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Clinical Practice Guideline for Adolescent and Adult Patients with Spinal Muscular Atrophy – Part 1

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Abstract: In recent years, the field of spinal muscular atrophy (SMA) has made progress in multidisciplinary care and disease-modifying therapies (DMTs). Survival and the quality of life of patients have significantly improved. However, no clinical practice guidelines exist for the management of SMA in adult and adolescent patients. Multidisciplinary experts from a number of tertiary medical centers in China, specializing in the diagnosis and treatment of SMA, came together to remedy this using evidence-based medicine. This guideline serves as an instrumental reference for the standardized care of Chinese SMA patients.

Keywords: Spinal Muscular Atrophy; Diagnosis; Multidisciplinary Treatment; Disease Modifying Therapy.

INTRODUCTION

This guideline is aimed at the multidisciplinary diagnosis and treatment of adolescent and adult SMA patients. To achieve this, we brought together experts from several medical centers across China, covering 12 departments of Neurology, Radiology, Psychology, Rehabilitation, Orthopedics, Anesthesiology, Respiratory Medicine, Endocrinology, Gastroenterology, Nutrition, Stomatology, and Pharmacy. A total of 198 experts contributed to this guideline.

1. OVERVIEW

Spinal muscular atrophy (SMA) is a lower motor neuron disease characterized by progressive weakness and atrophy of the innervated muscles due to degeneration of the anterior horn cells in the spinal cord and the motor nuclei in the lower brainstem. SMA is caused by biallelic deletions or mutations in the survival motor neuron 1 (SMN1) gene. The SMN1 gene and the disease modifying SMN2 gene(s) are located on chromosome 5q11.1-13.3, which is why SMA is more correctly referred to as 5q-SMA (OMIM* 600354). Although mutations in other genes can cause similar symptoms, they are relatively rare and outside the scope of this guideline. Although the spectrum of patients with 5q-SMA includes infants, children, adolescents and adults, this guideline focuses on the diagnosis and treatment of adolescents and adults.

SMA is a common hereditary neuromuscular disease, the diagnosis and treatment of which involves many departments such as neurology, pediatrics, rehabilitation, orthopedics, respiratory medicine, and nutrition. The carrier prevalence and incidence of SMA vary little among countries or races. Data based on large-scale population screening in China showed that the carrier prevalence of SMA is about 1 in 56 [1],

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with an incidence of about 1 per 9788 live births. [2] SMA was first reported by Werdnig, an Austrian physician, in 1891 [3], and the pathogenic gene was identified in 1990 [4-5] and cloned in 1995. [6] With animal models established, the research of precise therapies targeting the cause of SMA has developed fast. Since 2016, various disease-modifying drugs such as nusinersen, onasemnogene abeparvovec, and risdiplam have been approved for marketing. Nusinersen entered China in 2019 and was introduced into the national medical insurance reimbursement list in 2022. Risdiplam entered China in 2021. Onasemnogene abeparvovec is not currently available. With the promotion of multidisciplinary care and the application of disease-modifying treatments, survival has been significantly prolonged, with more and more pediatric SMA patients entering adolescence and adulthood. Apart from the milder type 3 and type 4, type 2 and even type 1 SMA patients can also enter adolescence and adulthood. However, the diagnosis and treatment of adolescent and adult SMA patients is quite different from that of infants and children, and patients face more new challenges. Although there have been several guidelines and consensus published both domestically and internationally [7-13], they either focus on the management of pediatric patients or prenatal diagnosis. For adolescent and adult SMA patients, there are few systematic and comprehensive clinical guidelines.

This guideline was drafted by experts from multiple specialties with practical experience in the diagnosis and treatment of SMA, based on the latest clinical evidence of SMA at home and abroad [7-10,12-13], and combined with the specific conditions of China. This guideline is centered on refined multidisciplinary management, covering adolescent-adult disease classification, the transition of management from childhood to adolescence, and disease assessment tools. It aims to promote standardized diagnosis and treatment of adolescent-adult SMA patients in China and further improve the prognosis of these patients.

This guideline has been registered on the International Platform for the Registration and Transparency of Practice Guidelines (IPGRP) with the registration number IPGRP-2022CN383. It has been developed by expert groups from 12 different specialties, which include Neurology, Radiology, Psychiatry, Rehabilitation, Orthopedics, Anesthesiology, Respiratory, Endocrinology, Gastroenterology, Nutrition, Stomatology, and Pharmacology. All members of the groups have declared that they have no conflict of interest. The expert groups conducted a systematic search and analysis of relevant evidence, and the grading of recommendations and level of evidence are made with reference to international and national guidelines, as well as commonly used standards, shown in Table 1.

2. CLINICAL MANIFESTATIONS AND CLASSIFICATION

SMA is an inherited autosomal recessive trait that is usually carried by both parents. It is rarely caused by de novo mutations and tends to affect nuclear siblings without a significant family history. SMA is characterized by symmetric muscle weakness, atrophy, and reduced muscle tone. Infantile-onset type (SMA type 1) is characterized by symptoms onset within the first six months of life. It often presents as floppy infants, delayed motor development, inability to achieve independent sitting, rapidly progressing motor, respiratory and bulbar deterioration, which can lead to the early mortality of most of them. Later-onset SMA (SMA types 2 and 3) also develops in childhood. Patients with SMA type 2 develop symptoms before the age of 18 months, have a similar though less severe pattern of muscle weakness as observed in SMA type 1. The disease is characterized by delayed motor development, with the brief acquisition of sitting and standing. However, this is followed by loss of these motor functions, and the development of scoliosis, joint deformities, and respiratory failure. Patients with SMA type 3 develop symptoms in childhood and adolescence, and typically achieve main motor milestones, but then develop progressive muscle weakness and atrophy, starting from the proximal lower limbs and extending to the proximal upper limbs, distal limbs, head and neck. This leads to the gradual loss of motor function. In advanced cases, complications can be observed such as scoliosis, joint contractures, limited mouth opening, and dyspnea.

