
Wee-FIM — Functional Independence Measure for Children
WISC-V — Wechsler Intelligence Scale for Children
6MWT — 6-Minute Walk Test

INTRODUCTION

Spinal muscular atrophy (SMA) is a genetically heterogenous group of hereditary diseases of the central nervous system caused by degeneration and death of motor neurons of the anterior horns of the spinal cord and motor nuclei of the cranial nerves. The disease is characterized by *loss of motor skills, gradual development of symmetric flaccid paralysis and atrophy of the striated muscles including respiratory, pharyngeal and cardiac muscles* [1]. SMA affects children more often than adults and is the most common cause of infant death [2].

The global incidence of SMA is 8.5–10.3 in 100 thousand newborns, carriage frequency is from 1 in 35 to 1 in 60 [3]. The incidence of SMA in the Russian Federation (RF), in general, corresponds to the global one — 1 in 11,000, carriage rate is about 1 in 47 [4]. There are no published scientific data on the prevalence of SMA in the Samara region.

The most common variant of SMA caused by mutations in the *SMN1* gene on the long arm of the 5th chromosome (SMA 5q), results from the deficit of survival of motor neuron (SMN) protein [5] which performs a number of functions associated with embryonic neurogenesis and maturation and transport of ribonucleic acids in the axonal regions of neurons. There also exists the *SMN2* doubler gene located in the same area a bit closer to the centromere region. It differs from the *SMN1* by a single nucleotide which converts 7th exon to splicing enhancer, which leads to more than 10 times reduction of the synthesis of full-sized survival of motor neuron protein [6]. SMA may also occur due to disorders in the interaction of SMN protein with polypeptides of the nucleus and plasma of cell [7]. Mutations leading to SMA, are mainly inherited by autosomal-recessive pattern, but a part of them have an autosomal dominant and X-linked type of inheritance [8]. With the most common cause of SMA — mutation of the *SMN1* gene — the existence of even a large number of copies of the *SMN2* gene does not guarantee production of the proper level of SMN protein, the factor that provides its survival and permits specific gene therapy.

Depending on when regression of motor skills and paresis develop, ***SMA 5q*** is classified into ***five clinical types***: from 0 to 4. According to a number of studies, SMA of these types is not accompanied by pronounced neuropsychiatric manifestations of the disease, in particular, by cognitive and affective disorders [9–11]. At the same time, other works with detailed examinations of mental functions identified certain peculiarities in patients with SMA, for example, reduction of visual and auditory attention and of executive functions in patients with type 1 SMA [12, 13]. Among other alterations in the mental sphere of patients with SMA, subjective fatigue is noted as part of psychasthenia, which correlates with the level of activity [14]. Examination of cognitive functions in adult patients with type 2 and 3 SMA revealed reduction of the intellect in patients with type 3 SMA and reduction of parameters of the working memory and attention in patients with type 2 SMA relative to the control function [15]. A study of spatial-numeric associations in children with SMA demonstrated differences in comparison with healthy children [16]. Most part of the above mentioned works *lack the data on the involvement of mental sphere in development of SMA, with this, the time of studying mental functions in these works was limited*. Besides, the relationship of the levels of biological markers

DOI: https://doi.org/10.17816/PAVLOVJ100672

with cognitive impairment in SMA is insufficiently studied, and, in our opinion, further studies of cognitive endophenotypes of SMA are required. These studies will help differentiate the variants of the course of the disease and approaches to patient management tactics.

To assess motor disorders in patients with SMA, it is recommended using different scales depending on age and individual phenotype (the Hammer smith infant neurological examination, HINE; the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, CHOP-INTENT; Motor Function Measure, MFM; the Hammersmith Functional Motor Scale Expanded, HFMSE; 6-Minute Walk Test, 6MWT; Revised Upper Limb Module, RULM). *None of these scales has yet been validated in the RF* [17]. Effective and cognitive disorders are assessed using the Wechsler Children's Scale (Wechsler Intelligence Scale for Children, WISC-V) of the fifth revision, tests of linguistic intelligence (Batterie d'Evaluation du Language; Test de vocabulary actif e passif; North Syntax screening test), the Raven's Colored and Standard Progressive Matrices, the Kaufman Assessment Battery for Children, the functional independence scale (the Wee-FIM); besides, cognitive functions can also be assessed by tests with selection of pairs of words with use of the eye movement recorder [13].

