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CURRENT MEDICAL AND SOCIAL PROBLEMS OF SPINAL MUSCULAR ATROPHY IN CHILDREN. LITERATURE REVIEW

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Abstract

Introduction: Neuromuscular diseases are one of the most common groups of hereditary diseases of the nervous system characterized by genetic heterogeneity. In the background of neuromuscular diseases one of the leading places belongs to spinal muscular atrophy. Spinal muscular atrophy (SMA) is an autosomal recessive disease of motor neurons, occurring with a frequency of 1 in 11,000 newborns. SMA is the most common inherited cause of pediatric mortality. In recent decades, intensive efforts have elucidated the molecular mechanisms of the disease and developed new disease-modifying therapies.

Aim. To analyze the existing medical and social problems in spinal muscular atrophy according to the current literature.

Search strategy. The literature search was performed in the electronic databases Web of Science Core Collection, Scopus, PubMed, Google Scholar for the last 10 years: from 2013 to 2023. *Inclusion criteria* were systematic reviews, original articles. *Exclusion criteria* were articles of poor methodological quality, cases of duplication, missing or incomplete data in articles, clinical case reports, letters, editorials, and expert opinions. 287 articles were retrieved, of which 51 were selected for analysis.

Results. The social aspects of the disease include the need for specialized care, family support, and integration of children with SMA into educational institutions. Most studies emphasize the need for comprehensive rehabilitation and psychosocial support programs, which should include not only medical care but also social adaptation, educational support, and counseling. The financial costs of treating and caring for children with SMA are a significant burden on families and health care systems. Ensuring the availability of expensive medicines such as nusinersen, zolgensma and risdiplam remains a major challenge for national health systems. In this context, government support and insurance programs are of particular importance.

Conclusion. Thus, solving the medical and social problems associated with spinal muscular atrophy in children requires an integrated approach and interdisciplinary cooperation. Only coordinated efforts of physicians, social workers, educators, government agencies and nongovernmental organizations can provide children with SMA and their families with a decent quality of life and prospects for the future. It is necessary to continue scientific research on SMA, develop innovative treatments and improve social support systems to achieve these goals.

Keywords: *spinal muscular atrophy, hereditary diseases, orphan diseases*

Резюме

СОВРЕМЕННЫЕ МЕДИКО-СОЦИАЛЬНЫЕ ПРОБЛЕМЫ СПИНАЛЬНОЙ МЫШЕЧНОЙ АТРОФИИ У ДЕТЕЙ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Нейромышечные заболевания - одна из наиболее распространенных групп наследственных болезней нервной системы, характеризующихся генетической гетерогенностью. На фоне нервно-мышечных заболеваний одно из ведущих мест принадлежит спинальной мышечной атрофии. Спинальная мышечная атрофия (СМА) - аутосомно-рецессивное заболевание двигательных нейронов, встречающееся с частотой 1 на 11 000 новорожденных. СМА является наиболее распространенной наследственной причиной детской смертности. В

последние десятилетия интенсивные усилия позволили выяснить молекулярные механизмы заболевания и разработать новые методы терапии, модифицирующие болезнь.

Цель. Анализ существующих медико-социальных проблем при спинальной мышечной атрофии по данным современной литературы.

Стратегия поиска. Поиск литературы был осуществлен в электронных базах Web of Science Core Collection, Scopus, PubMed, Google Scholar за последние 10 лет: с 2013 по 2023 годы. *Критериями включения* являлись систематические обзоры, оригинальные статьи. *Критериями исключения* являлись статьи низкого методологического качества, случаи дублирования, отсутствие или неполные данные в статьях, отчеты о клинических случаях, письма, редакционные статьи и мнения экспертов. Были найдены 287 статей, из них 51 были выбраны для анализа.

Результаты. Социальные аспекты заболевания включают в себя необходимость обеспечения специализированного ухода, поддержки семей и интеграции детей с СМА в образовательные учреждения. Большинство исследований подчеркивают необходимость создания комплексных программ реабилитации и психосоциальной поддержки, которые должны включать не только медицинскую помощь, но и социальную адаптацию, образовательную поддержку и консультирование. Финансовые затраты на лечение и уход за детьми с СМА являются значительным бременем для семей и системы здравоохранения. Обеспечение доступности дорогостоящих лекарств, таких как нусинерсен, золгенсма и рисдиплам, остается одной из главных задач для национальных систем здравоохранения. В этом контексте особую важность приобретают государственные программы поддержки и страхования.

