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Clinical Practice Guideline for Adolescent and Adult Patients with Spinal Muscular Atrophy – Part 3

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Yi Dai[a], Liying Cui[a]

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.

6.8. Endocrinology management

Studies have found that SMA can affect multiple systems, with the endocrine system often involved and osteoporosis caused by mobility impairment. [1-3] Weight-bearing activities are an essential stimulus for bone mass accumulation during growth. Insufficient weight-bearing activities in children will lead to inadequate bone mass growth and a significant reduction in peak bone mass. [4] The reduction of muscle mass in children with SMA may reduce the mechanical load on bone cells. Additionally, their anatomical proximity may further affect bone metabolism. Furthermore, a complex endocrine and paracrine regulatory network exists between bones and muscles. Muscles can secrete various myogenic factors to regulate bone and systemic energy metabolism. [5] Since progressive nerve and muscle damage in SMA patients can lead to a series of endocrine complications, including secondary osteoporosis, fractures due to minor trauma, abnormal glucose tolerance, diabetes, and hyperlipidemia. Some patients may also develop abnormal gonadal development, such as precocious puberty and cryptorchidism. [1] Chronic endocrine complications are often overlooked (as shown in Fig. 1), leading to inadequate treatment and a further decline in the quality of life of SMA patients.

This part focuses on endocrinal complications and relative issues concerning diagnosis, assessment and treatment in SMA patients, aiming to prevent and manage them effectively, thus improving the patient's quality of life.

[a] Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China.
State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China.

Corresponding Authors:
pumchdy@pumch.cn

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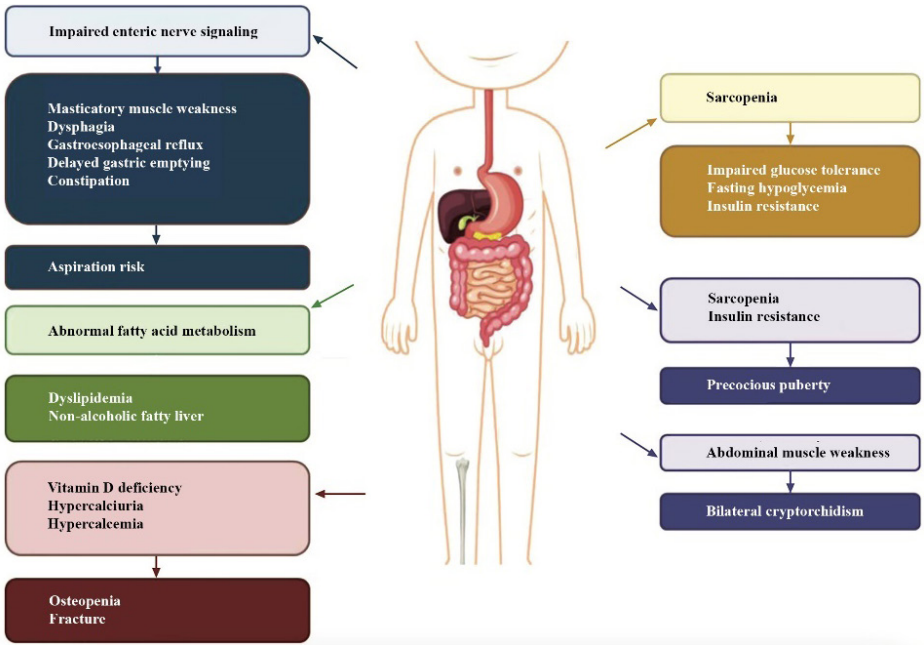

Figure 1. Common endocrine comorbidities and pathogenic mechanisms in SMA patients.

6.8.1. SMA complicated with secondary osteoporosis and fractures caused by minor trauma

The motor system comprises muscles, bones, and joints that interact through neural, mechanical, and endocrine mechanisms. Additionally, factors such as genetics, nutrition, neural networks, exosomes, circadian rhythm, chronic inflammation, aging, various diseases, and drugs can affect muscles and bones in combination. [4-5] SMA patients not only experience a decline in muscle mass, function, and strength, but also have reduced bone density and an increased risk of fractures during adolescence. The risk of fractures is related to the patient's reduced mobility, muscle weakness, and the impact of SMN1 gene mutations on bone metabolism. Healthcare providers should assess and mitigate osteoporosis and fracture risks in SMA patients. [2]

