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NEUROLOGICAL AND PSYCHIATRIC ASPECTS OF BIOLOGICAL MARKERS FOR THE PROVISION OF MEDICAL CARE TO PATIENTS WITH SPINAL MUSCULAR ATROPHY 5Q

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SUMMARY

Background: *Spinal muscular atrophy (SMA) is a rare genetic disorder, in which, for the common childhood onset forms, loss of function of the SMA 5q gene leads to disability and death before adulthood. Symptomatic treatment focusses on respiratory and nutritional support, and physical therapy, but there is little consideration of psychiatric manifestations of SMA.*

The aim of this study was to explore blood biomarker levels, electromyography (EMG) data, and clinical manifestations, including psychiatric impairments, in patients with SMA 5q. Our objectives were twofold: First, to assess the clinical relevance of standard biomarkers, i.e., creatinine, creatine kinase (CK), and lactate dehydrogenase (LDH) levels, and second, to obtain data supporting the development of an effective prognostic algorithm for the course of this disease.

Results: *We analyzed retrospective data from 112 medical records of 58 registered patients (2008-2022) with SMA. At the time of last registration, the 58 patients had a mean age 38.4 years [13.68; 55.0], of whom 32 (52%) were female. The subgroup of 21 pediatric patients had a mean age 12.32 years [6.57; 13.93], of whom 14 (24%) were girls. The ICD-10 diagnoses were as follows: G12.0 (n=7, 12%, children), G12.1 (n=14, 24% children; n=29, 50% adults), G12.8 (n=6, 10% adults), G12.9 (n=2, 1% adults). The archival data on psychiatric status indicated emotional lability (n=6, 10.3%), fatigue (n=10, 17.2%), and tearfulness (n=3, 5.2%) in some patients. There were no significant subgroup differences in serum creatinine and CK levels, but there were significant differences in LDH levels between the G12.0, G12.1, G12.8, and G12.9 subgroups.*

Among the serum biomarkers, only LDH levels showed significant differences among the subgroups of SMA 5q patients; higher levels in the G12.1, G12.8, and G12.9 groups compared to the G12.0 (infantile) group related to age, weight, gender, and level of physical activity. Data on psychiatric status were insufficient to identify group differences and associations with biomarker levels. Likewise, longitudinal data on repeat hospitalizations did not indicate associations with biomarker levels.

Conclusions: *Creatinine, CK, and LDH levels were insufficient for monitoring and predicting the course of SMA. Further prospective research is needed to elaborate the weak relationships between CK levels, the dynamics of the clinical presentation, and therapeutic interventions, and to investigate psychiatric co-morbidities in SMA 5q patients.*

Key words: *creatine phosphokinase – creatinine – neurofilaments - neuromuscular diseases – nusinersen - hereditary disease - pathogenetic therapy – risdiplam - spinal muscular atrophy*

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INTRODUCTION

Spinal muscular atrophy (SMA) is a genetically heterogeneous group of CNS disorders characterized clinically by the loss of motor skills, progressive symmetric peripheral paralysis due to degeneration of motor neurons, and resultant atrophy of striated muscles, which leads to difficulty in swallowing, general paralysis, and respiratory failure. SMA predominantly develops in childhood and is a major hereditary cause of infant mortality (Araujo et al. 2009). The worldwide prevalence of SMA is estimated to be 8.5-10.3 per 100,000 newborns, with carrier frequencies ranging from 1 in 35 to 1 in 60 (Kimizu et al. 2021). SMA is most commonly caused by autosomal inheritance mutations, resulting in a roughly equal distribution among both genders, although the gender frequency differs slightly according to SMA type (Verhaart et al. 2017, Gayduk & Vlasov 2019). The most common forms, known as SMA 5q, have no clear association with cognitive and affective disorders in numerous studies, which have nonetheless highlighted the lack of detailed information about neuropsychiatric status (Mix et al. 2021, Zappa et al. 2021, Rivière et al. 2007, Gayduk et al. 2022).