Заключение. Таким образом, решение медико-социальных проблем, связанных со спинальной мышечной атрофией у детей, требует комплексного подхода и междисциплинарного сотрудничества. Только скоординированные усилия медицинского сообщества, социальных работников, педагогов, государственных органов и неправительственных организаций могут обеспечить детям с СМА и их семьям достойное качество жизни и перспективы на будущее. Необходимо продолжать научные исследования в области СМА, развивать инновационные методы лечения и улучшать системы социальной поддержки для достижения этих целей.

Ключевые слова: *спинальная мышечная атрофия, наследственные заболевания, орфанные заболевания*

Түйіндеме

БАЛАЛАРДАҒЫ ЖҰЛЫН БҰЛШЫҚЕТ АТРОФИЯСЫНЫҢ ҚАЗІРГІ МЕДИЦИНАЛЫҚ ЖӘНЕ ӘЛЕУМЕТТІК МӘСЕЛЕЛЕРІ. ӘДЕБИ ШОЛУ

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Кіріспе: Жүйке бұлшықет аурулары – генетикалық гетерогенділікпен сипатталатын тұқым қуалайтын жүйке жүйесі ауруларының ең көп таралған топтарының бірі. Жүйке-бұлшықет аурулары аясында жетекші орындардың бірі жұлын бұлшықет атрофиясына жатады. Жұлын бұлшықет атрофиясы (SMA) - 11 000 жаңа туған нәрестеге 1 жиілікте кездесетін моторлы нейрондардың аутосомды-рецессивті ауруы. SMA-балалар өлімінің ең көп таралған тұқым қуалайтын себебі. Соңғы онжылдықтарда қарқынды күш-жігер аурудың молекулалық механизмдерін анықтауға және ауруды өзгертетін жаңа терапия әдістерін жасауға мүмкіндік берді.

Зерттеудің мақсаты. Қазіргі әдебиеттерге сәйкес жұлынның бұлшықет атрофиясындағы медициналық және әлеуметтік мәселелерді талдау.

Іздеу стратегиясы. Әдебиеттерді іздеу Web of Science Core Collection, Scopus, PubMed, Google Scholar электрондық базаларында соңғы 10 жылда: 2013 жылдан 2023 жылға дейін жүзеге асырылды. Қосу критерийлері жүйелі шолулар, түпнұсқа мақалалар болды. Алып тастау критерийлері сапасыз әдіснамалық мақалалар, қайталану жағдайлары, мақалалардағы деректердің болмауы немесе толық болмауы, клиникалық жағдайлар туралы есептер, хаттар, редакциялық мақалалар және сарапшылардың пікірлері болды. 287 мақала табылды, олардың 51 талдау үшін таңдалды.

Нәтижелер. Аурудың әлеуметтік аспектілері мамандандырылған күтімді қамтамасыз ету, отбасыларды қолдау және SMA бар балаларды білім беру мекемелеріне біріктіру қажеттілігін қамтиды. Зерттеулердің көпшілігі медициналық көмекті ғана емес, сонымен қатар әлеуметтік бейімделуді, білім беруді қолдауды және кеңес беруді қамтуы керек кешенді оңалту және психоәлеуметтік қолдау бағдарламаларын құру қажеттілігін көрсетеді. SMA бар балаларды емдеуге және күтуге арналған қаржылық шығындар отбасылар мен денсаулық сақтау жүйелері үшін

айтарлықтай ауыртпалық болып табылады. Нусинерсен, золгенсма және рисдиплам сияқты қымбат дәрі-дәрмектердің болуын қамтамасыз ету ұлттық денсаулық сақтау жүйелері үшін басты міндеттердің бірі болып қала береді. Бұл тұрғыда мемлекеттік қолдау және сақтандыру бағдарламалары ерекше маңызға ие.

Қорытынды. Осылайша, балалардағы жұлын бұлшықет атрофиясымен байланысты медициналық және әлеуметтік мәселелерді шешу кешенді тәсіл мен пәнаралық ынтымақтастықты қажет етеді. Дәрігерлердің, әлеуметтік қызметкерлердің, педагогтардың, мемлекеттік органдар мен үкіметтік емес ұйымдардың үйлестірілген күш-жігері ғана СМА бар балалар мен олардың отбасыларына лайықты өмір сапасы мен болашақтың болашағын қамтамасыз ете алады. СМА саласындағы ғылыми зерттеулерді жалғастыру, инновациялық емдеу әдістерін дамыту және осы мақсаттарға жету үшін әлеуметтік қолдау жүйелерін жақсарту қажет.