SMA can occur at any age, from before birth to adulthood, and the rate of progression varies greatly. Before the mapping of the pathogenic genes, SMA types 1, 2 and 3 were considered to be distinct. The Online Mendelian Inheritance in Man (OMIM) still assigns different numbers to these phenotypes. However, in 1990, the pathogenic genes of all forms of the disease were found to be located in the same region on chromosome 5q

Items	Classification	Definition
Strength of recommendation (4 levels, with level 1 being the strongest and level 4 being the weakest)	I	Level A evidence or a high degree of expert consensus
	II	Level B evidence or expert consensus
	III	Level C evidence or expert consensus
	IV	Level D evidence or expert consensus
Level of evidence of treatment (4 levels, with level A being the strongest and level D being the weakest)	A	≥ 1 randomized control trial or meta-analysis of such trials or 1 large conducted randomized control trial (high quality)
	B	≥ 1 randomized control trial (relatively high quality)
	C	Well-designed controlled trials without randomization, or well-designed cohort studies or case-control studies
	D	Case series analysis without controls or expert opinions
Level of evidence of diagnosis (4 levels, with level A being the strongest and level D being the weakest)	A	≥ 1 large prospective cohort studies with a reference (gold) standard and blind evaluation (high quality)
	B	≥ 1 large prospective cohort studies or well-designed retrospective case-control studies with a gold standard and blind evaluation (relatively high quality)
	C	Retrospective case-control studies without blind evaluation
	D	Case series analysis without controls or expert opinions

Table 1. Recommended intensity and level of evidence criteria.

and were eventually confirmed to be the same disease. SMA was classified into types 1-3 based on the age of onset and the achieved maximum motor milestone. [14] Later, types 1-3 were subdivided into subtypes, and types 0 and 4 were added. SMN2 copy number was recognized to be a major factor affecting disease severity and rate of progression, as shown in Table 2.

The international classification of SMA is widely recognized. However, the classification of adolescents and adults is ambiguous and fails to differentiate patients with different disease severity and functional status. For instance, the current classification of SMA type 3b includes patients with loss of walking ability before age 10 and later development of severe scoliosis, as well as patients with disease onset around age 10 but retained walking ability after the age of 40-50, with a near-normal survival and quality of life. This classification of patients with different severity of disease into the same category makes it difficult to provide precise management for patients with different conditions. In this guideline, we proposed a clarification and slight adjustment to the International Classification of SMA type 3 and also suggested adding SMA type 3c to better classify young adult patients, as shown in Table 3. The new classification needs testing and optimization in clinical practice. Additionally, it has been reported that a very small number of individuals with complete loss-of-function mutations in the SMN1 gene may remain asymptomatic for life. However, subclinical manifestations may appear, such as electromyography (EMG) indicating neurogenic damage.

Recommendation: The progression rate and age of onset of SMA can differ significantly between patients. It is suggested that a clearer classification based on the international classification of SMA be provided for adolescent and adult SMA patients (Class II recommendation, Level D evidence). The revised version should be tested in future clinical practice.

Type	OMIM	Onset Age	Motor Milestone Achieved	Manifestations	Subclassification	Natural History	SMN2 Copies
Type 0	—	Prenatal	None	No movement except extraocular muscle activity, congenital joint contractures, congenital heart defects, respiratory support after birth	—	Death < 1 mo	1
Type 1	253300	< 6 mo	Never sits	Floppy infants, flaccid paralysis, hypoactivity, weakness of head and facial muscles, bell-shaped chest, recurrent respiratory infection and failure	1a: onset < 2 w, no head control 1b: onset within 1-3 mo, no normal head control 1c: onset within 3-6 mo, head control	1a: death < 6 mo 1b: death 2 < yr 1c: median survival at 17 yr	1a: usually 1 1b: usually 2 1c:usually 3
Type 2	253550	6-18 mo	Sits but never stands	Delayed motor development, decreased upper limb muscle strength with age, joint contractures and scoliosis with thoracic deformities in the later stage	2a: short-term ability to sit with later loss 2b: long-term ability to sit	~70% alive at 25 yr	Usually 3
Type 3	253400	> 18 mo	Stands and walks	Childhood-onset progressive proximal muscle weakness and atrophy starting from the lower limbs, loss of walking ability followed by the development of scoliosis, joint contractures, and respiratory insufficiency	3a: onset with 18-36 mo 3b: onset > 36 mo, slow progress	Survival into adulthood, mildly reduced life expectancy	3 or 4
Type 4	271150	Adult	Runs and jumps	Adult-onset slowly progressive proximal muscle weakness starting from the lower limbs	—	Unaffected lifespan	≥ 4

Table 2. International classification of spinal muscular atrophy (SMA).

3. DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

3.1. Diagnosis

Medical history: SMA type 3 or 4 patients who first present with symptoms as adolescents or even adults typically present with insidious onset and slowly progressive limb weakness and atrophy. This usually begins with the proximal lower limbs and progresses to the proximal upper limbs, distal upper and lower limbs, trunk muscles, respiratory muscles, and bulbar muscles. The disease may progress more rapidly in the early adolescent and adult years, whilst in later years the rate of progression slows. Some patients may experience myokymia. Early-stage symptoms may include mild scoliosis and joint contractures, but patients may

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Table 3. International classifications of SMA (revised version).

not experience dysphagia or slurred speech. Despite slight motor development delays, adolescent and adult SMA type 3 or 4 patients can achieve all motor milestones. Patients usually have normal intelligence, with no sensory abnormalities or urinary or defecation disorders. A small number of patients have a family history of autosomal recessive inheritance.

Physical Examinations: Intelligence is normal. Typical signs are symmetrical limb muscle weakness and atrophy, especially worsened in proximal muscles including limb girdle muscles. Accompanied by decreased or absent tendon reflexes and negative Babinski's signs. Some patients with advanced disease may experience limited mouth opening, tongue fasciculations, and decreased gag reflex, without any involvement of extraocular muscles. The superficial and deep sensory examination is normal. [15] Based on the history and examinations, lower motor neuron disease is considered.

Tests: Creatine kinase (CK) level is usually normal or slightly elevated, within 3 times the upper limit of normal. However, CK level can reach up to 5 times the upper limit of normal in adult patients with rapid progression or muscle twitching. Electrophysiological examination reveals extensive neurogenic damage with marked reduction in compound muscle action potential (CMAP) amplitude and normal conduction velocity. In some patients, a small number of spontaneous potentials may be observed in the EMG. In advanced stages of the disease, electrophysiological examination may face difficulty in distinguishing between motor nerve axon and myelin involvement, or neurogenic or myogenic damage. With accurate electrophysiological examination, lower motor neuron syndrome can be diagnosed, with the involvement of the anterior horn of the spinal cord or motor axons.

