Spinal Muscular Atrophy in Samara Region. Epidemiology, Classification, Prospects for Health Care

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Abstract

In this article we discuss in detail the issue of spinal muscular atrophy in Russia and particularly in the Samara Regional Clinical Hospital n.a. V.D. Seredavin (Samara region) where a total of 58 living patients with SMA were registered by June 2019, 19 of them were children. The issues of classification and etiopathogenesis, prospects of pathogenetic treatment and prevention of SMA are being discussed.

Keywords: Hereditary Neuromuscular Diseases; Pathogenetic Treatment; Spinal Muscular Atrophy; Sma; Samara Region; Genetic Testing; Risdiplam; Nusinersen; Avxs-101

Spinal muscular atrophy (SMA) is a genetically heterogeneous group of hereditary diseases characterized by degeneration and death of the anterior horn cells (motor neurons) of the spinal cord. The disease is mainly expressed in the gradual development of symmetrical flaccid paralysis and atrophy of the striated muscle tissue, qualitative transformation of the corresponding muscles and reduction of their electro excitability [1].

The general population prevalence of SMA is approximately 8.5 - 10.3 per 100,000 living newborns, the prevalence of carrying varies from 1 per 60 cases to 1 per 35 cases. Since SMA is most often caused by mutations of autosomal nature of inheritance, the disease affects both genders equally.

From an epidemiological study of the childhood SMA incidence in Poland, the prevalence of the disease was 1.026 per 100,000 and carrying frequency was 1 per 35 [28]. In Cuba, the prevalence of type I SMA is 3.53 per 100,000 cases, but the total prevalence, together with other types of SMA is 8 per 100,000 for white people, 0.89 per 100,000 for black people and 0.96 per 100,000 for mixed nationalities [29]. The frequency of SMA of types I, II and III in Italy is 7.8 per 100,000 cases; the prevalence of type I exclusively is 4.1 per 100,000 cases; the frequency of carrying is 1 per 57 [30]. In the Western Cape of South Africa, in 30 unrelated SMA patients, out of whom 12 were afro Americans, type I SMA was revealed in 4 patients, type- II in 16 patients and type III in 10 patients. All of them were homozygous with loss of exon 7 or exons 7 and 8 in the SMN1 gene, which indicates that patient of different races share same etiology [31]. Out of 23,127 healthy people of different races and non-relatives screened for mutant SMN1 carrying in San Francisco, 405 carriers were identified, showing a frequency of 1 per 57. Some of the subjects consisted in relationships, 15 couples were identified. The probability of conception of a child with SMA in each of these couples is approximately 25% [33]. The prevalence of SMA in Russia is equal to that of European people: morbidity of 1 per 11,000, carrying frequency of about 1 per 47; similar works are carried out for certain regions of Russia [36,37].

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In the Samara Regional Clinical Hospital n.a. V.D. Seredavin (Samara region), a total of 58 living patients with SMA were registered by June 2019, 19 of them were children. Out of 58 patients, 6 were diagnosed with Infantile spinal muscular atrophy, type I (Werdnig-Hoffman) (G12.0), all of them were children, 4 girls and 2 boys. The oldest patient was born in 2005, two youngest were born in 2014.

ICD code G12.1 "Other inherited spinal muscular atrophy", which includes Progressive bulbar palsy of childhood [Fazio-Londe], Spinal muscular atrophy adult form, type II childhood form, distal SMA, type II SMA and scapuloperoneal form, was diagnosed in 37 patients, including 12 children. Of these, 16 patients were female and 21 were male; the youngest patient was born in 2014, the oldest patient was born in 1945.

G12.0			
Total	**9**	**Living**	**6**
female	5	female	4
male	4	male	2
born in 2014	2	born in 2014	2
born in 2010	2	born in 2010	1
born in 2008	1	born in 2008	1
born in 2007	1	born in 2007	1
born in 2005	1	born in 2005	1
born in 2003	1	born in 2003	0
born in 2000	1	born in 2000	0

Table 1: Gender and age of patients diagnosed with G12.0.

G12.1			
Total, Living	**37**	**Born in 2003**	**1**
female	16	born in 1999	2
male	21	born in 1997	1
born in 2014	1	born in 1982-1989	6
born in 2009	1	born in 1971-1979	5
born in 2008	3	born in 1962-1967	5
born in 2007	1	born in 1951-1959	6
born in 2005	2	born in 1945-1949	3

Table 2: Gender and age of patients diagnosed with G12.1.

