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SMArt Retro study: a retrospective data analysis of the Russian registry of patients with spinal muscular atrophy

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Background. Existing registries of patients with spinal muscular atrophy (SMA) 5q serve as a valuable source of information on identified patients. Information on the characteristics of Russian patients with SMA 5q and the therapy administered in real clinical practice is currently limited.
Aim. To describe a cohort of Russian patients with a confirmed diagnosis of SMA 5q and to evaluate patient routing data in real clinical practice settings in Russia.
Materials and methods. The present study was a descriptive non-interventional retrospective cohort study in patients diagnosed with SMA 5q who were enrolled in the Russian patient registry between January 1, 2020 and March 31, 2023. Study participants who met the inclusion criteria were automatically identified in the integrated database of the SMA 5q patient registry. Data were uploaded into validated electronic charts, verified and analyzed using descriptive statistics methods.
Results. As of March 31, 2023, the Russian SMA registry contained information on 1408 patients from all federal districts and obtained epidemiological, sociodemographic and clinical characteristics of patients, as well as routes to diagnosis and treatment regimens for patients. The median time from disease onset to confirmed diagnosis was 3 months in patients with SMA type 1, 9 months in patients with SMA type 2, 20 months in patients with SMA type 3 and 68 months in patients with SMA type 4. The median time from confirmed diagnosis to the start of disease-modifying therapy was 0.5 months in SMA patients identified by neonatal screening, 21 months in patients with SMA type 1, 59 months in patients with SMA type 2, 47 months in patients with SMA type 3 and 87 months in patients with SMA type 4.
Conclusion. This retrospective analysis was carried out in order to identify recent approaches to the diagnosis and treatment of SMA used in real-world clinical practice in Russia. The identified parameters (duration from the disease onset to confirmed diagnosis, duration from the confirmed diagnosis to disease-modifying therapy initiation) indicate that more widespread use of newborn screening and more rapid treatment initiation are unmet needs for SMA patients in Russia.

Keywords: spinal muscular atrophy 5q, demographic characteristics, detection rate, prevalence, genetic testing, diagnostic delay, neonatal screening

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Background

Spinal muscular atrophy (SMA) is a group of diseases characterized by degeneration of the anterior horn cells of the spinal cord and motor nuclei in the lower brain stem, leading to progressive muscle weakness and atrophy [1, 2]. The most common forms of SMA (5q SMAs) are caused by biallelic mutations in the survival motor neuron 1 (*SMN1*) gene on the long arm of chromosome 5 (5q13.2), leading to a deficiency of the SMN protein [3]. 5q SMA is a monogenic disease with an autosomal recessive type of inheritance; most often its natural course leads to the patient's death, and before disease-modifying therapy was developed, it had been the most common cause of genetically determined pediatric mortality [4].

The carrier frequency of *SMN1* mutations causing 5q SMA is 1 per 54 people, varying significantly depending on the ethnicity of the patient [5]; in Russia, it is 1 case per 36 people [6]. The incidence rate of 5q SMA is ~1 per 11,000 (~9.1 cases per 100,000) live births [5, 7], and its estimated detection rate in Russia is 1 per 5,184 live births [6]. The global prevalence of 5q SMA is ~1–2 cases per 100,000 population [8]. In Russia, according to the data of the newborn screening pilot projects, the incidence of SMA in Moscow was 1:7,801 newborns [9], and in Saint Petersburg, it was 1:9,009 [10].

5q SMA is classified as types 0–4 SMA depending on the age of the disease onset and the maximum achieved level of motor function development [11–13]. Type 0 SMA is the most severe form with the onset in the prenatal period and respiratory disorders after birth; type 1 SMA (Werdnig–Hoffmann disease) is a severe form with the onset before the age of 6 months characterized by the inability to sit without support; type 2 SMA (Dubowitz disease) is an intermediate form with the onset after the age of 18 months characterized by the ability to sit without support, but not the ability to stand or walk; type 3 SMA (Kugelberg–Welander disease) is a mild form with the onset after the age of 18 months characterized by the ability to stand and walk independently; and type 4 SMA is the mildest form with the onset over the age of 30 years. Classification of SMA into types 0–4 has clinical relevance for prognosis and treatment of patients. The severity of SMA is usually inversely proportional to the number of *SMN2* gene copies, which varies from 0 to 8 in the general population [14–17].

SMA patients require careful medical examination and ongoing monitoring, which necessitates intensive use of healthcare resources and a multidisciplinary approach to providing medical care.

Currently, available methods of disease-modifying therapy of SMA include single-dose gene replacement therapy (onasemnogene abeparvovec) and splicing modifiers (nusinersen, risdiplam), which must be taken continuously. Early detection and timely treatment of SMA are key factors for increasing survival and improving the prognosis of patients with SMA 5q in the long term [18].

Existing national and international registries of SMA patients serve as a valuable source of data on SMA patients and the methods used to diagnose and treat the disease [19–24]. However, currently, information on the clinical characteristics of Russian SMA patients is limited.

The aim of this project was to describe the socio-demographic, epidemiological and clinical characteristics of Russian patients with a confirmed diagnosis of SMA, as well as to analyze the methods of diagnosis and treatment used in real-world clinical practice.

Materials and methods

Study design. This study was a descriptive, non-interventional, retrospective cohort study in patients with diagnosed SMA included in the Russian SMA Patient Registry. The data was collected and analyzed using the Quinta platform (Certificate of state registration of software No. 2016615129, Quinta universal software package for collecting, processing, and managing geographically distributed clinical and epidemiological data; right holder: Aston Consulting JSC). The analysis of the collected epidemiological data started in 2019. The physicians involved in the Registry management represented 79 constituent entities of the Russian Federation located in all federal districts. These physicians included chief specialists in medical genetics and HCPs authorized by regional chief specialists in medical genetics, as well as other specialists, including chief neurologists. Six constituent entities were not included in the Russian SMA Patient Registry: the Republic of Kalmykia, the Jewish Autonomous Area, the Kamchatka Region, the Magadan Region, the Chukotka Autonomous Area, and the Yamalo-Nenets Autonomous Area.