Genetic testing: SMA is an autosomal recessive disease and diagnosis requires genetic testing. For patients who are suspected of having SMA, multiplex ligation-dependent probe amplification (MLPA) is usually used to detect the copy numbers of the SMN1 and SMN2 genes. If the copy number of SMN1 is 0, the diagnosis can be confirmed. However, in case the copy number is 1 and the suspicion of SMA is still high, further tests can be conducted such as long fragment Polymerase Chain

Reaction (PCR), Nested PCR, or RT PCR to search for pathogenic micro-mutations in SMN1. Homozygous deletion of exon 7 of the SMN1 gene is the cause of 90% to 95% of SMA patients, while the remaining patients have heterozygous deletion of the SMN1 gene combined with point mutations. A detailed genetic diagnosis process can be found in " Expert Consensus on genetic diagnosis of spinal muscular atrophy". [8]

Summary of the diagnostic process: SMA manifests as chronic symmetric muscle weakness and atrophy, which affects mostly the proximal muscles. It has decreased tendon reflexes and negative Babinski's signs on physical examination. Electrophysiological examination further localizes the involvement of the anterior horn of the spinal cord or motor axons. The diagnosis of SMA is finally confirmed by genetic testing.

3.2. Differential Diagnosis

If genetic testing does not confirm 5q-SMA or excludes it, then other possible causes of lower motor neuron syndrome should be considered. Further confirmation of history and physical signs is required based on which muscle magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) testing, muscle biopsy, nerve biopsy, and more extensive genetic testing can be performed to help confirm the diagnosis. For clinical evaluation, particularly for other hereditary diseases involving adolescents and adults with electrophysiologic findings of the anterior horn of the spinal cord or motor axonal involvement, the main differential diagnoses are as follows.

Amyotrophic lateral sclerosis: It typically onsets in middle age and progresses rapidly. The disease affects both upper and lower motor neurons with positive pyramidal signs. It is primarily sporadic but can be rare familial caused by mutations in SOD1, FUS genes.

Spinal and bulbar muscular atrophy (Kennedy's disease): It typically affects males around 40 years of age and progresses slowly. Besides lower motor neuron involvement, it may also cause sensory nerve conduction abnormalities and other symptoms such as androgen insufficiency. This disease may have an X-linked recessive family history and is caused by expanded CAG repeat in the AR gene.

Non-5q-SMA: The clinical manifestations and electrophysiological examination results are similar to SMA. Usually, weakness and atrophy in the distal limbs are more pronounced. It is caused by defects in genes like DYNC1H1 and CHCHD10. Differential diagnosis can be challenging, and genetic testing is needed to confirm the diagnosis.

SMA with an overlapping syndrome: In addition to the typical manifestations of lower motor neuron involvement in SMA, it is complicated with other clinical manifestations, such as severe arthrogryposis, cerebellar atrophy, and myoclonic epilepsy. It is caused by gene defects, including VRK1 and ASAH1. Diagnosis is confirmed through genetic testing based on clinical features.

Distal hereditary motor neuropathy: It primarily affects the motor axons of peripheral nerves, manifesting as weakness and atrophy of distal muscles. It can be challenging to differentiate it from anterior horn motor neuron involvement. This disease is caused by gene defects such as SIGMAR1 and DCTN1. Therefore, genetic testing is necessary for a definitive diagnosis.

Hereditary motor sensory peripheral neuropathy (Charcot-Marie-Tooth Disease) type 2: This disease affects peripheral nerves, mainly axonal involvement, with both motor and sensory nerves affected. Although some patients may not experience any sensory symptoms, electrophysiological examination shows damage to both motor and sensory axons. Limb weakness and atrophy usually occur in distal muscles. The disease is caused by gene defects such as MFN2 and HSPB1, and genetic testing is necessary for diagnosis.

Limb-girdle muscular dystrophies: It usually begins in adolescence to adulthood and is characterized by slowly progressive weakness and atrophy of the limb-girdle muscles and proximal limb muscles. EMG indicates myogenic damage, and many types of blood CK are significantly elevated. The disease is caused by gene defects such as CAPN3 and DYSF. A diagnosis can be confirmed by genetic testing and muscle biopsy.

Recommendation: SMA should be considered if the clinical diagnosis of lower motor neuron syndrome is consistent with the onset of the proximal lower limbs. For molecular genetic diagnosis, targeted mutation analysis can be used. If homozygous deletion of exon 7 of the SMN1 gene is confirmed, SMA can be diagnosed. However, if the SMN1 gene is heterozygously deleted, further Sanger sequencing needs to be performed to determine whether there is a pathogenic minor mutation in the SMN1 gene. (Class I recommendation, Level C evidence).

4. MEDICATION

4.1. Disease modifying treatment

Disease modifying treatments (DMT) are medications that target SMA gene defects and pathophysiological mechanisms. These drugs increase SMN protein levels through various means, which changes the progression of the disease. Currently, there are 3 DMTs available globally for the treatment of SMA.

4.1.1. Nusinersen

Nusinersen is an antisense oligonucleotide drug that requires intrathecal injection. It has 18 nucleotides and is complementary to the ISS-N1 segment of intron 7 on the SMN2 gene pre-mRNA. It can compete with the splicing regulatory factor hnRNP A1 to bind to this segment, weakening the effect of hnRNP A1 and promoting inclusion of exon 7 in the mRNA. During the translation phase, this full-length mRNA generates normal SMN proteins to exert physiological effects. Numerous preclinical studies have confirmed the safety and effectiveness of nusinersen, and the main phase III clinical trial evidence is as follows. CHERISH (NCT02292537) was an international multi-center, randomized, double-blind, sham-controlled study including a total of 126 patients with type 2 and type 3 SMA. After 15 months of treatment, it was observed that the Hammersmith Functional Motor Scale (HFMSE) score in the nusinersen group increased by an average of 3.9 points compared to the baseline, while the control group's score decreased by an average of 1.0 points (P=0.0000001). Furthermore, the Revised Upper Limb Module (RULM) score in the nusinersen group increased by an average of 4.2 points from the baseline. The long-term extension study, SHINE (NCT02594124), showed continued improvement in motor function with nusinersen treatment. In terms of safety, it was noted that the overall incidence of adverse events in the nusinersen group was similar to the control group and the nusinersen group had fewer severe adverse events. [16] ENDEAR/SHINE (NCT02193074) was an international multi-center, randomized, double-blind, sham-controlled study with a total of 121 type 1 SMA patients. After 13 months of treatment, the nusinersen group had a 61% event-free survival rate, while the control group had a rate of only 32% (P=0.005). The mortality rate in the nusinersen group was 63% lower than that of the control group. Additionally, 51% of patients in the nusinersen group was classified as a Hammersmith Neurological Examination Section 2 (HINE-2) responder, compared to 0% in the control group (P<0.0001). The nusinersen group had 71% of patients with an improvement of 4 or more points in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score compared to just 3% in the control group (P<0.001). The long-term extension study, SHINE, demonstrated that long-term treatment with nusinersen continued to enhance exercise capacity. In terms of safety, nusinersen's adverse event rates, serious adverse events, and discontinuation rates due to adverse events were lower than those in the control group. [17] A German prospective, multi-center observational real-world cohort study focused on 173 adolescent and adult SMA patients (age range 16-65 years old) who received nusinersen for at least 6 months and were followed for up to 14 months. Results showed that nusinersen significantly improved the patient's HFMSE score (at 14 months increased by 3.12 points from baseline, 95% CI: 2.06~4.19, P<0.0001), 6-Minute Walk test (at 14 months increased by 46m from baseline, 95%CI: 25.4~66.6, P<0.0001), and RULM score (at 14 months increased by 1.09 points from baseline, 95%CI: 0.62~1.55, P<0.0001). No serious adverse events were reported during the follow-up period. [18] It has been reported that several real-world studies have been conducted on the effectiveness of nusinersen. Gavriilaki *et al.* [19] conducted a systematic review and meta-analysis of 7 case series and 5 cohort studies, which together included a total of 428 SMA patients older than 12 years of age treated for longer than 6 months. The results showed that nusinersen significantly improved HFMSE scores (standardized mean difference (SMD) 0.17, 95% CI: 0.01~0.33) and RULM score (SMD 0.22, 95% CI: 0.06~0.38) at the longest follow-up. The study also found that 43.3% HFMSE and 38.9% RULM score improvements reached clinical significance. However, for patients of childbearing age, the effect of nusinersen on reproduction is unclear. Although animal experiments did not reveal any significant reproductive toxicity, more research is needed to understand its impact on human reproduction.