In view of clinical heterogeneity on the disease, diagnosis of SMA, apart from clinical method, requires a complex of laboratory and instrumental examinations [18]. The most reliable method of laboratory diagnosis remains to be *molecular genetic testing* for the amount of *SMN1 и SMN2* copies using multiplex ligation-dependent probe amplification (MLPA). In literature, there are also described methods of determination of the number of copies of the SMN1 и SMN2 genes using Next generation sequencing (NGS) technologies within the research activities [20, 21].

Currently, no specific biochemical markers have been identified that can be used to judge both the presence, and the course of the disease. According to some works, suitable for monitoring of disease progression and assessment of the effectiveness of treatment are such non-specific analytes as creatine phosphokinase (CPK) and creatinine, involved in energy metabolism of muscle cells [22, 23]. A promising non-specific marker of prognosis of SMA development is considered to be neurofilaments [NF]. With the existing neurodegenerative process, the elevated levels of NF can be found both in blood and in the cerebrovascular fluid, however, their changes can be used for prognosis of the course of the disease and monitoring of the effectiveness of treatment in children, but not in adult patients with SMA [24]. Studies on the search for SMA biomarkers show that there exist other analytes as well, whose levels correlate with the extent of impairment of motor functions [25, 26]. Thus, the cumulative data of plasma biomarkers of SMA can be used to monitor the prognosis of the activity of the disease and effectiveness of treatment.

One of the most sensitive methods for assessing neuromuscular functions is electroneuromyography (ENMG). The works performed using ENMG, evidence changes in electrophysiological parameters in SMA, which correlate with the number of copies of *SMN2* and with the type of SMA, and also correlate with the age of the patient, with the results of the assessment of motor functions, and respond to specific therapy [27, 28]. Diagnosis of SMA is established by such visualization techniques as quantitative magnetic resonance imaging (qMRI) and ultrasound examination (US) of muscles [29, 30]. In general, *imaging methods are not considered effective for monitoring the progression of the disease and evaluating the effectiveness of therapy* [31].

Confirmation of SMA diagnosis in the most common variant, SMA 5q, is an indication for administration of specific treatment to the patient [17]. Currently, three developed drugs are registered in the F: nusinersen, risdiplam and onasemnogene abeparvovec, and all of them, except for the last, are included in the list of vital and essential medicines (VEM) [32]. Provision of children up to 18 years with these drugs is financed in the RF by the “Circle of Good” Foundation (RF Presidential Decree dated January 01, 2021 No. 16 “On Creation of Foundation for Support of Children with Severe Life-Threatening and Chronic Diseases Including Rare (Orphan) Diseases, “Circle of Good”); currently, the need to provide adult patients with the above mentioned drugs is being actively discussed [33]. The effect of treatment with each of the drugs is evaluated not earlier than 4 months after its beginnng [34].

Pathogenetic therapy is most effective when it starts before the clinical manifestations of SMA have become evident [35]. The consequences of deficit of early diagnosis and long delays in the diagnosis of SMA in the Russian Federation consist in the fact that *most patients at the time of start of therapy have significant motor deficit, as well as other disorders such as respiratory and heart failure, skeletal deformities, disorders in nutrition and function of gastrointestinal tract*. Correction of these conditions requires the participation of a specialized interdisciplinary medical team, including a neurologist, pulmonologist, cardiologist, gastroenterologist, resuscitator, orthopedist, rehabilitologist, psychotherapist and pediatrician [17]. Thus, up-to-date information about SMA biomarkers permits to be oriented in the problems of timely diagnosis, choice of treatment approaches and monitoring of its effectiveness to improve the quality and life expectancy of this category of patients.

The **aim** of this study to determine peculiarities of management of patients with spinal muscular atrophies

with account of neuropsychiatric manifestations of the disease, to analyze the main problems and propose measures aimed at improving the quality of medical care for this group of patients, taking into account the experience of the Samara region.