The study covers the period from January 1, 2020, to March 31, 2023. This study was approved by the Independent Multidisciplinary Committee for Ethical Review of Clinical Trials, Moscow (protocol No. 08 dated May 13, 2022).

The study population included patients with a confirmed diagnosis of SMA with or without clinical manifestations.

Data sources and assessed characteristics of the Registry were entered into pre-approved electronic cards. Data entry into the Registry was approved by the regional chief geneticists participating in the study.

Patients who met the inclusion criteria were automatically identified in the integrated Registry database, and retrospective analysis was performed as part of the study. The results of comprehensive clinical examination, medical history analysis, instrumental examination, and test results for all identified patients were uploaded in an anonymized format.

Statistical analysis methods. The data were analyzed using software IBM SPSS Statistics 25. Only descriptive statistics methods were used in this study. For quantitative data, the mean value, standard deviation, median, minimum and maximum values (min, max), and 1st and 3rd quartiles (Q1, Q3) were calculated. For categorical data, absolute and relative values (*n*, %) were calculated. All data were analyzed descriptively in the general cohort of SMA patients and in individual subgroups.

Results

As of March 31, 2023, the Russian SMA Patient Registry contained information on 1,408 patients from all federal districts of the Russian Federation; 1,383 of them were alive, and 25 patients died.

Distribution of patients by constituent entity of residence. The largest number of SMA patients was reported in Krasnodar Territory, Moscow, and the Republic of Bashkortostan (104, 89, and 80 patients, respectively). A slightly smaller number of SMA patients was registered in Sverdlovsk Region, Saint Petersburg, Moscow Region, Rostov Region, and Stavropol Territory (64, 60, 51, 47, and 45 patients,

Table 1. *Distribution of patients with diagnosed spinal muscular atrophy 5q by region of residence in the Russian Federation*

Region	Number of patients entered in the registry
Krasnodar region	104
Moscow	89
Republic of Bashkortostan	80
Sverdlovsk region	64
Saint Petersburg	60
Moscow region	51
Rostov region	47
Stavropol territory	45
11 regions	21–37
22 regions	11–20
38 regions	1–10

respectively). The rest of the constituent entities (CE) were grouped: there were 11 CEs with 21–37 (inclusive) patients with SMA, 22 CEs with 11–20 (inclusive) patients with SMA, and 38 CEs with 1–10 (inclusive) patients with SMA (Table 1).

Epidemiology of SMA. In this study, **the SMA detection rate** was calculated for 2019, 2020, and 2021, depending on the patient's age. Statistical data on the population of 79 CEs were included in the calculation. To calculate the SMA detection rate by age, the population of 79 CEs was divided into age groups, and the SMA detection rate was calculated separately for each group. For example, the estimated detection rate of SMA in the 0–4 years group in 2019, 2020, and 2021 was 0.95, 1.11, and 0.44 cases per 100,000 children in this age group, respectively.

Also, there is a method for calculating the annual rate of SMA detection based on the total number of newborns per year and the number of new cases of SMA. It is acceptable when SMA can be diagnosed at birth for all patients through ongoing neonatal screening programs. However, until the beginning of 2023, newborn screening for SMA in Russia was carried out only in the pilot CEs. Once the number of newborns diagnosed with SMA in the year of birth or later was processed, the most complete information (by CE and the number of registered cases of SMA) was provided for children born in 2019 and 2020. The audit data in 52 CEs showed that the average detection rate of SMA in 2019 and 2020 was 6.5 and 5.6 cases of SMA per 100,000 live births, respectively.

Prevalence of SMA. In the current study, the prevalence was calculated as the total number of patients entered in the Registry at the end of the reporting period divided by the total number of the population of CEs (79 CEs) of the corresponding age, the data for which were entered in the Registry, recalculated per 100,000 population. For example, the estimated prevalence of SMA in the 0–4 years group in 2019, 2020, and 2021 was 4.45, 4.40, and 3.80 cases per 100,000 children in this age group, respectively.

Distribution of patients by gender. Among 1,408 patients in the Registry, 50.6 % (n = 712) were female and 49.4 % (n = 696) were male (Table 2).

Distribution of patients by ethnicity. Among 531 patients in the Registry for whom the data on nationality were available, 80.8 % of patients (n = 429) were Russian, 4.0 % (n = 21) were Tatar, 3.2 % (n = 17) were Bashkir, 2.1 % (n = 11) were Armenian, 1.3 % (n = 7) were Ukrainian, and 1.1 % (n = 6) were Azerbaijani; the remaining 7.5 % (n = 40) of patients belonged to other ethnic groups.

Distribution of patients by the Surviving/Deceased status. As of March 31, 2023, the deceased patients accounted for 1.8 % (n = 25) of all patients included in the Registry and were represented by patients with type 1 SMA (n = 22) and type 2 SMA (n = 3). The main cause of death was stated to be cardiopulmonary failure (Table 2).

Disability status. Among 556 patients of the Registry for whom the disability data were available, 15.1 % of patients (n = 84) had group I disability, 2.2 % (n = 12) had group II disability, and 2.0 % (n = 11) had group III disability; 80.8 % of patients (n = 449) had a childhood disability status. Patients with childhood disability status accounted for 97.7 % of patients with type 1 SMA (n = 125), 86.1 % of patients with type 2 SMA (n = 241), and 61.0 % of patients with type 3 SMA (n = 83); type 4 SMA patients had no disability since childhood. Most patients with type 4 SMA had disability group III (50.0 %, n = 6) and disability group I (41.7 %, n = 5) (Table 2).