ICD code G12.8 "Other spinal muscular atrophies and related syndromes" was diagnosed in 13 patients, including 1 child born in 2007; most of these patients were born after 1970. There were 5 women and 8 men.

G12.1			
Total, Living	**13**	**Born in 1983-1985**	**2**
female	5	born in 1970-1975	3
male	8	born in 1967	2
born in 2007	1	born in 1957	1
born in 1992-1994	3	born in 1949	1

Table 3: Gender and age of patients diagnosed with G12.8.

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ICD code G12.9 "Spinal muscular atrophy, unspecified" was diagnosed in 2 adult patients – a man and a woman born in 1968 and 1986, respectively, living in the Samara region.

In addition to spinal amyotrophy, the G12 group includes the G12.2 code, which refers to lateral amyotrophic sclerosis (LAS). Some manifestations of this disease are similar to those in patients with SMA. LAS was observed more frequently. In Samara Regional Clinical Hospital n.a. V. D. Seredavin, a total of 143 patients were registered by June 2019.

G12.2			
Total	**147**	**Living**	**143**
female	65	female	63
male	82	male	80

Table 4: *Gender and age of patients diagnosed with G12.2.*

SMA occurs due to lack of the survival motor neuron protein and other polypeptides interacting with it normally, which are encoded by several dozen genes. Most of SMA cases are caused by mutation in the SMN1 gene located in the long arm of chromosome 5 in band 3 of region 1. The SMN1 gene is duplicated by the SMN2 genome located slightly closer to the centromere region. Each of these genes has multiple copies. There are usually two copies of SMN1, one for each chromosome of the pair in all races, except for African-Americans, who have more than two copies [32].

There is a correlation between the number of copies of SMN1 and SMN2 genes and the course of SMA group diseases-the larger the number of SMN2, the later the disease manifests and the milder its course: if all copies of the SMN1 gene are damaged in children with type I SMA there are on average 1 - 2 intact copies of the SMN2 gene, in patients with SMA type II and III there are at least 3 copies, in patients with SMA type IV at least 4 copies of the SMN2 gene are present. The absence of intact SMN1 and SMN2 copies in the embryo results in spontaneous abortion. The course of diseases depends not only on the number of the SMN2 gene copies, but also on other factors, as evidenced by the lack of strict correlation [7,8].

The structure of the SMN2 gene differs from SMN1 by one nucleotide in exon 7, transforming this site of SMN2 into a splicing enhancer [6]. For the above reasons, without external interference SMN2 is unable to provide enough of survival motor neuron protein, which performs a number of critical functions: at the embryonic stage of development it regulates part of the components of the neurogenesis processes, further participates in the provision of active transport, in particular, transport of mRNA in axonal areas of neurons; plays one of the key roles in the regulation of splicing and transcription. It is also associated with the processes of cytoskeleton functioning and telomere regeneration [5,9,10].

Survival motor neuron (SMN) protein is found both in cytoplasm and nucleus, where it performs its functions with the help of SMN-interacting proteins: Bcl-2 apoptosis regulator, coilin, ATP-dependent helicase A, fibrillarin, far upstream element binding protein 1 (FUBP1), H/ACA ribonucleoprotein complex subunit (GAR1), protins of GEMIN family, heterogeneous nuclear ribonucleoprotein P (hnRNPR), Karyopherin Subunit Beta 1 (KPNB1) p53 protein and small ribonucleoproteins Sm D1 and D2 (SNRPD1 и SNRPD2) [11-22]. The deficiency of survival motor neuron protein and proteins interacting with it can be manifested by hyporeflexia, decreased muscle tone and mass, muscle weakness, "floppy infant" syndrome, lag or regression in motor development, weak coughing, weak screaming and crying, respiratory distress syndrome, fasciculations of the tongue, bulbar syndrome [23].

There are cases of mutations of other genes causing additional morphological and clinical manifestations. Inherited mutations leading to SMA are mainly autosomal recessive, but some of them have autosomal dominant and X-contiguous mode of inheritance [2].

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With the most common cause of SMA, i.e. a mutation of the SMN1 gene, the presence of even a large number of copies of the SMN2 gene does not guarantee the production of the survival motor neuron protein at required level, but it is presence of intact SMN2 copies in the genome of a patient with SMA that contributes to their survival and enables specific gene therapy.