MATERIALS AND METHODS

In the work, the archive data of Seredavin Samara Regional Clinical Hospital are used, 132 medical histories of 77 children and adults with the discharge dates from January 2008 to February 2022 with the diagnoses (ICD-10 codes): G12.0, G12.1, G12.8 and G12.9. All the data are published in the depersonalized form, no additional interventions beyond the standard procedures of management of patients with SMA were conducted, no signing of the informed consent was required.

Of 132 medical histories, 112 were included in the analyzed sample. Deceased patients (3 children, the mean age 6.2 (9.1) years, with G12.0) and 16 patients with diagnoses other than SMA (1 child, 13.1 years; 15 adults, mean age 51.1 (19.7) years) were *not included* in the study.

The analysis covered descriptions of clinical (data of general and neurological examinations with focus on motor disorders), laboratory (lactate dehydrogenase (LDG), creatine phosphokinase (CPK), creatinine), instrumental (magnetic resonance imaging (MRI) of the brain, ENMG) and neuropsychological diagnostic methods, tactics of the therapeutic management of patients and their changes in dynamics from 2008 to 2022.

Statistical analysis was performed in SPSS-27 program, license of Samara State Medical University, 2021. Methods of descriptive statistics were used. The data are described using median and interquartile range (given in brackets), absolute values and % (given in brackets).

RESULTS

As of February 2022, 58 patients with SMA were registered in Seredavin Samara Regional Clinical Hospital (mean age — 38.4 (41.3) years), of which 32 (55.2%) were women), including 21 children (mean age — 12.3 (7.4) years, 14 (24.1%) girls). Seven (12.0%) of 58 patients were diagnosed with "Pediatric SMA, type 1, Werdnig-Hoffmann" (G12.0), all children: 5 (8.6%) girls and 2 (3.4%) boys. The older patient was 14.3 years old, the younger one was 4.8 years old (mean age 7.7 (5.8) years). The diagnosis of G12.1, encoding type 2, 3 and 4 SMA, Facio–Londe progressive bulbar palsy, as well as the scapuloperoneal form, was established in 43 (74.1%) patients (mean age 37.3 (40.7) years), 14 (24%) children, of them 9 (15.5%) girls, and 29 (50.0%) adults, 13 (22.4%) women; SMA 5q was confirmed by molecular genetics in 10 adult patients (17.2%, mean age — 35.3 (19.0) years), 4 (6.9%) of them women. Other SMA and related syndromes coded G12.8 were found in 6 adult patients: 3 (5.2%) women and 3 (5.2%) men, the younger patient was 39.5 years old, the older one was 72.1 years old. The diagnosis "unspecified SMA" (G12.9) was established in 2 adult women aged 40 and 52 years (Table 1).

All patients at the time of study were stable, in satisfactory condition, breathing without use of invasive lung ventilation. The data on motor disorders in all the studied medical histories were the results of neurological examination; motor disorders varied from mild proximal lower paraparesis (n = 13; 22.4%) to evident tetraparesis (n = 7; 12.0%) (Table 1). Examination of the mental status was in general limited to the evaluation of the state of consciousness and effectiveness of contact using clinic-psychopathological method, without use of neuropsychological methods. All the patients were communicative, understood and exactly performed instructions by virtue of motor potentials. In part of children emotional lability (n = 6; 10.3%), easy fatigue (n = 10; 17.2%), tearfulness (n = 3; 5.2%) were noted.

Laboratory tests included a general urinalysis, a general blood test with a detailed formula, a biochemical blood test for creatinine, CPK, glucose, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and LDG (Table 1). Patients underwent instrumental examinations in the form of cutaneous or needle ENMG from muscles of limbs, in all patients SMA-specific electromyographic alterations were identified, evaluated by physiologists. As part of the diagnostic search and differential diagnosis, patients underwent MRI of the spinal cord and brain; no pathological changes of the examined organs were visualized in any patient. Ultrasound examination (US) and magnetic resonance imaging (MRI) of the muscles were not performed.

The diagnosis was confirmed with participation of the commission including a geneticist of Samara Medical and Genetic Center, and on the basis of a molecular genetic study performed by laboratories of acad. Bochkov Medical Genetic Scientific Center.