Palliative care. Of 804 patients in the Registry for whom the data on palliative care were available, 29.1 % of patients (n = 234) received palliative therapy. The population of patients receiving palliative therapy included 41.0 % of patients with type 1 SMA (n = 87), 34.1 % of patients with type 2 SMA (n = 126), 10.9 % of patients with type 3 SMA (n = 20) and 5.9 % of patients with type 4 SMA (n = 1). The rest, 570 patients (70.9 %), did not receive palliative care (Table 2).

Distribution of patients by diagnosis. Among 1,342 patients in the Registry for whom the data on SMA type were available, type 1 SMA was diagnosed in 33.2 % of patients (n = 446), type 2 SMA in 45.2 % of patients (n = 606), type 3 SMA in 20.3 % of patients (n = 273), and type 4 SMA in 1.3 % of patients (n = 17).

Distribution of patients by family history. Of 763 patients of the Registry who had data on the family history of SMA, 86.1 % of patients did not have SMA in their family history (n = 657), whereas 13.9 % of patients had cases of SMA in the family history (n = 106), of which in 48.1 % of cases (n = 51) SMA was diagnosed in the patients' sisters and in 43.3 % of cases (n = 46) in the patients' brothers (Table 3).

Table 2. *Sociodemographic characteristics of patients from the spinal muscular atrophy 5q registry*

Parameter		Type of spinal muscular atrophy				
		1	2	3	4	All patients*
Gender	Total number of patients	446	606	273	17	1408
	Male, *n* (%)	242 (54.3)	268 (44.2)	141 (51.6)	10 (58.8)	696 (49.4)
	Female, *n* (%)	204 (45.7)	338 (55.8)	132 (48.4)	7 (41.2)	712 (50.6)
Status of patient	Total number of patients	446	606	273	17	1408
	Alive, *n* (%)	424 (95.1)	603 (95.5)	273 (100)	17 (100)	1383 (98.2)
	Died, *n* (%)	22 (4.9)	3 (0.5)	0	0	25 (1.8)
Disability	Total number of patients	128	280	136	12	556
	First-class disability, *n* (%)	3 (2.3)	38 (13.6)	38 (27.9)	5 (41.7)	84 (15.1)
	Second-class disability, *n* (%)	0	1 (0.4)	10 (7.4)	1 (8.3)	12 (2.2)
	Third-class disability, *n* (%)	0	0	5 (3.7)	6 (50.0)	11 (2.0)
	Childhood disability, *n* (%)	125 (97.7)	241 (86.1)	83 (61.0)	0	449 (80.8)
Receiving palliative care	Total number of patients	212	370	184	17	804
	Yes, *n* (%)	87 (41.0)	126 (34.1)	20 (10.9)	1 (5.9)	234 (29.1)
	No, *n* (%)	125 (59.0)	244 (65.9)	164 (89.1)	16 (94.1)	570 (70.9)

**Here and in tables 3–8: "All patients" column also included patients with a deletion in the SMN1 gene detected at neonatal screening and patients with no data about spinal muscular atrophy type.*

Age at disease onset. In 1,077 patients for whom the data on age at disease onset were available, the median (Q1–Q3) age at disease onset in the total cohort of patients with SMA was 9.0 (5.0–17.0) months. In clinical subgroups based on the SMA type, the median (Q1–Q3) age at disease onset was 3.0 (1.0–6.0) months in patients with type 1 SMA ($n = 357$), 10.0 (6.5–14.0) months in patients with type 2 SMA ($n = 472$), 25.0 (16.0–48.0) months in patients with type 3 SMA ($n = 221$), and 180.0 (148.0–229.0) months in patients with type 4 SMA ($n = 15$) (Table 3).

Age at the time of confirmed diagnosis. In 1,253 patients in the Registry who had data on the age at the time of the confirmed diagnosis, the median (Q1–Q3) age at the time of diagnosis was 7.0 (3.0–14.0) months in patients with type 1 SMA ($n = 414$), 21.0 (14.0–32.0) months in patients with type 2 SMA ($n = 545$), 54.0 (31.0–133.0) months in patients with type 3 SMA ($n = 259$), and 274.5 (190.0–371.0) months in patients with type 4 SMA ($n = 16$) (Table 3).

Molecular genetic testing for SMA. Of 1,408 patients in the Registry, 93.9 % of patients ($n = 1,322$) had molecular genetic testing. Of these, 27 patients were identified as part of pilot projects of newborn screening in 2022.

Reasons for molecular genetic testing. In 693 patients of the Registry for whom information on the reasons for conducting molecular genetic analysis was entered, the reasons for referral for molecular genetic testing were: clinical signs of the disease in 91.3 % of patients ($n = 633$), burdened family history in 2.7 % of patients ($n = 19$), patient's request in 1.9 % of patients ($n = 13$), and other reasons in 4.0 % of patients ($n = 28$).

Laboratories used for molecular genetic testing in the diagnosis of SMA. Of 1,154 patients in the Registry who had data on the laboratories where molecular genetic testing was performed, 61.8 % of patients ($n = 713$) had a genetic test for SMA at the N.P. Bochkov Research Center for Medical Genetics, 21.3 % of patients ($n = 246$) in the laboratories of regional centers, in 11.8 % of patients ($n = 136$) in Russian commercial laboratories, in 1.6 % of patients ($n = 18$) in foreign laboratories; in 3.5 % of cases ($n = 41$), the type of laboratory could not be determined.

Sources of funding for molecular genetic testing for SMA. In 696 patients in the Registry with available data on sources of funding of molecular genetic testing for SMA, the distribution was as follows: the patient's own funds in 51.9 % of cases ($n = 361$), federal budget in 35.9 % of cases ($n = 250$), newborn screening, including pilot projects in 7.3 % of cases ($n = 51$), charity foundations in 4.6 % of cases ($n = 32$), and voluntary health insurance in 0.3 % of cases ($n = 2$).