ICD codes, which are part of the SMA group, traditionally differ in the degree of severity and progression of degeneration and clinical manifestations, as well as their topography; in the likeliness of manifestation in a specific period; in the concomitant specific and para specific disorders. Based on these characteristics, an approximate classification of SMA is formed, which includes SMA of adults, which include type IV SMA (OMIM 271150), Kennedy bulbospinal amyotrophy (OMIM 313200), Autosome dominant segmental SMA(OMIM 183020), Stark-Kaiser's autosome dominant scapuloperoneal SMA (OMIM 181400), Jokel's SMA(OMIM 615048), Finkel's autosome dominant late SMA (182980). In adults, SMA manifests after 30 years of life.

Infant SMAs manifesting before 18 years of age include diseases of proximal, distal and bulbospinal subgroups. The proximal subgroup includes types I-III SMAs (MIM 253300, MIM 253550, MIM 253400), Ryukyu SMA (OMIM 271200), SMA with pontocerebellary hypoplasia (OMIM 607596), SMA with progressive myoclonic epilepsy (OMIM 159950). According to the findings of American researchers, out of 100 living children suffering from proximal SMA, 58 have type I proximal SMA, 29 have type II and 13 have type III [3,4].

The distal subgroup includes Kugelberg-Welander SMA (OMIM 158600, OMIM 615290), Distal scapuloperoneal SMA (OMIM 181405), Autosomal recessive distal SMA with respiratory distress syndrome (OMIM 604320). The bulbospinal subgroup includes Brown-Vialetto-Van Laere syndrome (OMIM 211530, OMIM 614707) and Fazio Londe syndrome (MIM 211500).

Some of the diseases related to the SMA are manifested intrauterine and lead to death before or shortly after birth, they are referred to as congenital lethal SMAs. These include X-linked lethal SMA (OMIM 616866) and Type I proximal SMA with congenital fractures (OMIM 616867).

A complex of examination methods is used for the diagnosis of SMA, including genealogical analysis, neurological examination, electroneuromyography and molecular genetic methods of examination using Multiplex ligase detection reaction with subsequent amplification, which allows to accurately identify the number of SMN1 and SMN2 genes copies, which is important when specifying the genotype of each individual patient or carrier [1]. At the Samara Regional Clinical Hospital named after V.D. Seredavin, mainly the data obtained from the analysis of complaints, personal and family history of patients, clinical patterns and indications collected during MRI and EMG with skin and needle electrodes was used in order to diagnose patients with G12 group. In order to clarify the diagnosis and assess the curability of each case, the genetic examination was recommended for all patients.

After diagnosis, the volume of medical care is determined and an effective treatment plan is developed, implying symptomatic correction of concomitant disorders, which can be expressed by respiratory failure, gastroesophageal reflux, metabolic disorders. Patients undergo multidisciplinary monitoring with the participation of a pulmonologist, gastroenterologist, nutritionist, orthopaedist, rehabilitologist, medical geneticist and pediatrician on average every 3 - 6 months.

The necessary amount of medical care is determined by the functional state of the patient. The classification of patients according to functional status developed by European specialists on neuromuscular diseases is used for its evaluation:

- Children who cannot sit unaided ("bed-bound patients").
- Children who can sit on their own but cannot walk unaided ("sedentary patients").
- Children who can walk unaided ("walking patients") [24,25].

For the study of the severity of respiratory disturbances, the bed-bound patients undergo a physical examination with an assessment of the respiratory act and the efficacy of expectoration; cardio-respiratory monitoring and polysomnography to detect signs of hypoven-

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tilation in wakefulness and sleep states; pulse oximetry to control blood oxygenation; chest radiography in dynamics. The frequency of infectious diseases of the respiratory tract and antibiotic therapy for the last 6 months is also monitored. In case of acute inexplicable deterioration of respiratory functions and repeated pneumonia, swallowing function is studied to find the reasons.

Examination by the orthopedist and the X-ray evaluation of the dynamics of the torso bones deformations are added to the monitoring activities in bed-bound patients. External breathing function study and regular spirometry are also carried out in patients who can walk on their own.

The evaluation of gastroenterological pathology includes the search for early symptoms of gastroesophageal refulx, the execution of fiberoptic esophagogastroduodenoscopy to assess the possibility of installing the probe, the detection of structural anomalies and the confirmation of reflux. Examination of motor skills, including X-ray diagnostics, confirms the delay in the evacuation of stomach contents, which can aggravate the course of gastroesophageal reflux. Metabolic and orthopedic disorders are less dangerous to the lives of patients, their monitoring is based on the evaluation of anthropometric indicators and functional physical samples.