The genetic nature of SMA 5q variants calls for molecular-genetic research methods as essential tools for confirming the diagnosis. Here, the most relevant method is testing for the copy numbers of SMN1 and SMN2 using multiplex ligation-dependent probe amplification (MLPA) (Hong et al. 2020, Mercuri et al. 2018, Feng et al. 2020, Lopez-Lopez et al. 2020). At the time of writing, laboratory diagnostic methods other than MLPA do not accurately determine the presence of the disease or provide predictions regarding its progression and severity. However, some studies suggest that certain nonspecific biomarkers hold promise for monitoring disease progression and assessing treatment effectiveness (Alves et al. 2020, Freigang et al. 2021, Yuan et al. 2017, Kobayashi et al. 2013, Kolb et al. 2016, Gayduk et al. 2022). These biomarkers include plasma levels of creatine phosphokinase (CPK), creatinine, and neurofilaments (NF). For instance, a study involving 238 patients demonstrated an inverse between serum creatinine levels and disease severity in children and adolescents, with correction for age and muscle mass (Alves et al. 2020). Creatinine levels were highest in patients with type III SMA and lowest in patients with type I, but decreasing with age regardless of clinical subtype.

A study population of 22 infants diagnosed with preclinical SMA underwent repeated measurement of plasma creatinine levels and evoked potentials electromyography (EMG) over the course of a year (Alves et al. 2020). Results showed decreasing creatinine levels and evoked potential amplitudes during the first three months, in consideration of earlier findings that decreesing creatinine levels preceded the decline in evoked potential amplitudes in 8 of 12 type III SMA patients. Another study conducted with adult patients demonstrated a correlation between plasma CPK and creatinine levels and disease severity, indicating their potential utility in predicting treatment efficacy (Freigang et al. 2021).

NF are cytoskeletal proteins that provide structural integrity to neurons, particularly in their axons. Elevated levels of NF are present in blood and cerebrospinal fluid during ongoing neurodegenerative processes in several diseases and in traumatic brain injury. In the case of SMA, plasma levels of NF are more indicative for disease prognosis and treatment monitoring in children than in adult patients (Yuan et al. 2017).

Broader research on SMA biomarkers has revealed other analytes that correlate with the degree of motor function impairment; the Biomarkers for SMA (BforSMA) study published in 2013 identified 200 plasma markers correlating with motor and other impairments in infants with SMA up to two years of age (Kobayashi et al. 2013). The authors selected the most significantly correlating plasma metabolites to create the commercially available diagnostic panel known as SMA-MAP. Further studies with the SMA-MAP panel revealed statistically significant deviations in infants with SMA compared to healthy infants up to 6 months of age (Kolb et al. 2016).

Serum lactate dehydrogenase (LDH) is a cytoplasmic enzyme, which serves as a common indicator of tissue damage (Zhang et al. 2012). Despite its broad application at many local healthcare institutions, there is scant evidence for the fitness of LDH as a biomarker for SMA.

As noted above, EMG is among the most effective instrumental diagnostic methods for evaluating neuromuscular function (Querin et al. 2018). Changes in electrophysiological parameters in SMA patients correlate with the number of SMN2 copies, SMA type, motor function assessment results, and patient age. EMG results also serve for assessing the patient's response to specific therapies (Weng et al. 2021, Kariyawasam et al. 2020). The application of techniques such as EMG with motor unit number index (MUNIX) and motor unit size index (MUSIX) enables the detection of subtle electrophysiological changes, which is valuable for identifying specific patterns for differential diagnosis and therapy monitoring (Querin et al. 2018, Nandedkar et al. 2010). However, at the time of writing, there are no universal and cost-effective diagnostic and prognostic EMG-based tools, which poses a major challenge in providing medical care to SMA patients in Russia and around the world.

Thus, the currently most available and widely used blood biomarkers (serum creatinine, CK, and LDH) have the potential for utilizing as a tool for disease course monitoring. This approach is considerably cheaper than SMA-MAP (USD 500 per test), and calls for lower labor input than tests involving motor unit examinations.

The aim of this study was to investigate differences in an abbreviated panel of blood biomarkers (serum creatinine, CK, and LDH), EMG data, and clinical manifestations (including psychological/psychiatric impairments), among SMA patients at the main regional healthcare institution in the region of Samara, Russia Federation. Our goal was to obtain data that could contribute to the development of a practical and effective method for predicting the course of the disease, with potential application as an endpoint in intervention/treatment studies.