Table 3. *Characteristics of patients from the spinal muscular atrophy 5q registry*

Parameter		Type of spinal muscular atrophy				
		1	2	3	4	All patients
Age at disease onset, months	Total number of patients	357	472	221	15	1077
	Median	3.0	10.0	25.0	180.0	9.0
	Q1–Q3*	1.0–6.0	6.5–14.0	16.0–48.0	148.0–229.0	5.0–17.0
	0–6 months, *n* (%)	236 (66.1)	69 (14.6)	7 (3.2)	0	314 (29.2)
	7–17 months, *n* (%)	105 (29.4)	335 (71.0)	57 (25.8)	0	504 (46.8)
	≥18 months, *n* (%)	16 (4.5)	68 (14.4)	157 (71.0)	15 (100)	259 (24.0)
Age at diagnosis confirmation, months	Total number of patients	414	545	259	16	1253
	Median	7.0	21.0	54.0	274.5	19.0
	Q1–Q3	3.0–14.0	14.0–32.0	31.0–133.0	190.0–371.0	10.0–38.0
Family history of a patient with spinal muscular atrophy	Total number of patients	199	353	175	16	763
	Cases of spinal muscular atrophy in the family, *n* (%)	18 (9.0)	48 (13.6)	34 (19.4)	5 (31.3)	106 (13.9)
	No cases of spinal muscular atrophy in the family, *n* (%)	181 (90.6)	305 (86.4)	141 (80.6)	11 (68.7)	657 (86.1)
Motor skills**	Total number of patients	446	606	273	17	1408
	No control of the head, *n* (%)	180 (40.4)	68 (11.2)	6 (2.3)	0	262 (18.6)
	Can't roll over on his own, *n* (%)	213 (47.8)	175 (28.9)	28 (10.3)	2 (11.8)	432 (30.7)
	Doesn't sit with support, *n* (%)	162 (36.3)	69(11.4)	6 (2.2)	0	247 (17.5)
	Sitting with support, *n* (%)	99 (22.2)	201 (33.2)	33 (12.1)	1 (5.9)	341 (24.2)
	Walks independently, *n* (%)	128 (28.7)	272 (44.9)	76 (27.8)	4 (23.5)	492 (34.9)
	Difficulty lifting from a sitting position on the floor (uses Gowers' sign), *n* (%)	53 (11.9)	77 (12.7)	113 (41.4)	8 (47.1)	253 (18.0)
Other clinical parameters	Total number of patients	446	606	273	17	1408
	Invasive lung ventilation, *n* (%)	70 (15.6)	14 (2.3)	2 (0.7)	0	88 (6.3)
	Noninvasive lung ventilation, *n* (%)	102 (22.9)	81 (13.4)	7 (2.6)	0	193 (13.7)
	Probe feeding, *n* (%)	5 (1.1)	0	1 (0.4)	0	6 (0.4)
	Feeding through gastrostomy, *n* (%)	49 (11.0)	4 (0.7)	3 (1.1)	0	59 (4.2)

**Q1–Q3 – quartile.*
***The assessed indicators of motor skills are presented in accordance with the wording adopted in the electronic individual patient record.*

Methods of molecular genetic testing for SMA. In 748 patients of the Registry for whom the data on the method for determining the presence of exon 7–8 deletions in the *SMN1* gene, qualitative methods (restriction fragment length polymorphism) were used in 74.2 % of patients (n = 555), and quantitative methods (multiplex amplification of ligated probes and real-time polymerase chain reaction) were used in 25.8 % of patients (n = 193). Among 1,408 patients in the Registry, the number of *SMN2* copies was determined only in 51.0 % of patients (n = 718).

Heterogeneity of SMA genotypes/phenotypes. *SMN1* gene. Of 1,322 patients in the Registry with the results of genetic testing, homozygous deletion of exon 7 of the *SMN1* gene (del/del genotype) was found in 81.8 % of patients (n = 1,082); heterozygous deletion of *SMN1* exon 7 was found in 1.6 % of patients (n = 21) (del/point mutation in 14 patients; del/unknown pathogenic variant in 7 patients); a homozygous mutation in the *SMN1* gene (point mutation) was found in 0.2 % of patients (n = 2); 16.4 % of patients (n = 217) had no data on the *SMN1* gene status. The distribution of *SMN1* genotypes was similar for all clinical SMA phenotypes.

***SMN2* gene.** Of 718 patients in the Registry who had data on the number of copies of the *SMN2* gene, 22.7 % of patients (n = 163) had 2 copies, 61.8 % of patients (n = 444) had 3 copies, 13.6 % of patients (n = 98) had 4 copies, 1.1 % of patients (n = 8) had 5 copies, and 1 patient had 6 copies. Most patients with type 1 SMA had 2 or 3 copies of the *SMN2* gene (52.9 % (n = 111) and 44.8 % (n = 94) of patients, respectively); most patients with type 2 SMA had 3 copies of *SMN2* (79.2 % (n = 252)); most patients with type 3 SMA had 3 or 4 copies of *SMN2* (49.0 % (n = 75) and 40.5 % (n = 62) of patients, respectively); most patients with type 4 SMA had 4 copies of *SMN2* (50.0 % (n = 3) of patients) (Table 4).

Routing of SMA patients. Specialists referring to a geneticist. Of 1,408 patients in the Registry for whom data on specialists referring to a geneticist were available, 47.5 % of patients (n = 669) were referred by a neurologist, 6.9 % (n = 97) by a pediatrician, 0.3 % (n = 6) by a general practitioner, 0.2 % (n = 3) by an orthopedist, 0.3 % (n = 4) by an emergency room doctor, and 1.6 % (n = 22) by other specialists; 20.3 % (n = 286) of patients presented to a geneticist without a referral from a specialist, 22.8 % of patients (n = 321) had no information about the specialist who referred them for consultation with a geneticist (Table 5).