6.8.1.1 Possible mechanism of SMA complicated with osteoporosis

Osteoporosis is a systemic skeletal disease characterized by decreased bone strength and increased risk of fractures. Bone strength depends on bone mineral density and bone quality. [6] Multiple factors lead to insufficient peak bone mass accumulation and imbalance of bone turnover in SMA patients, resulting in reduced bone density and increased risk of fractures. During childhood and adolescence, people experience rapid skeletal growth with a focus on bone-building, bone formation dominance, and steadily growing bone mass, reaching peak bone mass around age 20. [7] Bone mass accumulation is influenced by both genetic and environmental factors, with mechanical stimulation playing a crucial role in achieving peak bone mass. In SMA patients, the reduced mechanical stress on bones leads to significantly decreased peak bone mass due to the early onset of disease and limited activities. Severe SMA symptoms correlate with lower bone density. [2, 8] Furthermore, SMA patients may have secondary hyperparathyroidism due to restricted mobility, insufficient sun exposure, and vitamin D deficiency, leading to accelerated bone loss, poor bone mineralization, and affected peak bone mass gain. [8-9] In addition, SMN1gene mutations can directly affect bone turnover, resulting in reduced bone density due to increased osteoclast activity, accelerated bone resorption, impaired osteoblast differentiation, and insufficient bone formation. [10] The risk of fractures also increases due to reduced mobility and poor balance. [1, 8]

Recommendation: It is recommended to assess bone turnover biochemical markers, vitamin D level, bone density, and fracture risk in SMA patients and take early measures to prevent osteoporosis and reduce fracture risk (Class II recommendation, Level B evidence).

6.8.1.2. Bone health assessment in SMA patients

For patients with SMA, it is recommended to monitor bone anabolism and catabolism. This includes levels of bone turnover markers and serum 25-hydroxyvitamin D levels (25-OHD), as well as bone density and fracture risk assessment.

(1) Detection of bone turnover biochemical marker. Bone turnover biochemical markers, referred to as bone markers, are products of the metabolism and anabolism of bones, respectively reflecting the activity of osteoblasts and osteoclasts and the overall bone metabolism status (Table 1). The levels of bone markers in blood or urine vary with different ages and diseases, which help differentiate bone diseases, predict fracture risks, and evaluate drug efficacy. [11]

Fasting serum procollagen type 1 N-terminal propeptide (P1NP) and serum carboxy-terminal cross-inked telopeptide of type 1 collagen (CTX) are recommended internationally as sensitive and specific markers of bone formation and bone resorption. [11]

Recommendation: Fasting serum P1NP and CTX levels in SMA patients can help dynamically evaluate bone metabolic status and the efficacy of osteoporosis treatment (Class II recommendation, Level B evidence).

(2) Assessment of vitamin D level of SMA patients. 25-OHD is the body's most abundant vitamin D metabolite and is recognized as an ideal indicator of vitamin D nutritional status. Vitamin D levels are considered sufficient at serum concentrations above 30 ng/mL (75 nmol/L), insufficient at 20-30 ng/mL (50-75 nmol/L), deficient below 20 ng/mL (50 nmol/L), and severely deficient below 10 ng/mL (25 nmol/L). [12] Since SMA patients often suffer from vitamin D deficiency, it is recommended to monitor patients' serum 25-OHD levels to guide vitamin D supplements. [12]

Recommendation: It is recommended to detect serum 25-OHD levels in SMA patients and serum parathyroid hormone levels when necessary to monitor the nutritional status of vitamin D and guide vitamin D supplementation (Class II recommendation, Level B evidence).

Bone formation marker	Bone resorption marker
Total alkaline phosphatase	24 h urine calcium/creatinine ratio
Bone specific alkaline phosphatase	Type I collagen N-telopeptide
procollagen type 1 N-terminal propeptide	C-Terminal Telopeptide of type 1 collagen
carboxy-terminal cross-inked telopeptide of type 1 collagen	Pyridinoline
Osteocalcin	Deoxypyridinoline
	Tartrate-resistant acid phosphatase 5b

Table 1. Classification of biochemical markers of bone turnover.

(3) Imaging evaluation of bones in SMA patients. Bone density is an essential indicator for the diagnosis of osteoporosis, measured using dual-energy X-ray absorptiometry (DXA) involving the lumbar spine, femoral neck, and total hip. If the above parts cannot meet the needs of measurement and diagnosis, the distal 1/3 of the non-dominant side of the radius can be selected for evaluation. [6] Pediatric-specific software is recommended to analyze children's DXA results. Z-score should be used to determine bone density for children, men under 50, or premenopausal female SMA patients. Z-score = (measured bone density value - mean bone density of peers of the same race and gender) / the standard deviation of bone density in peers of the same race, gender, and age. Bone mass is considered low when the Z value is less than -2.0. Bone density is analyzed using the T value for males over 50 years old or postmenopausal females. Osteopenia is defined as $-2.5 < T \text{ value} \leq -1.0$, while osteoporosis is defined as ≤ -2.5. Furthermore, osteoporosis can be diagnosed with a hip or vertebral body fracture or a history of fragility fractures in the proximal humerus, pelvis, or distal forearm, with T values of -2.5

to -1.0. [6] Since there may be significant differences in bone density results measured by different DXA instruments, it is recommended to compare bone mineral density measured by the same DXA instrument during follow-up.