Before 2021, therapy of patents with SMA was based on symptomatic correction of developed disorders, and also on metabolic and neuroprotective therapy. In the department of children with damage to the central nervous system and psyche of Seredavin Samara Regional Clinical Hospital, the patients were administered L-carnitine, piracetam, glycine, thiamine and cyanocobalamin in standard dosages, for correction of respiratory disorders, inhalations with bronchodilators were performed. The patients received physiotherapy in the form of magnetic laser and alternating magnetic therapy. In the adult neurologic departments, patients were given neuroprotective and nootropic therapy.

DOI: https://doi.org/10.17816/PAVLOVJ100672

Table 1. Sociodemographic, Clinical and Laboratory-Instrumental Characteristics of the Study Sample of Patients with SMA Depending on Nosological Category

Diagnostic Categories according to ICD-10		G12.0	G12.1		G12.8	G12.9	Total	
Parameter	Age Group	Children	Children	Adults	Adults	Adults	Children	Adults
Sample Size, n (%)								
	Female	5 (8.6)	9 (15.5)	13 (22.4)	3 (5.2)	2 (3.4)	14 (24.1)	18 (31.0)
	Men	2 (3.4)	4 (6.9)	16 (27.6)	3 (5.2)	0	6 (10.4)	19 (32.8)
	In total	7 (12.1)	14 (24.1)	29 (50.0)	6 (10.4)	2 (3.4)	21 (36.2)	37 (63.8)
Age, Median (Interquartile Range), years								
	Female	7.7 (4.2)	13.2 (7.8)	50.8 (19.7)	63.6 (16.3)	45.8 (6.2)	11.8 (7.7)	51.4 (22.9)
	Men	10.2 (3.7)	12.7 (8.7)	47.1 (30.0)	55.0 (8.9)	0	12.7 (8.0)	48.6 (28.5)
	In total	7.7 (5.8)	12.9 (8.3)	49.1 (24.8)	59.3 (15.5)	45.8 (6.2)	12.3 (7.4)	50.8 (24.1)
Distribution of Patients Depending on Force in Proximal Parts of Upper Limbs (in points), n (%)								
0–0.5	Female	1 (1.7)	0	0	0	0	1 (1.7)	0
	Men	1 (1.7)	0	0	0	0	1 (1.7)	0
	In total	2 (3.4)	0	0	0	0	2 (3.4)	0
1–1.5	Female	3 (5.2)	0	0	0	0	3 (5.2)	0
	Men	1 (1.7)	0	1 (1.7)	0	0	1 (1.7)	1 (1.7)
	In total	4 (6.9)	0	1 (1.7)	0	0	4 (6.9)	1 (1.7)
2–2.5	Female	0	1 (1.7)	3 (5.2)	1 (1.7)	0	1 (1.7)	4 (6.9)
	Men	0	3 (5.2)	5 (31.2)	0)	0	3 (5.2)	5 (26.3)
	In total	0	4 (6.9)	8 (13.8)	1 (1.7)	0	4 (6.9)	9 (15.5)
3–3.5	Female	1 (1.7)	3 (5.2)	3 (5.2)	0	1 (1.7)	4 (6.9)	4 (6.9)
	Men	0	0	5 (31.2)	1 (1.7)	0 (0)	0	6 (10.3)
	In total	1 (1.7)	3 (5.2)	8 (13.8)	1 (1.7)	1 (1.7)	4 (6.9)	10 (17.2)
4–4.5	Female	0	4 (6.9)	4 (6.9)	1 (1.7)	1 (1.7)	4 (6.9)	6 (10.3)
	Men	0	2 (3.4)	3 (5.2)	0	0	2 (3.4)	3 (5.2)
	In total	0	6 (10.3)	7 (12.1)	1 (1.7)	1 (1.7)	6 (10.3)	9 (15.5)
5	Female	0	1 (1.7)	3 (5.2)	1 (1.7)	0	1 (1.7)	4 (6.9)
	Men	0	0	2 (3.4)	2 (3.4)	0	0	4 (6.9)
	In total	0	1 (1.7)	5 (17.2)	3 (50.0)	0	1 (1.7)	8 (13.8)
Distribution of Patients Depending on Force in Distal Parts of Upper Limbs (in points), n (%)								
0–0.5	Female	1 (1.7)	0	0	0	0	1 (1.7%)	0
	Men	1 (1.7)	0	0	0	0	1 (1.7%)	0
	In total	2 (3.4)	0	0	0	0	2 (3.4%)	0
1–1.5	Female	0	0	0	0	0	0	0
	Men	0	0	0	0	0	0	0
	In total	0	0	0	0	0	0	0
2–2.5	Female	2 (3.4)	0	2 (3.4)	1 (1.7)	0	2 (3.4)	3 (5.2)
	Men	1 (1.7)	0	1 (1.7)	1 (1.7)	0	1 (14.3)	2 (3.4)
	In total	3 (5.2)	0	3 (5.2)	2 (3.4)	0	3 (5.2)	5 (8.6)
3–3.5	Female	0	3 (5.2)	2 (3.4)	0	1 (1.7)	3 (5.2)	3 (5.2)
	Men	0	4 (6.9)	6 (10.3)	1 (1.7)	0	4 (6.9)	7 (12.1)
	In total	0	7 (12.1)	8 (13.7)	1 (1.7)	1 (1.7)	7 (12.1)	10 (17.2)
4–4.5	Female	2 (3.4)	4 (6.9)	6 (10.3)	1 (1.7)	1 (1.7)	6 (10.3)	8 (13.8)
	Men	0	1 (1.7)	6 (10.3)	0	0	1 (1.7)	6 (10.3)
	In total	2 (3.4)	5 (8.6)	12 (20.7)	1 (1.7)	1 (1.7)	7 (12.1)	14 (24.1)