Specialists who follow-up SMA patients. Of 1,408 patients in the Registry, the majority were followed up by a neurologist (49.2 %, n = 693), a pediatrician (42.3 %, n = 596), and a geneticist (23.2 %, n = 327). Some patients with type 1–3 SMA also required follow-up by an orthopedist, pulmonologist, rehabilitation specialist, gastroenterologist, and general practitioner (Table 5).

Parameters characterizing the delay in diagnosis and treatment. For 1,058 patients in the Registry with data on the time from the disease onset to the confirmed diagnosis, the median (Q1–Q3) was 7 (2.0–17.0) months (for all patients): 1 (1–2) months in patients identified by newborn screening, 3 (1–7) months in patients with type 1 SMA, 9 (4–17) months in patients with type 2 SMA, 20 (8–62) months in patients with type 3 SMA, and 68 (24–145) months in patients with type 4 SMA (Table 6). For 529 patients of the Registry who had data on the time from the confirmed diagnosis to the pathogenetic therapy initiation, the median (Q1–Q3) was 39 (12–94) months (for all patients): 0.5 (0.0–1.5) months in patients identified at neonatal screening, 21 (8–47) months in patients with type 1 SMA, 59 (26–118) months in patients with type 2 SMA, 47 (14–109) months in patients with type 3 SMA, and 87 (29–144) months in patients with type 4 SMA (Table 6).

Treatment regimens for SMA patients. Information on therapy used was available in the Registry only for 40.5 % (n = 570) of patients. In total, four treatment modalities

Table 4. *SMN2 gene copy number in spinal muscular atrophy 5q patients*

Parameter		Type of spinal muscular atrophy				
		1	2	3	4	All patients
Number of patients with the identified *SMN2* gene copies number	1 copy, *n* (%)	0	2 (0.6)	1 (0.7)	0	4 (0.6)
	2 copies, *n* (%)	111 (52.9)	37 (11.6)	11 (7.2)	0	163 (22.7)
	3 copies, *n* (%)	94 (44.8)	252 (79.2)	75 (49.0)	2 (33.3)	444 (61.8)
	4 copies, *n* (%)	5 (2.4)	24 (7.5)	62 (40.5)	3 (50.0)	98 (13.6)
	5 copies, *n* (%)	0	2 (0.6)	4 (2.6)	1 (16.7)	8 (1.1)
	6 copies, *n* (%)	0	1 (0.3)	0	0	1 (0.1)
	Total number of patients	210	318	153	6	718

Table 5. *Doctors involved in patient routing for diagnosis and treatment of spinal muscular atrophy*

Parameter		Type of spinal muscular atrophy				
		1	2	3	4	All patients
Number of patients referred by a specialist to a geneticist	Total number of patients	446	606	273	17	1408
	Without referral from a specialist, *n* (%)	104 (23.3)	129 (21.3)	40 (14.7)	3 (17.6)	286 (20.3)
	Neurologist, *n* (%)	176 (39.5)	318 (52.5)	161 (59.0)	14 (82.4)	669 (47.5)
	Pediatrician, *n* (%)	38 (8.5)	38 (6.3)	19 (7.0)	0	97 (6.9)
	Orthopedist, *n* (%)	1 (0.2)	2 (0.3)	0	0	3 (0.2)
	Resuscitator, *n* (%)	4 (0.9)	0	0	0	4 (0.3)
	Therapist, *n* (%)	0	2 (0.3)	4 (1.5)	0	6 (0.3)
	Other specialist, *n* (%)	4 (0.9)	0	0	0	22 (1.6)
	No data, *n* (%)	119 (26.7)	117 (19.3)	49 (17.9)	0	321 (22.8)
Expert who observed the patient	Total number of patients	446	606	273	17	1408
	Neurologist, *n* (%)	176 (39.5)	321 (53.0)	171 (62.6)	12 (70.6)	693 (49.2)
	Pediatrician, *n* (%)	157 (35.2)	286 (47.2)	133 (48.7)	8 (47.1)	596 (42.3)
	Therapist, *n* (%)	2 (0.4)	13 (2.1)	18 (10.5)	4 (23.5)	37 (2.6)
	Pulmonologist, *n* (%)	33 (7.4)	43 (7.1)	7 (2.6)	0	83 (5.9)
	Rehabilitologist, *n* (%)	23 (5.2)	52 (8.6)	17 (6.2)	0	92 (6.5)
	Orthopedist, *n* (%)	53 (11.9)	155 (25.6)	85 (31.1)	1 (5.9)	295 (21.0)
	Gastroenterologist, *n* (%)	11 (2.5)	9 (1.5)	3 (1.1)	0	23 (1.6)
	Geneticist, *n* (%)	97 (21.7)	131 (21.6)	77 (28.2)	6 (3.5)	327 (23.2)

were registered in patients: disease-modifying therapy with splicing modifiers (monotherapy with nusinersen or risdiplam), disease-modifying therapy with one-time gene replacement therapy (monotherapy with onasemnogene abeparvovec), switching (initial prescription of another disease-modifying therapy (nusinersen or risdiplam) followed by a switch to gene replacement therapy), and combination therapy (initiation of another disease modifying therapy (nusinersen or risdiplam) after gene replacement therapy).