Recommendation: Multiple randomized controlled clinical trials, real-world research results, and meta-analyses have confirmed the effectiveness and safety of nusinersen in treating SMA (Class I recommendation, Level A evidence).

4.1.2. Risdiplam

Risdiplam is a small-molecule drug that targets the splicing regulation of SMN2 pre-mRNA. It binds with the exonic splicing enhancer 2 (ESE2) on exon 7 of the SMN2 precursor mRNA and the 5' splicing site (5'-ss) on intron 7 to enhance the recognition and binding of U1 snRNP. This leads to the inclusion of exon 7 into a greater proportion of mature mRNA, and more full-length mRNA is then translated into normal SMN protein to exert physiological effects.

The drug has completed preclinical research and has been in the clinical trial stage. The SUNFISH study (NCT02908685) [20] is a phase III international multi-center (including China) double-blind, randomized, placebo-controlled study. The study is divided into two parts: dose exploration and efficacy verification. Part 2 includes 180 non-ambulatory patients aged 2 to 25 years old with type 2 and type 3 SMA. The patients were randomly assigned to the treatment group and the placebo group in a ratio of 2:1. After 12 months, the Motor Function Measure 32 (MFM32) scores improved more from baseline in patients treated with risdiplam than in patients treated with placebo. The scores in the treatment group were greater than those in the placebo group with a difference of 1.55 (95% CI: 0.30 to 2.81, P=0.016). There were no adverse events leading to withdrawal, dose adjustment, or treatment interruption. The drug was approved in 2020, and real-world research data is still being accumulated. Patients of childbearing age should adjust their medication according to the instructions.

Recommendation: Risdiplam has high-quality randomized controlled clinical trial results on patients of different ages and with various disease states. It also includes data on Chinese SMA patients, which confirms the effectiveness and safety of the drug (Class I recommendation, Level B evidence).

4.1.3. Onasemnogene abeparvovec (OAV-101)

Onasemnogene abeparvovec (OAV-101) is a gene replacement therapy that is transported by a recombinant adeno-associated virus type 9 (AAV9). The virus is modified to load the SMN1 DNA sequence along with other supporting elements such as promoter, enhancer, intron, polyA tail. Once the viral vector enters the motor neuron, the introduced genome exists independently and does not integrate into the human genome. It then continuously produces SMN protein which exerts corresponding physiological effects. The drug has completed preclinical research and clinical trials in the United States and was approved for use in SMA children under 2 years old in 2019. However, it has not yet been approved in China. Currently, its latest global multi-center clinical trial of intrathecal injection is being launched simultaneously in mainland China.

4.2. Other medications

In addition to the above-mentioned DMTs targeting gene defects and SMN protein promotion, there are also drugs targeting other pathophysiological processes of SMA in different stages of development, such as muscle troponin activator (reldesemtiv) and myostatin monoclonal antibodies (SRK-015 and other medications). Some drugs have been already approved, such as salbutamol and sodium valproate, while some are used off-label.

4.3. Combination Medication

The use of different DMTs in combination or sequentially has been tested in a limited number of patients in real-world scenarios. However, there is still a lack of evidence to prove the effectiveness and safety of this approach. Furthermore, a preclinical study[24] has suggested that combining DMTs with other drugs may enhance the therapeutic effects. Therefore, it is crucial to conduct further clinical studies to observe the safety and effectiveness of such combinations and establish standardized usage methods.

5. GENETIC COUNSELING AND PRENATAL DIAGNOSIS

SMA is an autosomal recessive genetic disease. Usually, both parents of an affected individual are carriers of the disease, which means that two carriers have a 1 in 4 chance of having a child with SMA. In such cases, it is recommended that carriers seek genetic counseling before getting married and having children. Furthermore, a prenatal diagnosis should be considered when necessary. Parents of SMA patients are advised to seek guidance from the Department of Reproductive Genetics regarding prenatal diagnosis for future children.

If individuals with mild SMA plan to have children, the risk of their offspring having the disease is mainly determined by the SMN1 gene status of their spouses. Therefore, spouses should take carrier testing. If their spouses are carriers, prenatal diagnosis should be performed. [21-22] It is recommended that individuals consult with reproductive genetics department regarding relevant tests. In addition, children of SMA patients will carry the pathogenic SMN1. Consequently, their spouses should also undergo carrier testing before pregnancy. If necessary, prenatal diagnosis should be performed.

For couples without a family history of SMA who wish to evaluate the risk of having a child with SMA, pre-pregnancy screening can be performed. It is advisable to seek detailed genetic counseling and arrange screening through a reproductive genetics department.

Recommendation: SMA patients who plan to conceive offspring should have their spouses take carrier testing. If their spouses are carriers, prenatal diagnosis should be performed (Class I recommendation, Level C evidence). If both couples carry SMN1 gene mutations, prenatal diagnosis is required (Class I recommendation, Level C evidence).