Түйінді сөздер: *жұлынның бұлшықет атрофиясы, тұқым қуалайтын аурулар, орфанды аурулар.*

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Introduction

Medicine pays much attention to hereditary diseases because their share in the structure of morbidity and mortality is increasing. 35-40 children per thousand newborns suffer from genetic disease. Mortality of children under 5 years of age in 2-3% of cases is due to chromosomal anomalies, in 5-10% - gene disorders, in 35-40% - multifactorial hereditary diseases. Hereditary diseases are subdivided as follows: gene diseases; chromosomal diseases; pathologies with hereditary predisposition. All of them are associated with a violation of the process of storage, transmission and input of human genetic information [26,27].

Genetic inherited diseases are diseases resulting from DNA abnormalities at the gene level. They are divided into three types: autosomal dominant; autosomal recessive; X- or Y-chromosome related. Genetic diseases include various metabolic disorders, including: phenylketonuria, alkaptonuria; galactosemia, glycogen storage disease; hereditary gastrointestinal absorption disorder syndromes; Marfan disease; hemolytic anemia; Niemann-Pick disease, Gaucher disease; hemoglobinopathy;gout, Lesch-Nayan hereditary syndrome; Konovalov-Wilson disease, etc [1,28]

Autosomal recessive diseases occur when a mutation on an autosome is recessive, leading to the development of such a disease. For this pathology to manifest, all healthy versions of the gene must be replaced by the mutant versions. This results in the gene's expression being completely or partially halted. A child must inherit one copy of the recessive mutant gene from each parent to develop the condition. Additionally, parents who are heterozygous carriers of the mutation might not exhibit any symptoms of the disease [1]. One of these diseases can include spinal muscular atrophy. Spinal muscular atrophies are usually the result of autosomal recessive mutations that affect the survival of motor neuron 1 (SMN1) on the long arm of chromosome 5, often causing homozygous destruction of exon 7. Spinal muscular atrophy (SMA) affects not only the peripheral nervous system but also the central nervous system, highlighting its complexity beyond just a peripheral disease. The SMN2 modifier gene, almost identical to the SMN1 gene (99% similarity), is found on the long arm of chromosome 5 (5q). The presence of multiple SMN2 copies can impact disease severity and account for phenotypic differences among children with SMA. Moreover, there exist rare SMA variants that do not involve the 5q mutation[2].

Aim. To analyze the existing medical and social problems in spinal muscular atrophy according to the current literature.

Search strategy. The literature search was performed in the electronic databases Web of Science Core Collection, Scopus, PubMed, Google Scholar for the last 10 years: from 2013 to 2023. *Inclusion criteria* were systematic reviews, original articles. *Exclusion criteria* were articles of poor methodological quality, cases of duplication, missing or incomplete data in articles, clinical case reports, letters, editorials, and expert opinions. 287 articles were retrieved, of which 51 were selected for analysis.

Results and discussions

Characteristics of prevalence and classification of spinal muscular atrophy

On average, 1 in 6,000 to 10,000 children are born with SMA, with the frequency varying from country to country [3]. Since SMA is most often caused by mutations of autosomal inheritance, the ratio of patients of both sexes is about the same [4]. According to an epidemiological study on spinal muscular atrophy (SMA), the prevalence in Poland is 1.026 per 100,000 people, with a carrier rate of 1 in 35. In Cuba, the prevalence of SMA type I is 3.53 cases per 100,000 population. When considering all types of SMA, the overall prevalence is 8 cases per 100,000 for the white population, 0.89 for the black population, and 0.96 for mixed-race populations. In Italy, the incidence of SMA types I, II, and III combined is 7.8 cases per 100,000, with type I alone

accounting for 4.1 cases per 100,000 and a carrier rate of 1 in 57 [5,7]. Of 30 unrelated patients with SMA in the Western Cape province of South Africa, 12 were black, 4 had type I SMA, 16 had type II SMA, 10 had type III, In all patients SMN1 was 7th or 7th and 8th characterized by homozygous loss of exons, suggesting that the etiology is the same in people of all races [8]. Of 23,127 healthy people of different races and unrelated individuals screened for SMN1 mutant carriers in San Francisco, 57 identified 405 carriers with a frequency of 1 carrier. A proportion of the subjects were married. Fifteen couples were identified. The probability of having a child with SMA in each of these couples is about 25% [9].