Among 570 patients, 507 patients received disease-modifying therapy with splicing modifiers (monotherapy with nusinersen or risdiplam): 77.7 % of patients with type 1 SMA (n = 157/202), 94.5 % of patients with type 2 SMA (n = 223/236), 99.0 % of patients with type 3 SMA (n = 99/100), and 100 % of patients with type 4 SMA (n = 2/2). Twenty-six patients received gene replacement therapy (as monotherapy): 11.4 % of patients with type 1 SMA (n = 23/202) and 1.3 % of patients with type 2 SMA (n = 3/236). Switching from disease-modifying therapy with splicing modifiers to one-time gene replacement therapy was observed in a number of patients: 9.4 % of patients with type 1 SMA (n = 19/202), 4.2 % of patients with type 2 SMA (n = 10/236), and 1.0 % of patients with type 3 SMA (n = 1/100). Combination therapy was used in 1.5 % of patients with type 1 SMA (n = 3/202) (Table 7).

Age at treatment initiation. The median age of patients at treatment initiation was 2.0 months in patients identified at newborn screening and without the onset of clinical manifestations by initiation of therapy (n = 6), 3.5 months in patients identified at newborn screening and with the subsequent onset of clinical manifestations by initiation of therapy (n = 4), 29.5 months in patients with type 1 SMA (n = 204), 86 months in patients with type 2 SMA (n = 237), 135.5 months in patients with type 3 SMA (n = 100), and 354.5 months in patients with type 4 SMA (n = 2) (Table 8).

Table 6. *Parameters to assess delay at the stage of diagnosis confirmation and treatment initiation of patients in the spinal muscular atrophy 5q registry**

Parameter		Patients with deletion in *SMN1* gene detected at neonatal screening	Type of spinal muscular atrophy				
			1	2	3	4	All patients
Waiting time for genetic test results, months	Total number of patients	27	309	381	199	17	937
	Mean value (standard deviation)	0.3 (0.5)	0.7 (3.7)	0.6 (1.6)	0.8 (4.8)	0.6 (0.6)	0.6 (3.2)
	Median	0	0	0	0	1.0	0
	Q1–Q3	0–1	0–1	0–1	0–1	0–1	0–1
Period from the onset of the disease to confirmation of diagnosis, months	Total number of patients	9	350	463	218	15	1058
	Mean value (standard deviation)	3.4 (5.3)	5.9 (11.8)	18.6 (40.6)	56.6 (98.5)	108.0 (115.6)	23.4 (58.2)
	Median	1	3	9	20	68	7
	Q1–Q3	1–2	1–7	4–17	8–62	24–145	2–17
Period from confirmation of diagnosis to initiation of pathogenetic therapy, months	Total number of patients	4	192	229	96	2	529
	Mean value (standard deviation)	0.8 (1.0)	36.0 (49.3)	79.3 (73.9)	79.7 (91.9)	86.5 (81.3)	63.4 (72.3)
	Median	0.5	21	59	47	87	39
	Q1–Q3	0–1.5	8–47	26–118	14–109	29–144	12–94

**Represents data for the first quarter of 2023 (from the start of expanded neonatal screening).*
***Q1–Q3 – quartile.*

Table 7. *Treatment regimens for registry spinal muscular atrophy 5q patients (data are current as of the end of first quarter of the year 2023)*

Parameter		Type of spinal muscular atrophy				
		1	2	3	4	All patients
Type of therapy	Total number of patients	202	236	100	2	570
	Pathogenetic monotherapy with splicing modifiers: nusinersen or risdiplam, *n* (%)	157 (77.7)	223 (94.5)	99 (99.0)	2 (100)	507 (88.9)
	Gene replacement therapy as monotherapy, *n* (%)	23 (11.4)	3 (1.3)	0	0	26 (4.6)
	Switching therapies*, *n* (%)	19 (9.4)	10 (4.2)	1 (1.0)	0	34 (6.0)
	Combination therapy**, *n* (%)	3 (1.5)	0	0	0	3 (0.5)

**Switching therapy (initial administration nusinersen or risdiplam followed by switching to gene replacement therapy).*
***Combination therapy – administration of another pathogenic therapy (nusinersen or risdiplam) after gene replacement therapy (data from 2022, when the criteria for therapy selection and administration of gene replacement therapy through the Circle of Kindness Foundation did not have strict restrictions) [25].*

Table 8. *Age of registry patients at the time of therapy initiation*

Parameter		Neonatal screening for spinal muscular atrophy*		Type of spinal muscular atrophy				
		Patients with deletion in *SMN1* gene, asymptomatic at the beginning of therapy	Patients with a deletion in the *SMN1* gene with debut by the start of therapy	1	2	3	4	All patients
Age at the start of therapy, months	Total number of patients	6	4	204	237	100	2	572
	Mean value (standard deviation)	2,3 (1,9)	3,3 (2,5)	46,2 (54,4)	106,2 (79,6)	161,0 (113,4)	354,5 (163,3)	93,3 (89,4)
	Median	2,0	3,5	29,5	86,0	135,5	354,5	66,5
	Q1–Q3**	1,0–2,0	1,5–5,0	11,0–60,0	51,0–147,0	78,5–197,0	239,0–470,0	30,0–135,0

**Represents data for the first quarter of 2023 (from the start of expanded neonatal screening).*
***Q1–Q3 – quartile.*

Discussion

The conducted retrospective cohort study included data on SMA patients from all federal districts of the Russian Federation obtained from the SMA Patient Registry over the period from January 1, 2020, to March 31, 2023. The primary, secondary, and exploratory objectives of the study were achieved.

As of March 31, 2023, this retrospective cohort study provided data on 1,408 SMA patients from 79 CEs representing all federal districts of the Russian Federation. It should be noted that the considered period of adding patient data to the SMA Registry (from January 1, 2020, to March 31, 2023) did not allow obtaining sufficient information from the pilot newborn SMA screening projects (start date: Q2 2022) and from the federal expanded newborn screening program for SMA (start date: January 1, 2023), and therefore it was not possible to conduct the analysis of the true incidence of the disease [26].