(This part was written by Yi Dai and Xunzhe Yang)

6. MULTIDISCIPLINARY MANAGEMENT

SMA patients will experience a gradual decline in motor function and become physically disabled. Then they may also develop multi-system damage such as scoliosis, joint contractures, respiratory insufficiency, osteoporosis, limited mouth opening, dysphagia, gastroesophageal reflux, malnutrition or overnutrition. Therefore it is essential to implement a comprehensive multidisciplinary management strategy for patients. Researches [11-13, 23] have shown that multidisciplinary management can significantly improve patients' quality of life and increase longevity. Based on the current literature and the experience of domestic medical institutions, we recommend the formation of an SMA multidisciplinary team (MDT). This team should be led by adult and pediatric neurologists and include other medical professionals such as rehabilitation experts, orthopedists, anesthesiologists, gastroenterologists, nutritionists, endocrinologists, psychologists, and pharmacists. The MDT should work together to provide comprehensive individualized management for SMA patients. Apart from neurology, other departments involved in every visit should be based on the patient's condition, which provides not only consultation but also regular assessment to adjust management accordingly. Multidisciplinary diagnosis and treatment are also a key part of this guideline. Physicians from various disciplines involved in SMA management have set up expert groups to discuss and formulate recommendations.

Recommendation: Medical institutions should establish an SMA multidisciplinary management team to formulate individualized comprehensive diagnosis, treatment and follow-up plans for SMA patients (Class I recommendation, Level C evidence).

6.1. Neurology management

6.1.1. Formulation of medication regimens and follow-up plans

Neurologists are responsible for the clinical diagnosis and genetic confirmation of SMA patients. Once diagnosed, a clinical classification and multidisciplinary evaluation are required to develop and adjust management. The assessment includes motor function, scoliosis, mouth opening and swallowing function, nutrition, respiratory function, cardiovascular status, bone health, and family support. Nusinersen is a DMT that requires intrathecal administration. The difficulty of intrathecal injection in patients should be evaluated, and factors such as severe scoliosis and patient tolerance need to be considered. A comprehensive assessment is recommended before the first intrathecal injection, and detailed items are listed in Table 4. Neurologists are responsible for formulating long-term treatment and follow-up plans for patients, informing the next follow-up time. They should actively communicate with patients and their families and obtain full cooperation from patients and their families. The role of neurologists is crucial throughout the treatment process.

SMA is a gradually progressive disease that requires long-term follow-up with the MDT team to understand the changes after treatment and adjust the follow-up treatment plan promptly. Generally speaking, the maximum follow-up interval should not exceed 1 year. The intervals for each assessment are determined based on the patient's condition, disease stage, and relevant test results.

Examinations	Detailed items
Vital signs and general indicators	Weight Temperature Heart rate Blood pressure Respiratory rate
Blood tests	1. Blood routine examination, urinalysis + sediment, feces routine + occult blood, 8 h urine microalbumin 2. Liver function test, renal function test, cystatin C, creatine kinase + creatine kinase isoenzyme + myoglobin 3. Coagulation, hepatitis B virus surface antigen (HBs-Ag), hepatitis c virus antibody (anti-HCV), human immunodeficiency virus antibody (anti-HIV), Treponema pallidum particle agglutination assay (TRUST) 4. Arterial blood gas analysis 5. β-human chorionic gonadotropin (β-hcg)
Examinations	1. X-ray or Computer tomography (CT) densitometry 2. CT scan of the spine with 3d reconstruction 3. Splice-free whole spine imaging (additional for scoliosis surgery) 4. Pulmonary function test (capacity+volume+diffusion) 5. Magnetic resonance imaging (MRI) of lumbar spine 6. Cervical MRI (additional for some patients who may choose cervical approach) 7. Cranial MRI (To exclude co-morbidities and monitor possible medication side effects) 8. Echocardiogram 9. Electrocardiogram (ECG) 10. Ultrasound of liver, gallbladder, pancreas, spleen and kidneys 11. Chest CT 12. Electrophysiology: complex muscle action potential (CMAP), motor unit number index (MUNIX), etc.
Scales and functional assessment	Details shown in Rehabilitation Evaluation section
Cerebrospinal fluid (CSF) test	After a successful subarachnoid puncture, confirm that the CSF continues to flow smoothly and measure the CSF pressure and drip-rate. Performing tests of routine, biochemistry, cytology, and oligoclonal banding. Storing the remaining sample at -80 °C in a refrigerator.

Table 4. Recommended assessment items for first hospitalization in adolescent adult SMA patients

6.1.1.1. Motor function assessment

Appropriate motor function scales should be chosen based on the patient's condition, such as HFMSE, RULM, CHOP-ATEND, MRC scale for muscle strength, and Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS). For a more detailed quantitative evaluation, please refer to the rehabilitation section (subsequent report in this publication). Based on these assessments, we set realistic individualized treatment goals for each patient and conduct long-term follow-ups. It's essential to communicate fully with patients and their families to help them establish realistic treatment expectations.

6.1.2. Scoliosis and intrathecal injection

As SMA patients age and the disease course prolongs, they often develop scoliosis of varying degrees. Therefore, different intrathecal injection methods are required for patients with different conditions.

(1) For SMA patients with no scoliosis or only mild scoliosis, sequential intrathecal injection is less difficult, and routine intrathecal injection can be performed.
(2) For patients with severe scoliosis, lumber or cervical puncture and intrathecal injection should be performed by a medical professional with expertise in intrathecal injection under the guidance of ultrasound, CT, or X-ray C-arm.
(3) For patients with indications and willingness for orthopedic surgery, the orthopedics and anesthesiology departments will evaluate the patient's ability to tolerate the surgery. If the condition is permitted, based on the evaluation, they will fully communicate with the patient (and their family members) to decide whether to start with orthopedic surgery or start drug therapy first and then undergo elective orthopedic surgery. It is worth noting that orthopedic surgery may make intrathecal injection more difficult in the later stage. Therefore it's important to preset the puncture path according to the needs of subsequent intrathecal injection. Part of the bones should be clamped in the corresponding lamina space during orthopedic surgery to appropriately expand the puncture space. In cases where the patient's nutritional status or respiratory function is poor and they are temporarily unable to undergo orthopedic surgery, DMT and comprehensive management can be considered first. Orthopedic surgery can be done after the patient's conditions have been improved. For more information, please refer to the orthopedics section (subsequent report in this publication).
(4) For patients with severe scoliosis and difficulty undergoing lumbar punctures, they may try subarachnoid catheterization with the full informed consent of the patient and their family members, which can be used to further administer medication. Additionally, oral drug treatment may also be recommended.

Recommendation: It is recommended to help patients and their families develop realistic treatment expectations based on quantitative scores of motor function and comprehensive assessment results (Class I recommendation, Level C evidence). Individualized intrathecal injection should be determined by factors such as the patient's scoliosis and nutritional status in full communication with patients.