A study of a relatively large sample of SMA patients aged 12 months to 18 years old [2] found that 85% of patients had a Z value less than -2.0, and some patients had significant bone density loss at 3 to 4 years old. 38% of patients had fractures, of which the femur was the most common fracture site, indicating that SMA patients have lower bone density and a higher incidence of femoral fractures. Low bone density can predict fracture risk, and the bone health of SMA patients requires urgent attention. In addition, the skeletal X-ray changes should also be evaluated to detect whether there are vertebral compression fractures, especially the lateral X-ray images of the thoracolumbar spine. Skeletal deformity should also be assessed.

Recommendation: DXA should be used to evaluate bone mineral density in SMA patients to diagnose possible concurrent osteopenia or osteoporosis, and to evaluate the efficacy of osteoporosis treatment (Class II recommendation, Level B evidence).

6.8.1.3. Prevention of osteoporosis in SMA patients

Treatment for osteoporosis in SMA patients includes the following measures:

(1) Basic measures.
The treatment of SMA should be strengthened to improve neuromuscular function as much as possible while enhancing functional exercises to improve mobility and prevent falls. At the same time, enough sun exposure is required to promote vitamin D synthesis, and calcium and vitamin D can be supplemented when necessary.

(2) Proper functional exercise.
SMA patients should have the proper exercise intensity under the guidance of a physician to ensure certain mechanical stimuli on bones while improving mobility and balance.

(3) Supplementation of calcium and vitamin D.
Adequate calcium and vitamin D intake are essential to promote bone health. The amount of calcium supplementation for SMA patients of different ages can be referred to as the recommended intake of dietary nutrients for residents. [13] Patients should receive at least 15 to 30 minutes of sunlight exposure daily between 11:00 am and 3:00 pm and expose their skin as much as possible to promote vitamin D synthesis. [12] Vitamin D should be supplemented with a referral to the clinical consensus or dietary nutrient recommendations for Chinese residents. [12-13] The vitamin D supplement dose can be adjusted according to the serum 25-OHD level, with a serum 25-OHD level of more than 30ng/mL being proper (75nmol/L). [6, 12]

Recommendation: SMA patients should receive adequate calcium and vitamin D to ensure the nutrients needed for bone health (Class II recommendation, Level B evidence).

(4) Powerful anti-osteoporosis treatment.
Powerful anti-osteoporosis treatment should be given to SMA patients with low bone density, high risk of fracture, or a history of minimal trauma fracture to increase bone density and reduce the risk of fracture. [6, 14] Powerful anti-osteoporosis drugs are classified according to their mechanism as bone resorption inhibitors, bone formation accelerators, or dual-action drugs. Commonly used bone resorption inhibitors include bisphosphonates (such as alendronate sodium, zoledronic acid, risedronate sodium, ibandronate sodium, pamidronate disodium), denosumab, estrogen, selective estrogen receptor modulators. Commonly used accelerators of osteogenesis include teriparatide and dual-action drugs such as sclerostin monoclonal antibodies. [6] Bone resorption inhibitors can effectively inhibit osteoclast function and promote their apoptosis, thereby reducing bone loss. Foreign guidelines currently recommend them for the treatment of osteoporosis in SMA patients. Although teriparatide can effectively improve bone density and reduce the risk of fractures in SMA patients, it is not recommended for use in pediatric patients with unclosed epiphyses. The experience of using other drugs in minor patients' needs to be improved, with only small sample studies reported in SMA patients.

① Bone resorption inhibitors.
Bisphosphonates are widely used as anti-osteoporosis drugs. They can specifically bind

to the bone surface where bone remodeling is active, inhibit osteoclast function, and reduce bone resorption. A small sample study included SMA patients with osteoporosis or osteopenia who received an intravenous infusion of pamidronate sodium 1.5 mg/kg every 3 months (maximum dose: 60 mg) or intravenous infusion of zoledronate acid 0.05 mg/kg every 6 months (maximum dose: 4 mg). It observed a significant increase in bone density and declined fracture risk in SMA patients after treatment. Some patients experienced transient fever and general pain after the first infusion of bisphosphonate drugs. It has good safety [14], while bisphosphonates' long-term efficacy and safety in SMA patients with osteoporosis still need to be further studied. Denosumab is a humanized monoclonal antibody for nuclear factor kappa B receptor activator ligand. It inhibits bone resorption by reducing osteoclast formation, function, and survival. Case report shows that for SMA patients with severe osteoporosis, subcutaneous injection of denosumab 60 mg every 6 months can significantly increase the patient's bone density with good safety. [15] However, the efficacy and safety of denosumab in SMA patients with osteoporosis still need to be further confirmed by large-sample and long-term clinical studies.