5	Female	0	2 (3.4)	3 (5.2)	1 (1.7)	0	2 (3.4)	4 (6.9)
	Men	0	0	3 (5.2)	1 (1.7)	0	0	4 (6.9)
	In total	0	2 (3.4)	6 (10.3)	2 (3.4)	0	2 (3.4)	8 (13.8)
Distribution of Patients Depending on Force in Proximal Parts of Lower Limbs (in points), n (%)								
0–0.5	Female	2 (3.4)	0	1 (1.7)	1 (1.7)	0	2 (3.4)	2 (3.4)
	Men	2 (3.4)	0	1 (1.7)	0	0	2 (3.4)	1 (1.7)
	In total	4 (6.9)	0	2 (3.4)	1 (1.7)	0	4 (6.9)	3 (5.2)
1–1.5	Female	2 (3.4)	1 (1.7)	2 (3.4)	1 (1.7)	0	3 (5.2)	3 (5.2)
	Men	0	2 (3.4)	0	0	0	2 (3.4)	0
	In total	2 (3.4)	3 (5.2)	2 (3.4)	1 (1.7)	0	5 (8.6)	3 (5.2)
2–2.5	Female	1 (1.7)	3 (5.2)	5 (8.6)	0	0	4 (6.9)	5 (27.8)
	Men	0	1 (1.7)	7 (12.1)	0	0	1 (1.7)	7 (12.1)
	In total	1 (1.7)	4 (6.9)	12 (20.7)	0	0	5 (8.6)	12 (20.7)
3–3.5	Female	0	2 (3.4)	3 (5.2)	0	1 (1.7)	2 (3.4)	4 (6.9)
	Men	0	2 (3.4)	6 (10.3)	0	0	2 (3.4)	6 (10.3)
	In total	0	4 (6.9)	9 (15.5)	0	1 (1.7)	4 (6.9)	10 (17.2)
4–4.5	Female	0	3 (5.2)	0	0	1 (1.7)	3 (5.2)	1 (1.7%)
	Men	0	0	2 (3.4)	1 (1.7)	0	0	3 (5.2)
	In total	0	3 (5.2)	2 (3.4)	1 (1.7)	1 (1.7)	3 (5.2)	4 (6.9)
5	Female	0	0	2 (3.4)	1 (1.7)	0	0	3 (5.2)
	Men	0	0	0	2 (3.4)	0	0	2 (3.4)
	In total	0	0	2 (3.4)	3 (5.2)	0	0	5 (8.6)
Distribution of Patients Depending on Force in Distal Parts of Lower Limbs (in points), n (%)								
0–0.5	Female	1 (1.7)	0	0	0	0	1 (1.7)	0
	Men	1 (1.7)	0	0	0	0	1 (1.7)	0
	In total	2 (3.4)	0	0	0	0	2 (3.4)	0
1–1.5	Female	1 (1.7)	0	1 (1.7)	0	0	1 (1.7)	1 (1.7)
	Men	1 (1.7)	0	0	0	0	1 (1.7)	0
	In total	2 (3.4)	0	1 (1.7)	0	0	2 (3.4)	1 (1.7)
2–2.5	Female	1 (1.7)	2 (3.4)	1 (1.7)	2 (3.4)	1 (1.7)	3 (5.2)	4 (6.9)
	Men	0	2 (3.4)	2 (3.4)	0	0	2 (28.6)	2 (3.4)
	In total	1 (1.7)	4 (28.6)	3 (5.2)	2 (3.4)	1 (1.7)	5 (8.6)	6 (10.3)
3–3.5	Female	2 (3.4)	2 (3.4)	5 (8.6)	1 (1.7)	0	4 (6.9)	6 (10.3)
	Men	0	2 (3.4)	6 (10.3)	1 (1.7)	0	2 (3.4)	7 (12.1)
	In total	2 (3.4)	4 (6.9)	11 (19.0)	2 (3.4)	0	6 (10.3)	13 (22.4)
4–4.5	Female	0	2 (3.4)	3 (5.2)	0	0	2 (3.4)	3 (5.2)
	Men	0	1 (1.7)	3 (5.2)	1 (1.7)	0	1 (1.7)	4 (6.9)
	In total	0	3 (5.2)	6 (10.3)	1 (1.7)	0	3 (5.2)	7 (12.1)
5	Female	0	3 (5.2)	3 (5.2)	0	1 (1.7)	3 (5.2)	4 (6.9)
	Men	0	0	5 (8.6)	1 (1.7)	0	0	6 (10.3)
	In total	0	3 (5.2)	8 (13.8)	1 (1.7)	1 (1.7)	3 (5.2)	10 (17.2)
Number of Patients with Bulbar Syndrome, n (%)								
	Female	1 (1.7%)	0	0	0	0	1 (1.7)	0
	Men	1 (1.7%)	0	2 (3.4)	0	0	1 (1.7)	2 (3.4)
	In total	2 (3.4%)	0	2 (3.4)	0	0	2 (3.4)	2 (3.4)