6.1.2. Post-treatment motor function assessment

In addition to the motor function scale, post-treatment motor function evaluation also comprises a physical examination of the nervous system and a neuroelectrophysiological evaluation carried out by a neurologist. Furthermore, emerging evaluation methods such as wearable devices and remote interaction are also being actively explored. Regular evaluation of patients' motor function after treatment can help patients strengthen their confidence in long-term treatment and also provide objective data for the evaluation of the long-term efficacy of SMA drug treatment.

6.1.2.1 Neurological physical examination and record of condition changes

The physical examination involves a thorough assessment of muscle strength (MRC scale). It also includes evaluating articulation and swallowing function, checking for limited mouth opening, assessing joint mobility, and evaluating scoliosis. This examination is particularly useful for detecting subtle changes that might not be captured by motor function assessment scales. It allows for an objective recording of such changes through targeted physical examinations.

Patients and caregivers are encouraged to actively report all subtle changes they have experienced or observed by their caregivers during each follow-up to supplement the limitations of the motor function assessment scale. Neurologists should also record these functional changes in follow-up medical records for later review or clinical research reference.

6.1.2.2 Neuroelectrophysiological assessment

Neuroelectrophysiological examination can quantitatively evaluate the functional and quantity changes of motor units. In foreign studies, electrophysiological indicators such as CMAP amplitude and motor unit number estimation (MUNE) have been used to study the natural history of adolescent and adult SMA patients, as well as to evaluate the efficacy of DMT. However, not all hospitals are equipped to conduct these exams due to professional requirements and conditions. Therefore, only qualified hospitals are recommended to conduct

these exams based on their actual conditions and clinical research needs.

(1) Motor conduction velocity (MCV) measurement. In MCV examination, the most important indicator is the CMAP. SMA is characterized by motor axon damage secondary to motor neuron apoptosis. Indicators such as distal motor latency and nerve conduction velocity mainly reflect myelin function. The CMAP maximum amplitude represents the sum of all motor unit action potentials in the muscle fibers that are activated by stimulation of a specific nerve. Studies have used CMAP amplitude as an additional prognostic indicator. A foreign study on the treatment of nusinersen in children with SMA found that the CMAP amplitude remained relatively stable as the children's motor function continued to improve and their condition stabilized. [25]
(2) MUNE.
MUNE is a method of quantitatively evaluating the total number of functional motor units in a skeletal muscle or muscle group innervated by a specific nerve. It offers the advantage of being non-invasive, more sensitive than CMAP, and more suitable for regularly measuring the number of motor units. Motor Unit Number Index (MUNIX) may be better tolerated by patients in terms of discomfort and convenience of testing. However, more clinical research is needed to clarify the value of MUNE in evaluating the efficacy of SMA patients. Especially, it is important to design personalized examination strategies based on the patient's disease course and severity to achieve accurate evaluation.

Recommendation: Objective neurological physical examination and neuroelectrophysiological examination before and after treatment can help assess changes in motor function and patient's condition.

(This part was written by Yi Dai and Xunzhe Yang)

6.2. Radiology management

SMA is a rare disease that lacks specific imaging signs, and there is limited research on imaging-related studies. Imaging is primarily used to assess the severity of the disease, monitor its progression, and identify complications in SMA patients. It is recommended that appropriate examinations be selected based on clinical requirements.

6.2.1. X-ray

SMA patients are susceptible to developing scoliosis and kyphosis, and X-rays are preferred to evaluate a patients's skeletal system. It is recommended to use full spinal X-rays to evaluate the presence of scoliosis or kyphosis, as well as any concurrent vertebra malformation. The severity and progression rate of kyphosis can be measured by determining the Cobb angle. To comprehensively evaluate spinal mobility, it is also recommended to perform views of forward flexion, posterior extension, and left and right lateral flexion at the same time. [12] SMA patients often suffer from osteoporosis. To measure bone density and reflect the degree of osteopenia, it is advisable to use Dual Energy X-ray Absorptiometry (DEXA) of the lumbar spine and femoral neck, which has the advantage of being inexpensive and low radiation dose. Although there is no standard data on bone mineral density in children of different ages, DEXA has a certain significance in the follow-up of adolescent and adult patients with SMA.

Recommendation: SMA patients should be followed up regularly, and full spine X-ray and DEXA examination should be performed routinely once a year (Class II recommendation, Level C evidence).

6.2.2. Computed tomography (CT)

CT scan is used to further evaluate the vertebral body and accessory bone structure of the entire spine. Multiplanar reconstruction and volume imaging can fully display the three-dimensional (3D) structure of the spine. For patients with severe scoliosis, a physician experienced in intrathecal injection can perform lumbar or cervical puncture and intrathecal injection under CT guidance. In the case of trauma suffered by SMA patients, a CT scan can not only determine whether there is a fracture but also clearly show the space relationship between the fracture ends. However, the disadvantages of CT are low soft tissue resolution and radiation exposure. So it is less used to evaluate the degree of muscle atrophy.

SMA can involve respiratory muscles, often leading to respiratory dysfunction complicated by pulmonary infection. A chest CT scan can be used to check whether patients have complications such as pulmonary infection and atelectasis. SMA is also prone to lung function impairment, such as reduced forced vital capacity (FVC), decreased forced expiratory volume in the first second (FEV1), and

reduced peak expiratory flow (PEF). [26] For some patients who cannot tolerate or fully cooperate with pulmonary function tests, CT-based biphasic (end-inspiration and end-expiration) lung volume quantitative measurement, along with average CT value measurement, can reflect the patient's pulmonary ventilation function to supplement pulmonary function tests.

6.2.3 Magnetic resonance imaging (MRI)

MRI has the advantages of no radiation, high resolution of soft tissue, and multi-directional multi-parameter imaging. Moreover, it is particularly effective in detecting muscle lesions. SMA is characterized by progressive weakness and atrophy of muscles starting from proximal lower limbs. The degree of atrophy of lower limb muscles can be assessed by MRI. During the examination, it is advisable to use the field of view (FOV) and assess the involvement of both limbs simultaneously. Axial and coronal planes are most commonly used. T1 Weighted Imaging (T1 WI) can display the muscle's anatomical structure, and assess the presence and severity of fat infiltration in the muscle. Short-Time Inversion Recovery (STIR) phase or Fat-suppressed T2 WI is used to show the presence of muscle edema. [27] T2 WI based on the DIXON technique can simultaneously obtain separation of water-lipid images and evaluate fat infiltration and edema in muscles. MRI examination before muscle biopsy can help select the biopsy site and reduce false negatives in the biopsy.