② Accelerators of osteogenesis.

The accelerators of osteogenesis available in China include recombinant human parathyroid hormone 1-34 (rhPTH1-34), which can increase osteoblast activity, promote bone formation, and increase bone density. A study has shown that daily subcutaneous injection of 20 μg of rhPTH1-34 can increase bone density and improve quality of life in patients with neuromuscular diseases. [16] However, there has been no clinical study on SMA patients. This drug is not recommended for children and adolescent patients. Further research is needed to determine whether it is safe and effective for adult SMA patients with osteoporosis.

Recommendation: For SMA patients with low bone density, high risk of fracture, or a history of minimal trauma fracture, bisphosphonates (Class II recommendation, Level B evidence) and denosumab (Class II recommendation, Level C evidence) can be used for anti-osteoporosis treatment with regular follow-up for efficacy and safety.

6.8.2. SMA complicated by abnormal glucose metabolism

Skeletal muscle plays a crucial role in regulating glucose metabolism. It is among the main tissues that insulin targets to promote glucose uptake, metabolism, and utilization. Unfortunately, SMA patients experience a significant reduction in muscle mass and function, which can result in various abnormalities in glucose metabolism.

Abnormal glucose metabolism in SMA patients was first reported in 1995 when two SMA patients were admitted to the hospital due to repeated hypoglycemia. This was accompanied by an increase in ketone bodies without noticeable abnormal changes in glucose-regulating hormone levels. [17] Since then, it has been found that patients with SMA can develop various abnormal glucose metabolisms. A study on a relatively large sample of type 1 SMA patients found that some patients developed hypoglycemia after fasting for 4 to 6 hours. [18] SMA patients are also prone to hypoglycemia after surgery, fever, and other stress conditions. [19] This may be related to the patient's severe reduction in muscle mass and insufficient muscle glycogen energy supply. [18] However, another retrospective study of a small sample of type 1 SMA patients showed that some patients may have hyperglycemia. [20] A study with a relatively large sample of type 2 or 3 SMA children revealed that 29.7% of the patients were prediabetic. [21] SMA children who are overweight or obese and have lost mobility are prone to impaired glucose tolerance or insulin resistance. In contrast, underweight children are prone to fasting hypoglycemia. [21-23]

Insulin-like growth factor 1 (IGF-1) is an anabolic hormone affecting muscle tissue. A large sample study measured serum IGF-1 levels in SMA patients and used homeostatic model assessment of insulin resistance (HOMA-IR) to evaluate insulin resistance. The degree of insulin resistance correlates with the serum IGF-1 level. [24] In addition, SMA patients may have hyperleptinemia, which indirectly promotes insulin resistance, [23] and some SMA patients may even be complicated by diabetes or diabetic ketoacidosis. [25-26]

6.8.2.1. Assessment of glucose metabolism status in SMA patients

Glucose metabolism should be evaluated in SMA patients as they can have various abnormal glucose

metabolism. [27] Overweight or obese SMA patients should undergo biochemical tests such as fasting blood glucose, postprandial blood glucose, glycated hemoglobin, glycated albumin, fasting and postprandial insulin and C-peptide levels. Additionally, an oral glucose tolerance test (OGTT) and insulin release test may be necessary. Lean SMA patients, particularly those who eat less, should be monitored for hypoglycemia. [28]

OGTT is commonly used to evaluate abnormal glucose metabolism. In ordinary people, blood glucose and insulin levels peak 0.5 to 1.0 hours after taking sugar, gradually decreasing and generally returning to normal in about 2 hours. The results of OGTT can be interpreted as follows: The venous fasting plasma glucose <6.1mmol/L and the 2-hour plasma glucose <7.8 mmol/L is considered normal. The fasting plasma glucose ≥7.0 mmol/L or 2-hour plasma glucose ≥11.1 mmol/L indicates diabetes. The fasting plasma glucose < 7.0 mmol/L and 2-hour plasma glucose between 7.8-11.1 mmol/L indicate impaired glucose. The fasting plasma glucose between 6.1-7.0 mmol/L with 2-hour plasma glucose ≤7.8mmol/L indicates impaired fasting blood glucose. [29]

Recommendation: The glucose metabolism status of SMA patients should be monitored. If any metabolic abnormalities such as hypoglycemia, insulin resistance, abnormal glucose tolerance, or diabetes occur, patients should be referred to an endocrinology department. Appropriate measures should be taken to manage the abnormal glucose metabolism. (Class II recommendation, B level of evidence).