According to the conducted retrospective analysis, the estimated SMA detection rate in the Russian Federation in 2019 and 2020 was 6.5 and 5.6 cases per 100,000 live births, respectively. These figures in Russia were lower than the average annual rate in the world (~9.1 cases per 100,000 newborns) [5, 7]. The prevalence of SMA in Russia was calculated by age groups, so it was not possible to compare the estimated values with the average global prevalence of SMA (1–2 cases per 100,000 population). The estimated prevalence of SMA in Russia by age groups was the highest in the 0–4 years group, which was associated with the onset of SMA symptoms in majority of patients during this period (Table 3).

Since 2023, SMA 5q has been included in the expanded neonatal screening, which allows for the correct calculation of the annual detection rate of SMA 5q based on the total number of newborns in Russia. Thus, according to data for 2023, 117 cases of SMA 5q were detected among 1,230,000 newborns examined. Thus, the detection rate of SMA 5q was 1:10,512 newborns [27].

The structure of the SMA detection rate in different regions of the Russian Federation was heterogeneous, while in some regions the frequency of detection was low. The largest number of SMA patients was observed in larger CEs of the Russian Federation: Krasnodar region ($n = 104$), Moscow city ($n = 89$), the Republic of Bashkortostan ($n = 80$), Sverdlovsk Region ($n = 64$), Saint Petersburg ($n = 60$), Moscow Region ($n = 51$), and Rostov Region ($n = 47$). These results can be explained by a higher prevalence of SMA in the population of these territories, a more diverse ethnic composition, and, probably, higher accessibility of medical care for patients with genetic diseases in these CEs. Further study of this issue and obtaining information on the prevalence of SMA 5q in various regions is required for the purpose of further developmentdevelopment of medical genetic services in the constituent entities of the Russian Federation.

The proportions of male and female patients in the SMA Patient Registry were similar: 50.6 % ($n = 712$) of patients were female and 49.4 % ($n = 696$) were male. Also, there were no significant differences in the distribution of patients by gender depending on the type of SMA.

The distribution of patients in the Russian Registry by the SMA type was similar to that in the Iranian, Argentinian, and Spanish SMA Registries: most patients

had type 2 SMA (45.2 % in the Russian Registry, 44.9 % in the Argentinian Registry, 36.6 % in the Iranian Registry, and 48.5 % in the Spanish Registry) and type 1 SMA (33.2 % in the Russian Registry, 30.0 % in the Argentinian Registry, 36.8 % in the Iranian Registry, and 22.0 % in the Spanish Registry) [28–30]. Thus, the distribution of patients with different types of SMA 5q in the Russian Federation differed from the previously published estimates of SMA detection rates in the United States, according to which type 1 SMA accounts for ~60 % of patients, type 2 SMA for 29 % of patients, and type 3 SMA for 13 % [31]. It is suggested that the observed difference in the distribution of patients with different types of SMA 5q may be due to the earlier implementation of neonatal screening programs in the United States [32].

As is known, families with a burdened history of hereditary diseases are at risk and require careful monitoring. In our analysis, a family history of SMA 5q was detected in 13.9 % of cases (n = 106). A particularly important step in monitoring such families is genetic counseling when planning pregnancy to prevent the recurrence of sick children in these families. However, in our retrospective analysis, most patients had sporadic cases of SMA 5q (86.1 % of patients, n = 657).

Clinical manifestations of the disease were the main reason for referral for molecular genetic testing in 91.3 % (n = 633) of patients.

Molecular genetic testing for SMA was carried out mainly in the N.P. Bochkov Research Center for Medical Genetics laboratory (61.8 % of patients, n = 713) and in the laboratories of regional centers (21.3 % of patients, n = 246).

Currently, according to the clinical guidelines for the treatment of 5q SMA, quantitative methods (multiplex amplification of ligated probes and real-time polymerase chain reaction) should be used for the diagnosis of SMA. However, in real-world practice during the retrospective analysis, these methods were used in as low as 25.8 % (n = 193) of patients, with more frequent use of qualitative methods (restriction fragment length polymorphism) (74.2 % of patients, n = 555). Data on the number of the *SMN2* gene copies (the main modifying factor of SMA) were present in the Registry only in half of the patients in the Registry (51.0 % of patients, n = 718). Most patients with type 1 SMA had 2–3 copies of the *SMN2* gene, patients with type 2 SMA had 3 copies, patients with SMA type 3 had 3–4 copies, and patients with type 4 SMA had 4 copies of the *SMN2* gene. The identified low *SMN2* gene copy number detection (for comparison, the level of testing for the number of the *SMN2* gene copies in the Iranian SMA Registry was significantly higher, at 77 % [28]) is due to the fact that this testing was not mandatory until the registration of pathogenetic therapy in the Russian Federation.

Currently, the number of *SMN2* gene copies is one of the criteria for choosing the type of therapy in patients with SMA 5q and is determined in all newborns with a confirmed diagnosis of SMA 5q. Extended neonatal screening allows us to regularly obtain objective information on the distribution of patients depending on the number of *SMN2* gene copies. Thus, according to the results of screening for 2023, the distribution of patients was as follows: among 120 patients with a diagnosed disease, 43 (35.83 %) had 2 copies of the *SMN2* gene, 31 (25.83 %) had 3 copies of the *SMN2* gene, 32 (26.67 %) had 4 copies of the *SMN2* gene, and 1 (0.8 %) had 5 copies of the *SMN2* gene. Chimeric genotype variants were also found in 13 (10.83 %) [27]. The identified trend towards an increase in the number of patients with a large number of copies of the *SMN2* gene (≥4 copies) is similar to data obtained in Germany in the framework of pilot newborn screening projects, in which the proportion of such patients was approximately 40 % [33].