In the early stages of most neuromuscular diseases, muscles tend to show mild to moderate hyperintensity on STIR phase or fat-suppressed T2 WI, indicating the presence of edema. However, it is not clear whether patients with SMA have any imaging findings of muscle edema. The primary MRI findings in patients with SMA are intramuscular fatty infiltration and muscle atrophy. Fat infiltration shows a high signal in both T1 WI and T2 WI, and a low signal in the fat-suppression sequence, which is similar to the signal characteristics of subcutaneous fat. According to a case report, [28] SMA patients had severe atrophy of the thigh and calf muscles with selective preservation of the adductor longus muscle, demonstrating an "exemption" performance. This muscle involvement pattern may prove helpful in the differential diagnosis of other neuromuscular diseases.

Further assessment of the severity of muscle fat infiltration includes semi-quantitative scoring and quantitative methods. The semi-quantitative scoring method uses conventional MRI sequences and divides the degree of muscle fat infiltration into 5 levels (0 points: no fat infiltration; 1 point: <30% fat infiltration; 2 points: 30%~60% fat infiltration; 3 points: >60% fat infiltration; 4 points: all muscles are replaced by fat). [29] On the other hand, quantitative methods can use fat quantification sequences provided by MRI equipment vendors to measure muscle fat fraction (FF). Both semi-quantitative scoring methods and quantitative methods are still in the research stage and have not been routinely used in clinical practice.

There are only a few studies on the imaging changes in brain tissue of SMA. In case reports of SMA types 0 and 1, some patients showed extensive cerebral hemisphere cortical atrophy, some showed extensive white matter atrophy, and some had abnormal signals in the thalamus and putamen. [30] A study compared 25 SMA type 3 and 4 adult patients to healthy controls, and found no significant differences in cortical thickness, gray matter volume, and white matter volume between patients and controls. However, the gray matter density in the motor regions of SMA patients was higher than that of healthy controls, which may indicate a compensatory change. [31] In addition, adult patients with SMA type 3 or 4 also have significant atrophy in certain areas of the cerebellum. [32]

There are limited reports on the imaging changes in the spinal cord of patients with SMA. Some studies indicate that the cross-sectional area of the cervical spinal cord in adult SMA patients is significantly smaller than that of healthy controls [31], while other studies (including children and adults with SMA types 2 and 3) have found no significant difference in the cervical spinal cord cross-sectional area between SMA patients and normal controls. [33]

Recommendation: MRI can be used to objectively evaluate the severity of muscle atrophy and disease progression in SMA patients. It is expected to be used in clinical evaluation after accumulating more data (Class III recommendation, Level D evidence).

There is limited research on neurological imaging changes in SMA patients and further research is required.

(This part was written by Fengdan Wang, Lan Song and Hui You.)

6.3. Psychology

As there is a limited amount of literature on psychiatric monitoring and management related to SMA, this section was primarily developed by referring to psychiatric issues in other chronic diseases. The content of this section stresses the principles of supportive and resource-oriented therapy in psychology, with a focus on the feelings of patients, doctors, and the experience of the doctor-patient relationship.

It is important to provide comprehensive care and attention to SMA patients and their families, which includes monitoring and managing their mental health. Psychological management should cover the patient's social and cognitive development, quality of life, and factors that affect the patient's family functioning. The specific needs vary depending on the patient's age and SMA subtype. The MDT should be equipped with neurologists, psychiatrists, nutritionists, and sports rehabilitation experts, as well as psychotherapists and social workers experienced in helping patients with chronic diseases.

6.3.1. Basic psychological monitoring and management

Psychological monitoring and management are crucial for patients at critical time points [34], such as before and after the diagnosis, during treatment and as the disease progresses. Mental health and quality of life of patients should also be paid attention when visiting different departments. Standardized assessment tools like the Patient Health Questionnaire-9 (PHQ-9) the Generalized Anxiety Disorder-7 (GAD-7), the symptom check list 90 (SCL-90), the self-rating anxiety scale (SAS), and the self-rating depression scale (SDS) can be used by non-psychiatrists to complete psychological assessments of patients. The MINI can also be considered when conditions permit. If there are abnormal scores, it is recommended to refer the patients to a psychiatric department. Additionally, it is essential to monitor the mental health status of the patient's family members, such as parents, siblings, and caregivers.

Recommendation: SMA patients and families need to undergo psychological monitoring and management at critical time points of diagnosis and during long-term follow-up. If abnormalities are found using routine assessment tools, it is recommended to be referred to a psychiatric department (Level II recommendation, Level D evidence).

6.3.2. Psychological characteristics of SMA patients of different ages and subtypes

6.3.2.1. Children and adolescents with SMA

It is vital to understand the cognitive and psychological characteristics of children and adolescents before providing psychological treatment, as they are in the special period of developing and maturing.

(1) It is important to focus on the development of cognition and social function of SMA children. They may experience movement disorders earlier than the development of their intelligence, behavior, and language. These movement disorders can limit children's psychological, and social-cognitive development. [12] However, some studies have shown that the cognitive functions of some children with SMA types 1 to 3 are not significantly different from normal children. This may be because SMA patients can compensate for their physical limitations by developing cognitive skills through their environment. It has also been found that children with SMA type 1 may be at a higher risk for impairments in attention and executive function. Therefore, it is important to comprehensively monitor the cognitive development, learning skills, social functioning, emotional adjustment, and behavioral regulation abilities of children with SMA through standardized neuropsychological tests and interviews. Based on the assessment results and the child's overall medical condition, a home or school education plan will be created that meets the child's needs and goals. This plan will provide an adaptable educational environment that includes necessary equipment and corresponding nursing staff and technology to ensure transportation convenience. The education plan will be regularly maintained and updated by clinicians, school medical staff, and the child's family to ensure a smooth transition to adulthood.

(2) Palliative care.
Palliative care should be incorporated into the daily care of children with SMA. [12-13] While providing medical care, it is important to

consider and respect the emotional well-being of children. For instance, children may experience stress, anxiety, or fear before, during, and after lumbar puncture, and specific supportive psychological interventions can be helpful. These may include listening to children's favorite fairy tales or cartoon theme music and conducting situational games and interesting riddles. Distracting attention can effectively reduce the anxiety of both children and parents. Mindfulness therapy can also be used to help children relieve anxiety and reduce pain.

(3) Hospice care.

Providing hospice care for children with SMA in the terminal stage is based on managing symptoms and providing psychological support for patients and their families. [35] Typically, children in the end stage require help with dyspnea and pain management, nutrition, and postural care. Active intervention should be implemented to alleviate pain in children, and the dosage and frequency of medication can be increased if necessary. If symptomatic treatments are not effective, deep sedation may be considered. It is vital to provide psychological support to the families of the children at this time. Techniques such as bucket lists can be used to communicate with patients about their wishes before death, such as what clothes to wear, whether they have any desire to travel, and their concerns and wishes. Additionally, attitudes towards invasive treatment and resuscitation should be discussed with patients in advance. If a child dies at home, the psychological impact on family members may be more lasting and without the support of medical staff, the parents of the child will be more emotionally burdened. Therefore, it is important to communicate with the child and their family to choose the time and place when the child dies in advance.