6.8.2.2. Abnormal glucose metabolism management

Due to the reduced ability of muscles to store glycogen in SMA patients, prolonged fasting should be avoided to prevent hypoglycemia. Since they are prone to ketone body accumulation during illness or stress, adequate protein and carbohydrate intake should be taken to prevent the occurrence of hypoglycemia, ketoacidosis, and electrolyte imbalance. Obese patients should receive scientific diet and exercise guidance to lose weight to avoid abnormal glucose tolerance and even diabetes. Diabetic patients should follow a strict diabetic diet and take oral hypoglycemic drugs, even insulin, under the guidance of an endocrinologist. The type and dosage of hypoglycemic drugs or insulin should be individualized according to plasma glucose levels to control ideal plasma glucose levels. [29]

Recommendation: For SMA patients with abnormal glucose tolerance or diabetes, the hypoglycemic plan should be individualized under the guidance of an endocrinologist to achieve ideal blood glucose control (Class II recommendation, Level B evidence).

6.8.3. SMA complicated with abnormal lipid metabolism

Patients with SMA may develop hyperlipidemia or fatty liver. Two studies evaluated lipid metabolism in a relatively large sample of children with SMA with a median age of 3.8 years and found that about one-third of the children had hyperlipidemia or hepatic steatosis. Abnormal lipid metabolism or fatty liver is especially common in overweight or obese patients. [21, 30] This may be related to changes in body composition, imbalance of energy intake and consumption, and reduced physical activity caused by neurodegeneration. [21] Some studies also believe that SMA patients may have abnormal fatty acid oxidation and abnormal mitochondrial function, leading to excessive fat accumulation in the liver and causing fatty liver. [31-32]

Recommendation: SMA children should evaluate their blood lipid levels and liver function, especially those overweight or obese children. If necessary, a liver ultrasound should be performed to evaluate whether there is a fatty liver. SMA patients with dyslipidemia should receive dietary and exercise guidance to lose weight and be referred to an endocrinology department if necessary for lipid-lowering treatment (Class II recommendation, Level B evidence).

6.8.4. Other endocrine abnormalities in SMA patients

SMA patients may also have a variety of endocrine abnormalities, and some children may have abnormal gonadal development. A study evaluated the pubertal development of a relatively large sample of SMA patients aged 3 months to 31 years old and found that 60% of male children with type 1 SMA and 30% of male children with type 2 SMA had bilateral cryptorchidism and the proportions were significantly higher than normal children. Ultrasound often revealed testicles in the groin, which may be related to severe abdominal muscle weakness.

Among them, 1/4 of children may also have precocious puberty, with children with type 1 SMA more affected. The hypothalamic-pituitary-gonadal axis function of children with SMA was normal, so their precocious puberty may be related to low body weight, insulin resistance, and muscle atrophy, but the specific mechanism remains to be studied. [33]

Recommendation: The gonadal development should be evaluated in children and adolescents with SMA. Complete physical exams should be conducted, with gonadal function monitored every two years. SMA patients with abnormal gonadal development should be referred to an endocrinology department for further diagnosis and treatment (Class III recommendation, Level C evidence).

6.8.5. Summary

Muscles not only play a crucial role in the motor system but also regulate bone, glucose, and lipid metabolism. Due to progressive degeneration of nerve and muscles, SMA patients may suffer from various endocrine disorders like osteoporosis, hypoglycemia, abnormal glucose tolerance, diabetes, hyperlipidemia, fatty liver, and cryptorchidism. These conditions can reduce the quality of life of SMA patients and even pose a threat to life, requiring urgent attention.

The multiple endocrine disorders of SMA patients should be alerted, which requires multidisciplinary cooperation among neurology, endocrinology, orthopedics, radiology, and pediatrics. Examinations should be performed to evaluate the bone, glucose, lipid metabolism, and gonadal development. Effective measures should be taken to protect patients' bone health, regulate glucose and lipid metabolism, reduce patients' endocrine disorders, enhance the management of SMA, and improve disease prognosis.