Laboratory-Instrumental Parameters								
Creatinine, Median (Interquartile Range), μmol/l								
	Female	41.4 (54.0)	25.9 (5.4)	74.1 (15.1)	65.4 (7.6)	66.9 (6.5)	33.4 (18.6)	73.1 (14.6)
	Men	28.9 (12.5)	31.4 (22.6)	57.9 (6.1)	50.6 (5.3)		28.9 (30.0)	57.4 (7.4)
	In total	41.4 (8.0)	25.9 (15.9)	61 (18.9)	56.9 (8.3)	66.9 (6.5)	33.4 (18.5)	60.4 (17.5)
Creatine Phosphokinase, Median (Interquartile Range), U/l								
	Female	168.0 (48.4)	190.0 (129.9)	222.5 (157.7)	345.3 (224.4)	224.0 (94.9)	168.0 (138.7)	222.5 (189.7)
	Men	36.4 (13.5)	972.0 (3341.5)	303.6 (453.5)	144.4 (5.0)		206.0 (1236.2)	264.6 (390.7)
	In total	106.1 (118.1)	248.4 (201.7)	265.6 (349.3)	144.4 (119.8)	224.0 (94.9)	168.0 (188.2)	245.0 (236.9)
Lactate Dehydrogenase, Median (Interquartile Range), U/l								
	Female	267.5 (22.5)	287.0 (56.2)	211.0 (39.4)	299.7 (10.8)	195.5 (18.5)	275.0 (44.4)	214.0 (70.4)
	Men	86.2 (9.2)	684.1 (421.0)	204.0 (26.9)	206.7 (4.2)	–	534.0 (588.7)	204.0 (15.3)
	In total	263.0 (172.1)	305.7 (259.0)	206.5 (37.7)	250.0 (85.5)	195.5 (18.5)	287.0 (72.9)	210.0 (37.4)