SUBJECTS AND METHODS

In a retrospective study of archived data from the V.D. Seredavin Samara Regional Clinical Hospital (SRCH), we assembled 112 medical records from 58 patients from hospitalizations spanning from January 2008 to February 2022. Patients were divided into groups based on gender, age (children under 18 years and adults), and the ICD-10 diagnostic categories (G12.0, G12.1, G12.8, and G12.9). When available, we included data from subsequent hospitalizations. The analysis included clinical data from general

Table 1. Socio-demographic, clinical and laboratory characteristics of the study sample of patients with SMA, depending on the nosological category

ICD-10 categories	G12.0	G12.1		G12.8	G12.9	Total		Statistics
Age group Gender	Children n=7	Children n=14	Adults n=29	Adults n=6	Adults n=2	Children n=21	Adults n=37	
Socio-demographic indicators of the sample; 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%)	χ^2=4,163, df=4, p=0.384, for distribution by sex between groups
Male:	2 (3.4%)	4 (6.9%)	16 (27.6%)	3 (5.2%)	-	6 (10.4%)	19 (32.8%)	
Total:	7 (12.1%)	14 (24.1%)	29 (50.0%)	6 (10.4%)	2 (3.4%)	21 (36.2%)	37 (63.8%)	
Age - Median (Q1, Q3), years								
Female:	8.0 (8.0, 11.0)	13.0 (6.0, 14.0)	51.0 (39.0,59.0)	64.0 (51.5, 68.5)	38.4 (14.0, 55.0)	11.9 (6.2, 13.8)	51.5 (39.5, 62.5)	KW=40.125, df=4, p<0.001 to compare age between groups
Male:	10.5 (8.7, 12.2)	12.0 (6.0, 16.0)	47.5 (32.0,63.5)	55.0 (51.0, 60.0)	-	12.2 (6.3, 15.1)	48.6 (34.2, 63.8)	
Total:	8.0 (7.5, 12.5)	12.5 (6.0, 14.8)	50.0 (38.0, 63.0)	59.5 (49.0,64.8)	38.4 (14.0, 55.0)	12.2 (6.0, 14.0)	51.0 (39.1, 63.6)	
Estimation of motor functions during neurological examination, gradation taking into account the sum of points of four limbs, median (Q1, Q3)								
Female:	1.5 (1.0, 2.2)	3.9 (3.0, 4.0)	3.2 (3.0, 4.1)	2.9 (2.4, 3.5)	3.2 (2.5, 4.1)	3.1 (2.1, 3.9)	3.2 (2.9, 4.1)	KW=14.196, df=4, p=0.007 to compare scores between groups
Male:	0.5 (0.2,0.7)	2.5 (2.5, 3.6)	3.2 (2.7, 4.0)	4.5 (3.9, 4.6)	-	2.5 (1.5, 3.1)	3.2 (2.9, 4.2)	
Total:	1.0 (0.5,1.9)	3.6 (2.6, 4.0)	3.2 (2.7, 4.1)	3.7 (3.0, 4.4)	3.2 (2.5, 4.1)	2.7 (2.0, 3.9)	3.2 (2.9, 4.1)	
Bulbar syndrome, n (%)								
Female:	1 (1.7%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%)	0 (0)	χ^2=5,418, df=4, p=0.247 for the distribution of cases of bulbar syndrome between groups
Male:	1 (1.7%)	0 (0)	2 (3.4%)	0 (0)	-	1 (1.7%)	2 (3.4%)	
Total:	2 (3.4%)	0 (0)	2 (3.4%)	0 (0)	0 (0)	2 (3.4%)	2 (3.4%)	
Laboratory and instrumental indicators; Creatinine - Median (Q1, Q3), μmol/l								
Female:	41.4 (37.4, 91.4)	25.9 (24.3, 29.8)	74.1 (61.0, 76.1)	65.4 (61.6,69.3)	57.4 (41.8, 73.3)	33.4 (25.9, 41.2)	73.1 (60.4, 75.0)	KW= 15.0324, df=4, p=0.005 to compare creatinine between groups
Male:	28.9 (22.6, 35.1)	31.4 (20.2, 42.7)	57.9 (57.1, 63.2)	50.6 (48.0,53.3)	-	28.9 (14.5, 44.5)	57.4 (56.2, 58.6)	
Total:	41.4 (33.4,41.4)	25.9 (21.4, 37.2)	61.0 (57.2, 76.1)	56.9 (53.3,61.6)	57.4 (41.8, 73.3)	33.4 (22.8, 41.4)	60.4 (57.1, 74.5)	
CPK - Median (Q1, Q3), U / l								
Female:	168.0 (137.0, 186.0)	190.0 (132.0, 262.0)	222.0 (154.0, 312.0)	345.0 (233.0 ,458.0)	203.0 (126.1, 324.0)	168.0 (123.0, 222.0)	222.5 (127.1, 316.7)	KW=6. 460, df=4, p=0.167 to compare CPK between groups
Male:	36.5 (29.7,43.2)	972.0 (266.0, 3608.0)	304.0 (200.0, 654.0)	144.0 (142.0, 147.0)		206.0 (58.9, 1295.0)	264.6 (151.9, 628.5)	
Total:	106.0 (49.9,168.0)	248.0 (132.0, 334.0)	266.0 (172.0, 522.0)	144.0 (135.0, 255.0)	203.0 (126.1, 324.0)	168.0 (112.2, 300.4)	245.0 (147.0, 383.9)	
LDH - Median (Q1, Q3), U/l								
Female:	268.0 (265.0, 288.0)	287.0 (248.0, 304.0)	211.0 (196.0, 235.0)	300.0 (294.0, 305.0)	220.5 (199.5, 275.0)	275.0 (263.0, 305.7)	214.0 (195.6, 266.0)	KW= 14.2622, df=4, p=0.006 to compare LDH between groups
Male:	86.2 (81.6, 90.8)	684.0 (609.0, 1030.0)	204.0 (196.0, 223.0)	207.0 (205.0, 209.0)		534.0 (95.4, 684.1)	204.0 (198.0, 212.7)	
Total:	263.0 (95.4, 268.0)	306.7 (275.0, 534.0)	206.5 (195.0, 233.0)	250.0 (209.0, 294.0)	220.5 (199.5, 275.0)	287.0 (244.8, 317.8)	210.0 (196.2, 233.6)	