(This part was written
by Jing Hu and Mei Li)

6.9. Gastroenterology management

6.9.1. Common manifestations and evaluation of digestive system in SMA patients

SMA patients can experience gastrointestinal symptoms due to muscle atrophy and limited activity, especially gastrointestinal motility disorders, including masticatory muscle weakness, dysphagia, gastroesophageal reflux, gastroparesis, constipation, and abdominal distension or bloating, pseudo-intestinal obstruction. These conditions can lead to an increased risk of aspiration and aspiration pneumonia, which is the leading cause of death in patients with SMA. Therefore, it is crucial to identify and manage gastrointestinal symptoms in SMA patients. [1] SMA gastrointestinal symptoms are caused by SMN defects in the central nervous system and by disruption of colonic smooth muscle signaling mediated by the enteric nervous system. The section focuses on the diagnosis and treatment strategies for gastroesophageal reflux, gastroparesis, and constipation.

6.9.1.1. Gastroesophageal reflux

Gastroesophageal reflux (GER) refers to the reflux of gastroduodenal contents into the esophagus or throat, characterized by regurgitation and heartburn. SMA patients are often prone to postprandial regurgitation, vomiting, nausea, chest or abdominal discomfort, and halitosis. SMA children may refuse food or cry continuously. These atypical manifestations can easily mask possible GER. GER can also cause respiratory complications, including cough, dyspnea, increased energy expenditure in breathing, and repeated aspiration pneumonia. [34]

The assessment of GERD starts with the early identification of typical or atypical reflux symptoms. Upper gastrointestinal contrast indirectly reflects GER, excludes anatomical abnormalities, and should be performed routinely before gastrostomy. There is currently no data to support the use of esophagus pH-impedance monitoring in diagnosing GER in SMA patients.

6.9.1.2. Gastroparesis

Gastroparesis is delayed gastric emptying without mechanical obstruction, characterized by nausea, vomiting, retching, early satiety, postprandial fullness, and abdominal distension. Gastroparesis may lead to reduced nutritional intake in SMA patients and increase the risk of malnutrition. A high-fat diet can lead to delayed gastric emptying and an increased risk of GER. The gold standard for the diagnosis of gastroparesis is gastric emptying scintigraphy. In addition, 13C octanoic acid breath test, wireless power transfer, and ultrasound can also assist in diagnosing gastroparesis. Mechanical

obstruction should be ruled out before diagnosing gastroparesis with gastroscopy or gastrointestinal contrast. [35]

6.9.1.3. Constipation

Constipation is common in patients with SMA and has complex causes, including insufficient dietary fiber and fluid intake, hypotonia of abdominal wall muscles, and gastrointestinal motility disorders. It can manifest as less frequent defecation, dry and hard feces, laborious defecation, a feeling of incomplete defecation, and manual assisted defecation. [36] Severe constipation can cause complications such as intestinal obstruction. The evaluation of constipation includes colonoscopy, barium enema, and colon CT, and the functional assessment includes gastrointestinal transit time, anorectal pressure measurement, and balloon expulsion test.

Recommendation: SMA patients may have gastroesophageal reflux, gastroparesis, and constipation. Symptoms should be identified early, and gastrointestinal morphology and functional evaluation should be performed if necessary (Class III recommendation, Level D evidence).

6.9.2. Management of gastrointestinal manifestations

6.9.2.1. Gastroesophageal reflux

The management of GERD in SMA patients includes ① General treatment. Avoid formula meals or foods that increase reflux, use liquid thickeners, avoid reclining after eating, and elevate the head of the bed during sleep. ② Drug treatment. Including acid suppressants (H2 receptor blockers, proton pump inhibitors, potassium-competitive acid blockers), acid neutralizers (aluminum magnesium hydroxide carbonate), prokinetic agents (metoclopramide, erythromycin), and probiotics. Acid suppressants are recommended for short-term use due to the possibility of gastroenteritis and pneumonia with long-term use. ③ Laparoscopic anti-reflux surgery. Nissen fundoplication can treat PPI-refractory GERD with gastrostomy under general anesthesia, but no consensus exists. [34]

6.9.2.2. Gastroparesis

The management of gastroparesis in SMA patients includes [35]: ① Dietary adjustment and nutritional support. Consume small and frequent meals that are easy to digest, and employ tube feeding when necessary. ② Drug treatment. Including antiemetics (dopamine-2 receptor antagonist like domperidone), prokinetic agents (5-hydroxytryptamine receptor 4 agonist like mosapride, motilin receptor agonist like erythromycin), proton pump inhibitors (applied with reflux symptoms). ③ Other treatments. Including traditional Chinese medicine, acupuncture, and gastric electrical stimulation, which also promote gastric emptying.