Spinal muscular atrophy (SMA) is divided into several types:

- SMA Type 0: This prenatal form is characterized by decreased fetal movement late in pregnancy, severe weakness, and hypotonia at birth. Newborns often present with facial diplegia, areflexia, heart defects, and sometimes arthrogryposis. Respiratory failure typically results in death within the first six months.

- SMA Type 1 (Infantile SMA or Werdnig-Hoffman disease): Symptoms typically appear around six months of age, with muscle hypotonia often present from birth, hyporeflexia, tongue fasciculations, and severe difficulties in sucking, swallowing, and breathing. In 95% of cases, death occurs within the first year, and all affected children die before age four due to respiratory failure.

- SMA Type 2 (Intermediate form or Dubowitz disease): Symptoms usually develop between 3 and 15 months. About 25% of children with this form can sit but are unable to walk or crawl. They experience paralysis and fasciculations, which are difficult to detect in young children. Common issues include impaired deep tendon reflexes and swallowing difficulties. Most children require a wheelchair by ages 2-3. Respiratory complications often lead to early death, although disease progression may suddenly halt, resulting in persistent weakness and a high risk of severe scoliosis and its complications.

- SMA Type 3 (Kugelberg-Welander disease): Symptoms typically manifest between 15 months and 19 years of age. This form progresses more slowly than Type 1, allowing for a longer, sometimes normal, life expectancy. It may be associated with enzyme defects like hexosaminidase deficiency. The disease starts with symmetrical weakness and atrophy in the quadriceps femoris and hip flexors, spreading distally in the lower limbs before affecting the arms. Life expectancy varies based on respiratory complications.

- SMA Type 4 (Adult-onset): This form can be inherited in a recessive, dominant, or X-linked manner, with symptoms appearing between 30 and 60 years of age. It involves slowly progressive weakness and atrophy of proximal muscles, making it difficult to distinguish from amyotrophic lateral sclerosis, which primarily affects lower motor neurons [51].

Specifics of organization of medical care for children with spinal muscular atrophy.

The required volume of medical care is determined by the patient's functional status. This status is evaluated using a classification system developed by European neuromuscular disease specialists, categorizing patients into three groups:

- Children unable to sit up without assistance ("bedridden patients");

- Children who can sit independently but cannot walk unassisted ("patients who can sit");

- Children who can walk independently ("walking patients") [11].

To study the severity of respiratory disorders in bedridden patients, physical examination with assessment of the efficiency of breathing and coughing, cardiorespiratory monitoring and polysomnography to detect signs of hypoventilation in waking and sleeping states; pulse oximetry to monitor blood oxygen saturation; chest radiography in dynamics are performed. The frequency of respiratory tract infections and the use of antibiotic therapy have been monitored over the past six months. When there is an acute, unexplained decline in respiratory function or recurrent pneumonia, swallowing function is evaluated to determine the underlying cause. In sedentary patients, orthopedic examination and radiologic evaluation of bone deformity dynamics are added to the monitoring measures. Patients who can walk independently are investigated by external respiratory function and regular spirometry. Evaluation of gastroenterologic pathology involves checking for early signs of gastroesophageal reflux, performing esophagogastroduodenoscopy to assess the feasibility of probe placement, identifying structural abnormalities, and confirming the presence of reflux. Motility studies, including radiological examinations, can confirm delayed gastric emptying, which can worsen gastroesophageal reflux. Metabolic and orthopedic disorders are less life-threatening and are monitored by assessing anthropometric parameters and conducting functional physical tests [4].

Until the recent advent of disease modifiers, treatment of SMA was only supportive. However, even after their introduction, supportive measures are still important to prevent or treat complications of SMA [40,41]. The main of these complications are airway injuries, which are the leading cause of death from SMA. Noninvasive ventilation can be used in milder forms of SMA and should be preferred when possible. The use of tracheostomy and invasive ventilation for children with SMA has become more common over the years but still presents ethical dilemmas [42]. Medical practice varies widely in this regard [43,44]. The prospect of new disease-modifying drugs complicates this decision.