Note: SMA – spinal muscular atrophy 5q; CPK – creatine phosphokinase; LDH – lactate dehydrogenase

and neurological examinations, laboratory test indicators (LDH, CK, creatinine levels), and instrumental diagnostic methods (EMG). Statistical analysis was performed using MedCalc and IBM SPSS Statistics (Version 27, license from Samara State Medical University, 2022) with descriptive statistics and non-parametric methods due to the small sample size and non-normal distributions of the data. The Kruskal-Wallis test, a non-parametric equivalent of one-way analysis of variance (ANOVA), was used to compare median values between groups, with pairwise comparisons adjusted for multiple comparisons using the Dunn method. The data were described using the median, first and third quartiles, absolute frequencies, and percentages (indicated in parentheses).

RESULTS

From January 2008 to February 2022, 58 SMA patients (38.4 [quartiles 13.7, 55.0] years old) had been registered at SRCH, of whom 32 (55.2%) were female. Among the 58 patients, 21 were children (12.3 [6.6, 13.9] years old), including 14 (24.1%) girls. The diagnosis of "Infantile spinal muscular atrophy, Type I, Werdnig-Hoffmann" (G12.0) was established in 7 patients (12.0%), all of whom were children: 5 (8.6%) girls and 2 (3.4%) boys. The oldest such patient was 14.3 years old, and the youngest was 4.8 years old (median of 7.7 [6.8, 12.7] years). The diagnosis of G12.1, encoding SMA II, III, and IV, was assigned to 43 patients (74.1%) (median age of 37.3 [14.5, 55.6] years), including 14 (24%) children, 9 (15.5%) of whom were girls, and 29 (50.0%) adults, 13 (22.4%) of whom were women. The diagnosis of G12.8 was assigned to 6 adult patients: 3 (5.2%) women and 3 (5%) men, with mean age 59.3 [37.3, 62.1] years. Two women, aged 40 and 52 years, were diagnosed with G12.9, "Unspecified spinal muscular atrophy."

According to the general and neurological examinations, all patients included in the study were clinically stable, in a satisfactory condition, and not on mechanical ventilation. Data on motor impairments were obtained from the results of neurological examinations recorded in all medical records. Motor impairments ranged from mildly expressed proximal lower paraparesis (n=13, 22.4%) to severely pronounced tetraparesis (n=7, 12.1%) (Table 1). Assessment of the mental status primarily involved evaluating the level of consciousness and rapport using the clinical-psychopathological method, without the use of neuropsychological tests. All patients were responsive, and could understand and accurately follow instructions, within the constraints of their motor capabilities. Some pediatric patients showed emotional lability (n=6, 10.3%), fatigue (n=10, 17.2%), and tearfulness (n=3, 5.2%).