6.9.2.3. Constipation

The management of constipation in SMA patients includes: ① Diet and general treatment. Increase the amount of water and dietary fiber intake, increase a certain amount of exercise, and establish good bowel habits. ② Drug treatment. Including bulk-forming laxatives (such as psyllium, and wheat bran.), osmotic laxatives (such as polyethylene glycol, and lactulose.), prokinetic agents (5-hydroxytryptamine receptor 4 agonists like prucalopride), guanylate cyclase C agonists (linaclotide), microecological preparations (probiotics), which can relieve constipation in SMA patients. ③ Other treatments. Including traditional Chinese medicine, biofeedback, and sacral nerve stimulation, which help improve refractory constipation and defecation disorders. [36]

Recommendation: The management of gastrointestinal symptoms in SMA patients involves lifestyle changes, medication, and other treatments similar to non-SMA patients, with additional considerations specific to SMA. (Class III recommendation, Level D evidence).

(This part was written by Xiaoqing Li)

6.10. Nutritional management

Nutritionists or nutrition physicians should serve as multidisciplinary consultants for SMA patients due to their significant individual differences in activity status, body metabolism, gastrointestinal function, body composition, and comorbidities that are related to nutrition. Nutritionists are responsible for conducting nutritional screening, assessment, intervention, and monitoring, based on the patient's medical history, physical examination, laboratory data, and food intake. Nutritional treatment and monitoring should be individualized according to

the patient's age, physiological needs for nutrients, and clinical conditions, as well as nutritional education and guidance, to achieve the best nutritional management. [37]

6.10.1. Nutritional screening and assessment

SMA patients should undergo regular nutritional screening and assessment to identify malnutrition early and actively intervene to improve clinical outcomes. The Chinese Medical Association recommends the first nutritional screening within 24 hours after admission for patients by medical staff with relevant professional qualifications, combined with consultation and physical examination. Patients with nutritional risk should undergo an assessment promptly. Patients with no nutritional risk at first screening and extended hospitalization should undergo a second screen after one week. Outpatients with insufficient intake or weight loss should also undergo nutritional screening and assessment.

2018 Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis of malnutrition includes a two-step approach: nutritional screening and assessment of diagnosis and grading. The screening tools include Nutritional Risk Screening 2002 (NRS 2002), mini nutritional assessment-short form (MNA-SF), and malnutrition universal screening tool (MUST). For adolescent patients, the 2010 China guideline [38] and 2017 American guideline [39] both recommend quick nutritional screening based on growth and development parameters. Commonly used anthropometric indicators for adolescents include weight-for-age, height-for-age, weight-for-height, and body mass index (BMI) for age. In addition, the screening tool for assessing malnutrition in pediatrics (STAMP) [40] has good stability and reliability and can be used for nutritional screening of hospitalized children.

People with nutritional risks should undergo further nutritional assessment, including dietary surveys, physical examinations, laboratory tests (including inflammatory and metabolic indicators), physical fitness tests, nutritional assessment scales, and body composition analysis (including muscle mass and strength). [41] The "Expert Consensus on Multidisciplinary Management of Spinal Muscular Atrophy," released by the Chinese Medical Association in 2019, recommends that SMA patients be assessed for their gastrointestinal symptoms, frequency of choking, and dietary habits. This includes closely monitoring the duration of meals, food intake, and variety to ensure adequate intake of energy, fluids, macro-, and micronutrients. It's also essential to assess the intake of calcium and vitamin D, as both are intimately linked with bone health. [42] Reduced lean and muscle mass and increased body fat mass are notable body composition characteristics observed in patients with SMA. Research indicates that abnormal body composition in SMA patients is positively correlated with the severity of motor ability impairment. [43] DXA or bioelectrical impedance is recommended to analyze the body composition of SMA patients in the 2022 "Expert Consensus on Rehabilitation Management of Spinal Muscular Atrophy". [44] Strength testing is an essential indicator of muscle and nutritional health. A systematic review highlights that handheld dynamometry (HHD) is a prevalent method for evaluating muscle strength, specifically through isometric grip strength and lateral pinch strength measurements, in multiple cohorts of SMA patients over 11 years old. In addition, the British Medical Research Council (MRC) score is also used to assess muscle strength in some cohorts. [45] Laboratory tests commonly include alkaline phosphatase, serum calcium, phosphorus, 25-OHD3, hemoglobin, glucose metabolism, lipids profile, other biochemical indicators, and bone density examination. [42, 44] Various nutritional indicators can be selected and combined according to clinical needs, providing a more accurate basis for formulating nutritional intervention plans. Adult and adolescent SMA patients should undergo nutritional assessment at least once a year. [46-47] Nutritional status should be routinely assessed before surgery for SMA patients scheduled to undergo surgery. [48]

Recommendation: SMA patients should undergo regular nutritional screening and assessment to provide a more accurate basis for formulating nutritional intervention plans (Grade I recommendation, Level A evidence).