Weight gain and increased contracture may be associated with more dramatic deterioration of SMA [45]. Thus, stretching and lifting exercises are used to improve function and prevent the development of contractures. The prevalence of scoliosis in children with type I and type II DECA is about 80% [46].Thoracic support is used as first-line treatment in children with low-grade scoliosis.

In more severe cases, surgery may be used to stabilize pulmonary function and improve comfort [47].

In addition to these well-known neurologic symptoms, a growing body of literature points to the involvement of other organs in SMA. Indeed, SMA is a protein that is expressed ubiquitously and may play a role outside of the central nervous system [48]. Several studies have found preclinical data with a higher than expected incidence of cardiac defects also point to a primary dysfunction of the nerve-muscular junction of SMA [49,50]. These results suggest

that restoring SMN expression in the body may be necessary to fully correct SMA pathology [51].

Importance and specificity of screening measures performed to detect spinal muscular atrophy.

Today, spinal muscular atrophy is diagnosed after the onset of symptoms, resulting in irreversible loss of motor neurons. Before the onset of symptoms, the diagnosis can only be made in patients with a severe family history [13]. Newborn screening(NS) can detect genetic disease before symptoms appear [14].

In January 2016, New York State began a pilot study of screening newborns with spinal muscular atrophy at four New York hospitals. According to a July 2020 report, 31 states have already implemented newborn screening for muscular atrophy. Since 2018, SMA has been part of a mandatory newborn screening program in the southern region of Belgium. When a diagnosis is made, treatment begins immediately [16]. Since 2018, newborn screening for spinal muscular atrophy has been conducted in Germany, the regions of Bavaria and North Rhine-Westphalia; based on the results of this pilot project, the implementation of newborn screening for spinal muscular atrophy in Germany is being worked on [13]. Since June 2019, pilot projects are underway in two provinces in Italy, Barcelona, Spain, and the start of the program in Warsaw, Poland is being finalized [17]. Testing newborns for spinal muscular atraphia can detect the presence of the genetic “disorder” during the first week of a child's life before the first signs of the disease appear. The procedure is performed as a routine neonatologic screening. Using a blood test from the heel of the newborn. Diagnosis is based on molecular genetic testing. The MLP test confirms the cause of spinal muscular atrophy in 95% of cases . For the remaining 5%, a smn1 gene sequencing test is required (if the first test does not confirm the diagnosis but the patient has clinical manifestations of spinal muscular atrophy) [13].

Currently, intrauterine screening of infants is recommended for parents with a family history of confirmed or suspected SMA [20] deletion of exons 7 and 8 of the SMN1 gene is associated with the development of SMA. They can be detected in the embryo or fetus by 10,11 prenatal diagnostic techniques, which are performed by the following methods:

- maternal blood sample to detect free fetal DNA in the bloodstream (analyzed around 8 weeks of pregnancy),
- chorionic villus biopsy (BVC): a sample of chorionic villi (placental tissue) is taken through a tube inserted through the cervix (analyzed around 10-12 weeks of pregnancy).
- amniocentesis: spinal muscular atrophy: obtaining a small amount of amniotic fluid (including fetal cells) through a needle for parents who have a child with spinal muscular atrophy (tested at about 14 weeks of pregnancy) [14].

In fulfillment of the instructions of the Head of State Kasym-Jomart Tokayev, given at the fifth meeting of the National Council of Public Trust under the President of the Republic of Kazakhstan, the Ministry of Health made changes and additions to the order of the Minister of Health of the Republic of Kazakhstan from September 9, 2010 № 704 “On Approval of the Rules of Organization of Screening”. These rules, aimed at early diagnosis of diseases in children, have been expanded and improved. Thus, according to the rules, medical support for the future child begins in utero during pregnancy and includes perinatal screening to assess fetal development and detect malformations. In accordance with the order of the Minister of Health of the Republic of Kazakhstan from September 9, 2010 № 704 “On approval of the Rules of organization of screening ‘at the first stage of prenatal screening doctor specialty’ Obstetrics and Gynecology ‘or’ General Medicine ‘at the second visit to a pregnant woman with the results of prenatal screening refers her for consultation with a doctor specializing in ’Medical Genetics” according to the following criteria:

- determination of ultrasound markers of chromosomal pathology and (or) detection of anatomical anomalies of fetal development during ultrasound screening of the first, second and third trimesters;
- determination of individual genetic risk of chromosomal pathology of the fetus 1:150 and above after the combined test of the first trimester;
- the presence of an age factor (women over 37 years of age).
- neonatal screening for hereditary diseases, including screening of all newborns for phenylketonuria and congenital hypothyroidism, is carried out in maternity hospitals immediately after birth. Audiologic screening is also conducted for the timely detection of hearing impairment in all newborns and young children [23].