During their examinations, all patients underwent a biochemical blood analysis to measure creatinine, CK, and LDH levels (Table 1). Diagnosis confirmation through molecular-genetic testing conducted by the laboratories of the Federal State Budgetary Scientific Institution "Medico-Genetic Scientific Center named after Academician N.P. Bochkov," was performed on 10 children and 2 adult patients at the time of data collection. EMG was performed on all patients with limb muscles using surface or needle electrodes. Specific electromyographic changes characteristic of SMA were detected in all patients, but quantitative descriptions of these changes were often lacking, which hindered establishing correlations between the EMG findings and other clinical results. The research results are presented in Table 1. There were no statistically significant differences in creatinine and CK medians between the G12.0, G12.1, G12.8, and G12.9 groups, nor were there any significant associations with motor impairments (Figure 1). However, we did detect subgroup differences in LDH levels between the G12.1 Children and G12.1 Adult subgroups: G12.1 Children VS G12.1 Adult (median [1 and 3 quartiles]): 305.7 [275.0, 534.0] VS 206.5 [195.0, 233.0], mean rank difference = 16.84, Dunn's p=0.003.

Analysis of archival medical records of patients (n=4, 6.9%) with repeated hospitalizations showed highest CK levels (up to 9000 U/L) in patients of the G12.1 group at clinical onset, followed by a decline in subsequent 3-17 months, depending on the records date. Individual data from cases with repeat hospitalizations also indicated increased CK levels in patients of the G12.0 and G12.1 groups upon initiating disease-modifying therapy with nusinersen or risdiplam. Archival data did not reveal significant correlations between CK levels, disease stage, and the age at start of therapy.

DISCUSSION

The total number of patient records is greater than the number of persons due to inclusion of elderly patients with a milder course of the disease, who had been regularly hospitalized for the 14 years of record collection. Statistical analysis of laboratory test results and neurological examination data obtained from 112 archival medical records of 58 SMA patients diagnosed with G12.0, G12.1, G12.8, and G12.9 codes did not show any associations between creatinine and CK levels with diagnostic categories. Numerically higher CK levels in the G12.1, G12.8, and G12.9 groups compared to the G12.0 group were not statistically significant and were more likely related to age, weight, gender, and the level of physical activity of the patients. These factors were also likely to have been associated with the corresponding group differences in