According to the results of the monitoring, the amount of necessary assistance is determined in the form of frequency of airway cleaning by aspirator, non-invasive ventilation of lungs with constant positive pressure, postural and other methods of drainage, oxygen therapy, antibacterial, mucolytics and bronchodilators or, if ineffective, intubation and artificial lung ventilation. The expediency of the use of antacids, proton pump blockers and prokinetics in gastroesophageal refulx and gastrointestinal motor disorders is also being discussed; the volume of use of nootropic, neuro- and cardioprotective, metabolic and other drugs, as well as orthopedic, including surgical, correction of relevant pathologies are undergoing approval procedure [26].

Presence of such patients in the family requires constant specific care, primarily related to the prevention of respiratory disorders, for which the special methods of laying down children with SMA have been developed. Most patients require help in expectoration and pulmonary secretion removal. For this purpose, caregivers can use postural and manual techniques, such as draining massage. If necessary, they can use a mechanical airway clearance device or aspirator. The use of non-invasive lung ventilation equipment with constant positive pressure at home is also controlled by the caregiver. Effectiveness of care can be assessed by parameters of pulse oximetry and duration of absence of respiratory tract complications. Care for SMA patients also includes diet therapy program and patient accommodation recommendations related to feeding, using the most out of the orthopaedic products for convenience and safety of patients, as well as the performance of other appointments [27].

Prospects of symptomatic correction are incomparable with those of pathogenetic therapy drugs. There currently are two FDA approved pathogenetic drugs for spinal muscular atrophy caused by damage to the survival motor neuron-1 gene (SMN1), another one passes the third phase of clinical trial, the study of two more is in the second phase; several more drugs are being developed and prepared for trials. None of these drugs has been registered in the Russian Federation yet.

The first drug to treat SMA, Nusinersen, approved by the FDA in December 2016, was developed in collaboration with the laboratory at Cold Spring Harbor, the Medical School of Massachusetts University and Ionis Pharmaceuticals; subsequently Biogen Company acquired intellectual property rights [34]. This drug contains antisense nucleotides, the mechanism of action of which is based on the ability to suppress alternative splicing in the SMN2 gene, which functionally makes it resemble SMN1 gene and allows to increase the production of survival motor neuron protein. Subject to timely prescription, there is a therapeutic effect, expressed in increasing body weight and improving motor skills. It is introduced per rectum once every few months for the life term. Now, Nossinersen has been approved for use in more than 40 countries.

The second drug approved by the FDA in May 2019, AVXS-101, was developed by AveXis, owned by Novartis. It is a solution containing viral vectors filled with the virus genome except for the DNA area necessary for self-reproduction and native copies of the SMN1 gene with

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promoters. This configuration allows to integrate the contents of the vector into the specific areas of the host chromosome 19, launch the transcription of the SMN1 gene and replete the survival motor neurons protein [39]. Infantile patients receive the drug via IV injection; late childhood, adult and elderly patients receive it per rectum. The issue of the frequency of the administration is discussed - it is now known that after a single intravenous injection of AVXS-101, clinical deterioration does not occur for at least two years; there is a reason to believe that the duration of therapeutic activity of the drug may be much longer [38]. The price for a dose of the drug at the time of registration was greater than 2 million USD and at the current time virtually has not decreased. [35].

There is a class of experimental pathogenetic drugs that are included in the "small molecules" class, which are derivatives of coumarins, iso-coumarin and pyrido pyrimidinones [41]. The usage of this drug is promising due to the ability of "small molecules" to selectively modify SMN2 splicing during oral administration, which simplified the procedure of their introduction in relation to other drugs and leads to SMN synthesis outside the central nervous system, which determines the systemic therapeutic effect. This group of pathogenetic drugs includes Risdiplam, developed by the F. Hoffmann-La Roche company in collaboration with PTC Therapeutics and SMA Foundation non-profit organization. It is now undergoing the third phase of clinical trials [38,40].

Conclusion

Today in Russia it is possible to use methods capable to reduce the number of patients with SMA and other hereditary diseases in the near future, that are potentially available for medico-genetic service of the Russian Federation, which would have a lot of positive consequences, including those associated with a decrease in the burden on the budget of the Ministry of Health of the Russian Federation and a decrease in the number of patients falling into preferential social groups and those receiving state sponsorship. Preventive use of molecular genetic diagnostics for prenatal detection of such diseases and their carrying in childbearing adults in combination with the rapidly developing technologies of genetic editing give us a hope for extremely favourable forecasts regarding the future organization of medical care for hereditary neuromuscular diseases.

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