In addition, family members should be provided with relevant resources and training in home care, such as training on sputum suction and postural care.

6.3.2.2. Adults with SMA

The mental health of SMA adults can be improved by increasing their social participation and satisfaction of basic psychological needs, such as autonomy (limited independence and the ability to live an independent life), social relevance (social development and shame), and ability (self-control, self-confidence, social value). [36] To help patients with chronic, life-threatening physical illnesses, supportive and resource-oriented psychological interventions should be used, which help them discover resources, solve problems, obtain support, and effectively meet their own needs. The resources checklist technology can be helpful. If conditions permit, psychiatric professionals can lead mutual support among patients or patient family groups, such as mutual aid clubs, and group therapy.

6.3.2.3. Families and caregivers of SMA patients

It is important to pay attention to the siblings of pediatric SMA patients. [37] Research shows that these siblings have a higher chance of developing behavioral problems, low self-esteem, social isolation, and psychological disorders such as depression and anxiety. This is because they may feel dissatisfied with the attention that is given to the affected child, and may feel overwhelmed with excessive family responsibilities.

Physicians should be aware of the different ways SMA can impact children and their siblings within the family context. SMA is a progressive and disabling disease that requires crisis management and psychological intervention for all family members to help them cope with the loss of function and the prospect of early death. Non-psychiatric psychiatrists can use various psychological assessment tools, such as PHQ-9, GAD-7 to evaluate the impact of disease on families. [35]

The psychological distress and burden experienced by caregivers of SMA patients are related to the disease characteristics, including physical and behavioral problems, as well as the caregiver's characteristics, such as their coping style and ability to find positive meaning in caregiving. As the disease progresses, caregivers are faced with increasing psychological and physical demands from patients, and are required to take responsibility and accept the reality of their loved one's illness and impending death. Additionally, caregivers may lack relevant knowledge and skills, such as how to communicate about disease and death, deal with changes in patient behavior, manage their own emotions, or establish personal boundaries.

When providing psychological intervention to caregivers, general psychological support, resource-oriented psychological intervention, and acceptance and commitment cognitive behavioral therapy can be employed. These interventions can encourage caregivers to clarify important values in their lives, adapt to reality and move on while improving their mental health.

Recommendation: It's recommended that support be provided to patients and family members of different ages and disease stages based on their unique psychological needs. This approach can help improve the overall quality of life for SMA families (Level II recommendation, Level D evidence).

Author Contributions

The corresponding authors (Yi Dai and Liying Cui) were responsible for planning the entire guideline, forming the expert team, and promoting the formulation of the guideline. The leading writers of the 12 specialty sections are marked after each section. All experts participated in the discussion of the corresponding part of the guideline, put forward many revisions, and improved the guideline. Finally, the final draft, approved by all experts, was submitted for publication.

Conflict of interests

None.

List of abbreviations

SMA spinal muscular atrophy; SMN1 survival motor neuron 1; OMIM Online Mendelian Inheritance in Man; EMG electromyography; CK creatine kinase; CAMP compound muscle action potential; MLPA multiplex ligation-dependent probe amplification; PCR Polymerase Chain Reaction; MRI magnetic resonance imaging; cerebrospinal fluid CSF; DMT disease modifying treatment; HFMSE Hammersmith Functional Motor Scale Expand; RULM Revised Upper Limb Module; HINE-2 Hammersmith Neurological Examination Section 2; CHOP-INTEND Children's Hospital of Philadelphia infant test of neuromuscular disorders; SMD standardized mean difference; ESE2 exonic splicing enhancer 2; MFM32 Motor Function Measure 32; AAV9 adeno-associated virus type 9; MDT multidisciplinary team; ALSFRS Amyotrophic Lateral Sclerosis Functional Rating Scale; MUNE motor unit number estimation; MCV motor conduction velocity; MUNIX Motor Unit Number Index; DXEA Dual Energy X-ray Absorptiometry; 3D three-dimensional; FVC forced vital capacity; FEV1 forced expiratory volume in the first second; PEF peak expiratory flow; FOV field of view; T1 WI T1 Weighted Imaging; STIR Short-Time Inversion Recovery; FF fat fraction; PHQ-9 Patient Health Questionnaire-9; GAD-7 Generalized Anxiety Disorder-7; SAS self-rating anxiety scale; SDS self-rating depression scale; SCL-90 symptom check list 90; ICF International Classification of Functioning, Disability, and Health; GMFM Gross Motor Function Measure; CHOP-ATEND Children's Hospital of Philadelphia Adult Test of Neuromuscular disorders; TUGT Timed Up and Go test; 6MWT 6-Minute Walk Test; ATS American Thoracic Society; ROM range of motion; SMA-FRS Spinal Muscular Atrophy Functional Rating Scale; SF-36 36-Item Short Form Survey; HRQoL health-related quality of life; PF physical functioning; RP), role-physical; BP bodily pain; SF social functioning; MH mental health; RE role-emotional; VT role-emotional; GH general health; PEmax maximum expiratory pressure; PImax maximum peak inspiratory pressure; PCF peak cough flow; REM rapid eye movement; CSA central sleep apnea; OSA obstructive sleep apnea; PSG polysomnography; BPAP bilevel positive airway pressure; 25-OHD 25-hydroxyvitamin D levels; PINP procollagen type 1 N-terminal propeptide; CTX carboxy-terminal cross-inked telopeptide of type 1 collagen; DXA dual-energy X-ray absorptiometry; rhPTH1-34 recombinant human parathyroid hormone 1-34; IGF-1 Insulin-like growth factor 1; HOMA-IR homeostatic model assessment of insulin resistance; OGTT oral glucose tolerance test; GER Gastroesophageal reflux; GLIM Global Leadership Initiative on Malnutrition; NRS2002 Nutritional Risk Screening 2002; MNA-SF mini nutritional assessment-short form; MUST malnutrition universal screening tool; BMI body mass index; STAMP screening tool for assessing malnutrition in pediatrics; HHD handheld dynamometry; ONS oral nutritional supplements; EN enteral nutrition; ESPGHAN European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; VAS visual analogue scale; FOIS functional oral intake scale; ASO antisense oligonucleotide; CDE Center for Drug Evaluation; LP lumbar puncture; VG vectorgenomes; FSTAs fast skeletal muscle troponin activators;

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