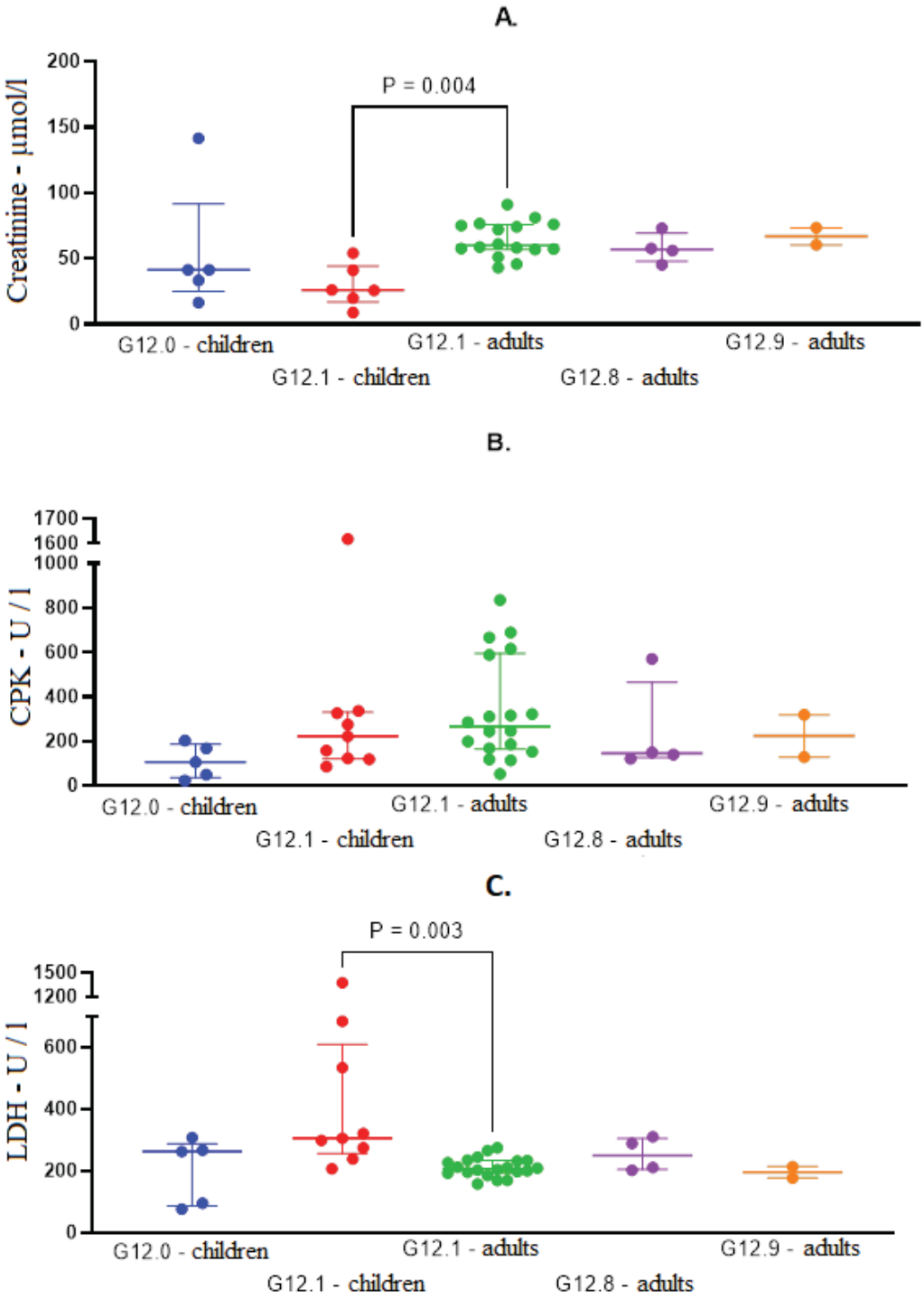


Figure 1. Levels of creatinine (A), CPK (B) and LDH (C) in patients with diagnoses G12.0, G12.1, G12.8 and G12.9, taking age into account

LDH levels. Due to limited sample size and heterogeneity of the data, results for patients with repeat hospitalizations did not support strong conclusions about time-dependent individual changes biomarker levels. Similarly, the collected data on the patients' mental status was insufficient to identify group differences or establish associations with biomarker levels; emotional lability, fatigue, and tearfulness are not specific symptoms.

CONCLUSIONS

Routine laboratory diagnostic methods for SMA, particularly the measurement of creatinine and CK levels, did not reveal differences between the ICD subgroups, nor any association with severity of motor impairments. Although serum LDH levels did show significant differences among the groups, these differences were likely related to body weight and age

rather than disease progression and motor impairments. Therefore, we cannot draw strong conclusions regarding the effectiveness of assessing creatinine, CK, and LDH levels for evaluating and predicting the course of the disease. As such, we do not recommend these laboratory tests as part of current clinical practice. Further research is needed to identify possible correlations between baseline CK levels and clinical presentation dynamics, and response to pathogenetic therapies such as nusinersen, onasemnogen abeparvovec, and risdiplam. Results also highlight the need for prospective investigations of the possible relationship between psychiatric impairments or symptoms, motor manifestations of SMA 5q, and the three widely accessible biomarker levels.

Limitations

The study included archival material from the main regional institution, therefore omitting data from SMA patients residing in the greater Samara Oblast who have not undergone diagnosis and treatment at our hospital. Additionally, the advanced age of some patients in the sample raises concerns about the accuracy of their diagnosis; genetic confirmation was only available in 12 subjects. The study is subject to the typical limitations of a retrospective design. The limited amount of data also does not allow for a comprehensive assessment of the dynamic changes in present blood biomarker levels in individual patients.

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Contribution of individual authors:

Arseny J. Gayduk, Timur Syunyakov & Yan V. Vlasov have composed the primary idea and specified the hypothesis.

Arseny J. Gayduk & Timur Syunyakov have been responsible for the literature data collection, its systematization and analysis, and wrote the first draft of the manuscript.

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