Notes: W — women; M — men, ICD-10 — International Classification of Diseases and Problems Related to Health, 10th revision

Since March 2021, on the basis of the pediatric neurosurgical department of Seredavin Samara Regional Clinical Hospital, nusinersen has been administered to patients with SMA, the drug was introduced intrathecally under endotracheal anesthesia with sevoflurane (the average dose 9.45 (0.98) mg). As of February 2022, 8 children with SMA were receiving nusinersen (13.8% of the total number of patients; mean age 7.3 (8.8) years), of them 5 girls, 8 children were receiving risdiplam (13.8%; 9.5 (6.9) years), of them 6 girls; parents of 3 more patients (5.2%; mean age — 7.5 (2.4) years) refused administration of drugs. Of 10 adult patients with confirmed SMA 5q (17.2%; mean age — 35.3 (19.0) years), 1 patient (36-year-old man with type 3 SMA) was given nusinersen, 3 (5.2%) adults at the time of the study were achieving the right to receive drugs through juridical procedure.

DISCUSSION

As of 2021, in the Samara region with population of 3.15 million people, 58 patients with SMA were living. Thus, the prevalence of SMA in the Samara region, based on the archive data of the main regional institution, is *1.84 cases per 100 thousand population*, which is about 5 times lower than the average level for the RF and the world [3]. This may indicate *shortcomings in the diagnosis of SMA in the region*. According to the archive of the Samara Regional Clinical Hospital, of 10 people with type 1 SMA (G12.0), 3 patients died in the Samara region in the period from 2008 to 2022, so the mortality rate for type 1 SMA is 30%.

In general, in the Samara region all the necessary laboratory examinations are being conducted to diagnose patients having clinical manifestations of the disease, however, in the region there is *deficit of preclinical diagnostics of SMA and of use of laboratory instruments for prognosis of the course of the disease* [23, 24].

The results obtained in the study of creatinine and CPK levels, in general, confirm the results of the above mentioned works, namely, *the tendency of individuals with the mildest course of the disease to demonstrate higher levels of creatinine and CPK* [22, 23]. However, to assess the statistical significance of differences between the groups with different degrees of severity of the disease, it is required to analyze the data of an expanded sample of patients that is planned to be done in further studies. Molecular genetic diagnosis of SMA required to confirm the diagnosis, is performed in the Samara region by taking biological samples of patients and sending them to the laboratories of acad. Bochkov Medical and Genetic Research Center for study according to SMA diagnostic program; the lack of necessary tools for molecular genetic diagnosis in the region slows down the confirmation of the diagnosis of SMA and creates obstacles to the introduction of early diagnosis.

In whole, distribution of clinical forms of SMA in the region corresponds to that in the world; no special clinical manifestations in patients of the Samara region are noted [1, 3]. The cognitive and affective disorders in patients with SMA were studied without use of special tests. This restricts the possibility of their evaluation and may negatively influence the quality of life of patients and the results of their rehabilitation [10, 12, 13].

Since 2021, therapy of patients with SMA in the Samara region has been conducted with use of pathogenetic drugs funded by "Circle of Good" foundation. Currently, the treatment of patients with SMA of minority age in the region corresponds to the international standards [17], however, absence of

validation of CHOP-INTEND, MFM, HFMSE and RULM scales in Russia limits their use and complicates evaluation of the effectiveness of treatment. Treatment of adult patients with SMA does not correspond to the international standards, since most of them do not receive the required therapy.

Limitations to the study. The study includes the archive materials of the main regional institution — Seredavin Samara Regional Clinical Hospital, which excluded the possibility of taking into account the data of all patients with SMA who live in the Samara region and have not been diagnosed and treated at the Samara Regional Clinical Hospital.

CONCLUSION

The conducted analysis revealed the shortcomings of the diagnosis of spinal muscular atrophy in the region, in particular, deficit of early diagnosis (all the diagnoses were established in patients with evident clinical symptoms), deficit of evaluation of neuropsychiatric (affective, cognitive) disorders, absence of monitoring of effectiveness and of evaluation of the quality of the conducted therapy (absence of validated scales of assessment of motor skills), and also low availability of drug therapy for adult patients, which, in the authors' opinion, requires:

- introduction of the neonatal screening for spinal muscular atrophy and reformation of the work of regional medical genetic center with provision of the possibility for molecular genetic examinations and early diagnosis of spinal muscular atrophy;
- study and registration of affective and cognitive disorders and their dynamics in treatment with focus on the diagnostic recommendations of foreign specialists with the aim of personalization of the therapeutic management tactics to improve the quality of life and life expectancy of patients with spinal muscular atrophy.