Today, the situation with molecular genetic testing of the disease has significantly improved due to the development of medical care for patients with SMA. As of 2024, the diagnosis is established using quantitative diagnostic methods both at the asymptomatic stage of the disease as part of expanded newborn screening, and in the presence of symptoms that are alarming in relation to SMA in patients who, for various reasons, are not covered by the newborn screening program [34].

Timely diagnosis of hereditary diseases and the appointment of pathogenetic therapy are key factors that can significantly affect the prognosis of the disease and patient outcomes. A number of parameters requiring dynamic assessment are important from the point of view of practical healthcare. These include the duration of the period from the onset of the disease to confirmation of the diagnosis of SMA 5q. Analysis of the time from the disease onset to the specified diagnosis demonstrated a delay in the diagnosis of SMA: the median values were 3 months for SMA type 1 (n = 350), 9 months for type 2 SMA (n = 463), 20 months for type 3 SMA (n = 218), and 68 months for type 4 SMA. Delayed diagnosis is a common problem in SMA [28, 29, 35]. The duration of the diagnostic delay in our study depended on the type of SMA and was longer in SMA types 3 and 4, which can be explained by the late onset of the disease in these types of SMA and minimal clinical manifestations of the disease, requiring differential diagnosis performance with other neurological diseases. Lack of awareness of the characteristics of SMA types 3–4 usually leads to a long differential diagnostic search for other neurological diseases. Newborn screening allows identifying patients at a presymptomatic stage of the disease. However, in patients with a severe variant of the disease, the development of clinical symptoms may be noted even before confirmation of the diagnosis as part of screening, which was recorded in 4 patients in our analysis.

Studies on the natural history of the disease have shown that an earlier onset of the first symptoms correlates with the severity of the disease [36]. Compared with the data

presented by C.W. Lin et al. (2015), the age of Russian patients with SMA types 1–2 at the time of disease onset (median age – 3.0 and 10.0 months, respectively) was similar, and for SMA type 3 at the time of disease onset (median age 25 months) it was significantly lower than in the cited study (median age 39 months) [35].

Other important time parameters characterizing the timing of medical care for patients with SMA 5q include the duration of the period from confirmation of diagnosis to the start of pathogenetic therapy. According to the analysis of the time from the confirmed diagnosis to the disease-modifying therapy initiation, there was a significant delay in the start of therapy for all types of SMA: the median values were 21 months for type 1 SMA ($n = 192$), 59 months for type 2 SMA ($n = 229$), 47 months for type 3 SMA ($n = 96$), and 87 months for type 4 SMA ($n = 2$). These data indicate a significant medical and social problem, since pediatric patients, in particular patients with type 1–2 SMA, do not receive timely disease-modifying therapy, which may lead to their early disability (according to the data of the conducted retrospective analysis, 97.7 % of patients with type 1 SMA and 86.1 % of patients with type 2 SMA had the status of childhood disability). At the same time, the limited data for Q1 2023 showed that the median of this indicator in patients with the *SMN1* gene deletion identified by newborn screening was as low as 0.5 months, which reflects the efficacy of mass newborn screening in real-world clinical practice in terms of optimizing the timing of therapy in patients with SMA.

Our study also noted that at the time of the retrospective analysis information on the used disease-modifying therapy was available only for 40.5 % of patients in the Registry. This parameter did not reflect accurate information on access to therapy due to incomplete source data. In different countries, the rate of access to therapy varies. For example, according to the Iranian and Argentinian SMA Registries, 76.6 % and 68 % of patients had access to therapy, respectively [28, 29]. At the moment, in the Russian Federation, almost all pediatric patients receive pathogenetic therapy through the Circle of Kindness Foundation, which regulates the provision of drugs to children with orphan diseases, including SMA 5q [25].

The conducted registry analysis showed that most patients receive monotherapy with various disease-modifying drugs. In rare cases, patients are switched from disease-modifying therapy with splicing modifiers to one-time gene replacement therapy. The analysis of the reasons that led to the need for switching was not carried out in this study.

In isolated cases, combination therapy was used (prescription of splicing modifiers after gene replacement therapy). The reasons for using this approach were not analyzed. In 2024, the international consensus on gene replacement therapy for SMA 5q was updated, stating that combination therapy should not be used in clinical practice due to the lack of convincing evidence of the superior efficacy of combination therapy compared to monotherapy [37]. Russian experts have similar opinion and do not consider it necessary to recommend combination therapy in patients with SMA [38].

Study limitations. This study had limitations typical of observational studies. The data source could contain incomplete data on patients if they were obtained in institutions outside the integrated data transfer network registered by Aston Consulting JSC. In addition, individual patient records could contain possible technical errors when filling out and be incomplete due to missing data. It was also possible that not all the chief specialists in medical genetics in the CEs entered patient data into the system, so the SMA population could be incomplete and not reflect the real rate of detection and prevalence of SMA in the country (selection bias).

Conclusion

This conducted retrospective study enabled us to evaluate current approaches to the diagnosis and treatment of SMA patients in real-world clinical practice in the Russian Federation, to evaluate them in accordance with national clinical guidelines, and to reveal the potential for optimizing the timing of diagnosis and access to therapy in order to close the unmet medical needs of SMA patients.

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D.V. Vlodavets: development of the study design, interpretation of the obtained data;
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Conflict of interest. D.V. Vlodavets is the principal investigator in clinical trials of the drug riddiplam NCT02913482, NCT02908685, NCT03779334 (F. Hoffmann La Roche Ltd), nusinersen NCT04089566, NCT04729907 (Biogen Idec Research Limited), branaplam NCT02268552 (Novartis Pharmaceuticals), ANB-004 NCT05747261 (Biocad JSC). The remaining authors declare no conflict of interest.

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