One in 35 people is an asymptomatic carrier of a mutation that leads to spinal muscular atrophy , and a sick child is born when there are 2 such mutations on the maternal and paternal side. This occurs about 1 in 6000 births-in families where no one has heard of the disease, in families where there are no sick relatives, no harmful environmental factors,-it is very important to know the perceived risk before waiting for a child diagnosed with spinal muscular atrophy to arrive in a world that does not suspect a high risk of genetic problems. To this end, many private laboratories perform screening tests for SMN1, SMN2 gene carryover [23].

Socioeconomic problems of spinal muscular atrophy. The challenges of Spinal Muscular Atrophy (SMA) start with a lengthy and often difficult diagnostic process. Similar to other rare diseases, SMA imposes a significant economic burden on society. The costs associated with treatment, hospitalization, emergency consultations, and visits to general practitioners and other specialists contribute heavily to healthcare expenses. Additionally, due to the severe disability caused by SMA, most patients depend on family support and/or social services for their daily activities. Therefore, quantifying the economic burden should encompass not only healthcare costs but also the expenses of formal care, unpaid care provided by family members, and other household costs. The three included studies reported the (indirect) costs of families caring for children with spinal muscular atrophy . [30, 31,32]. All used self-developed approaches to estimate the costs of providing health care to affected families. Total health care costs varied widely between countries, with average costs being similar. For Australia ($33,000 per year) [32] for Spain (€33,721) [30] and for France (€32,042), Germany (€51,983) and the UK (€54,295 were high costs) [31] two studies using parts of the same choice assessed how a

family would cope with a family crisis. The Personality Assessment Scale (F-COPES) showed the same results in families with spinal muscular atrophy and sick children and in families with healthy children with age groups. [33, 34]. One study reported significantly lower levels of perceived social support in families with spinal muscular atrophy, [33] while another study found the same level compared to families with spinal muscular atrophy and families with healthy children and older adults [34]. The predominant theme across the included articles (five out of eight studies) focused on the varied needs of families. Parents expressed a significant need for information [35,36,37-39]. Although many relied on their child's doctor as the primary source of information about the disease, they often felt inadequately informed and sometimes isolated. As a result, they turned to the internet, social networking groups, and support organizations for additional information [35,36,37,39]. Several articles noted that parents took on the task of bridging this information gap, which was described as time-consuming and frustrating due to the complexity and limited accessibility of the information [35,36,37]. Their desire for information extended beyond disease and treatment specifics to include support services, financial aid, access to equipment, paid caregiving, and educational options [35,36,37,39].

Conclusion: The treatment of spinal muscular atrophy requires a comprehensive and multidisciplinary approach. It is especially important to keep under strict control the state of the respiratory system in “bedridden” patients. For parents and newlyweds when planning a child, it is necessary to carry out a wide educational, promotional work on this issue among the population, as passing genetic counseling is the main means of prevention of spinal muscular atrophy. For the purpose of early diagnosis of spinal muscular atrophy, it is necessary to actively screen newborns for this disease in maternity hospitals. It is necessary to slightly increase economic support from the state to families with children with spinal muscular atrophy. It is necessary to enhance the understanding of pediatricians and general practitioners regarding spinal muscular atrophy. This improvement aims to deliver accessible, evidence-based information and ensure that parents and caregivers of affected children can easily access information about the condition.

Overall, there have been many advances in the field of SMA in the last 5 years. The main of these advances are the introduction of 2 therapies aimed at modifying SMN3 splicing or gene replacement therapy. Both approaches emphasize the importance of early diagnosis and treatment. The incidence, clinical presentation, and outcome of sma may change significantly in the coming years through a combination of carrier testing, newborn screening, and early treatment. Gene therapy significantly alters the natural history of CM A, but some patients may retain signs of the disease, especially if treatment is given after the onset of symptoms. Consequently, additional efforts are needed to determine whether treatment efficacy can be improved with combination therapy. The long-term efficacy and outcomes of gene therapy also require further monitoring.

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