Besides, it is important to take into account the following:

1. for assessment of the dynamics of motor disorders in patients with spinal muscular atrophy, a neurological examination is not sufficient; correct data of the effectiveness of the conducted therapy can be obtained using specialized scales of assessment of motor skills of patients with spinal muscular atrophy , which requires their validation in Russia;

2. since 2021, children with spinal muscular atrophy in the region started to receive pathogenetic therapy drugs, and creation of "Circle of Good" foundation in the early 2021 influenced the treatment tactics of patients with spinal muscular atrophy and gave them the opportunity to receive expensive pathogenetic treatment according to recommendations of the world professional community without leaving their region. Nevertheless, adult patients with spinal muscular atrophy do not receive treatment in most cases, and the authors think it necessary to make pathogenetic therapy available to adult patients by adoption of clinical recommendations on spinal muscular atrophy-5q for adults with the account of the available international experience.

ADDITIONAL INFORMATION

Funding. The work was carried out within the framework of the project «Bank of Innovative Neuropsychiatric Research: Priority 2030» (Grant Priority 2030, Samara State Medical University).

Conflict of interests. The authors declare no conflicts of interests.

Contribution of the authors: *A. Ya. Gayduk* — research concept and design, processing of the material, text writing; *V. V. Chernikova* — collection and processing of material, statistical processing, writing the text; *Ya. V. Vlasov* — research design and editing; *D. A. Smirnova, P. Cumming* — conception and editing. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Финансирование. Работа проводилась в рамках проекта «Банк инновационных нейропсихиатрических исследований: Приоритет-2030» (грант Приоритет 2030, Самарский государственный медицинский университет).

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Вклад авторов: *Гайдук А. Я.* — концепция и дизайн исследования, обработка материала, написание текста; *Черникова В. В.* — сбор и обработка материала, статистическая обработка, написание текста; *Власов Я. В.* — дизайн исследования и редактирование; *Смирнова Д. А., Камминг П.* — концепция и редактирование. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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ОБ АВТОРАХ

***Гайдук Арсений Янович**;
ORCID: https://orcid.org/0000-0002-4015-3162;
eLibriary SPIN: 6119-6992; e-mail: a.j.gayduk@gmail.com

Камминг Пол, профессор;
ORCID: https://orcid.org/0000-0002-0257-9621;
e-mail: paul.k.cumming@gmail.com

Черникова Виктория Валериевна;
ORCID: https://orcid.org/0000-0002-2147-9212;
e-mail: v.v.chernikova@mail.ru

Власов Ян Владимирович, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-9471-9088;
eLibriary SPIN: 1494-6296; e-mail: sams99@inbox.ru

Смирнова Дарья Александровна, к.м.н.;
ORCID: https://orcid.org/0000-0002-9591-4918;
eLibriary SPIN: 8248-0194; e-mail: daria.smirnova.md.phd@gmail.com

AUTHOR'S INFO

***Arseniy Ya. Gayduk**;
ORCID: https://orcid.org/0000-0002-4015-3162;
eLibriary SPIN: 6119-6992; e-mail: a.j.gayduk@gmail.com

Paul Cumming, MD, PhD, Professor;
ORCID: https://orcid.org/0000-0002-0257-9621;
e-mail: paul.k.cumming@gmail.com

Viktoriya V. Chernikova;
ORCID: https://orcid.org/0000-0002-2147-9212;
e-mail: v.v.chernikova@mail.ru

Yan V. Vlasov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-9471-9088;
eLibriary SPIN: 1494-6296; e-mail: sams99@inbox.ru

Dar'ya A. Smirnova, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0002-9591-4918;
eLibriary SPIN: 8248-0194; e-mail: daria.smirnova.md.phd@gmail.com

* Автор, ответственный за переписку / Corresponding author