6.10.2. Weight Management

Studies have found that 17% to 27% of SMA patients suffer from malnutrition or significant loss of lean mass, and may experience a progressive decline in weight-for-age Z-score during follow-up. [49-50] Maintaining a healthy weight and ensuring adequate intake of energy and protein is essential for improving muscle function and reducing the risk of complications like infections. Indirect calorimetry can measure resting energy consumption to

accurately assess energy needs if the condition allows. [44] If there are no conditions, empirical energy prediction formulas alongside various nutritional indicators -such as knee height, upper arm circumference, triceps skinfold thickness, plasma protein level, and serum creatinine- can aid in tailoring and refining nutritional plans. When patients are malnourished or unable to take sufficient food, oral nutritional supplements (ONS) should be initiated promptly. Enteral nutrition (EN) via tube feeding is indicated when ONS fails to meet 60% of the target energy requirement, is expected to last for 3-7 days, or when conditions cannot be improved via ONS, such as dysphagia or regurgitation. The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends tube feeding to improve children's food intake with neuromuscular disease when their eating time is over three hours. [49] In addition, gastrointestinal malformations of SMA patients are also indications for tube feeding. The main tube feeding routes include nasogastric, nasointestinal, gastrostomy, and jejunostomy. The appropriate tube feeding route can be selected according to the disease status, expected tube feeding time, patient's condition, and gastrointestinal function. [51] Gastrostomy is employed when the tube feeding time is expected to be more than 4-6 weeks in adults and 2-3 months in children and adolescents to establish long-term EN access. For those with severe gastroesophageal reflux, jejunal feeding can be given. If contraindications to EN exist, or in cases of severe gastrointestinal dysfunction where the gastrointestinal route is infeasible for feeding, or when EN alone fails to meet 60% of the targeted energy requirements in the short term, supplementation with parenteral nutrition is recommended. [51-52]

On the other hand, the study suggests that 29% of SMA patients are obese or overweight, with insufficient lean mass and significantly increased body fat mass. [41] Such patients must avoid excessive energy intake or overfeeding during nutritional management, most commonly seen in tube-feeding situations. The patient's energy intake should be limited based on activity status, metabolic consumption, and energy demand to take adequate protein while promoting weight and body composition improvements.

Recommendation: SMA patients with malnutrition or insufficient food intake should be given appropriate nutritional support intervention. Overweight or obese patients should avoid excessive energy intake or overfeeding (Grade II recommendation, Level B evidence).

6.10.3. Swallowing disorders

Following the evaluation of swallowing function, it is crucial to modify the dietary intake to align with the nutritional needs and functional abilities of patients with dysphagia. [53] For patients capable of oral feeding, the swallowing ability of SMA patients can be enhanced through the adjustment of eating posture, modification of food properties and texture, utilization of feeding aids, engagement in swallowing function training and application of oral sensory stimulation. Based on the outcomes of a swallowing assessment and The International Dysphagia Diet Standardization Initiative (IDDSI) framework, [54] appropriate texture-modified foods can be selected. When needed, agents like modified starch and xanthan gum may be employed to thicken liquid foods (including juice, milk, tea, and soup), aiming to minimize the hazards of aspiration and choking. Adjusting the "mouthful size" of food to between 5-20 mL can aid in the formation of a food bolus during the oral stage, facilitating its movement to the pharynx and esophagus. [53] This adjustment can partially compensate for oropharyngeal dysfunction, reduce the duration of meals, and enhance the efficiency of food bolus intake.

When dietary intake cannot meet nutritional needs, ONS or EN preparations with modified thickening properties can be administered as supplements. If nutritional objectives are unattainable or if swallowing difficulties persist despite dietary interventions, EN via tube feeding may be administered, adhering to the escalating principles of nutritional support. [52]

Recommendation: For patients with swallowing disorders who are still capable of oral feeding, safe and effective feeding can be promoted by adjusting the feeding posture and thickening the food texture. When food intake fails to meet nutritional needs, oral supplementation with ONS or EN preparations with modified thickening properties can be selected. If it is difficult to meet dietary goals through feeding, EN support via tube feeding should be given (Grade II recommendation, Level B evidence).

6.10.4. Gastrointestinal dysfunction

For patients with delayed gastric emptying and gastroesophageal reflux, ESPGHAN advises that

liquid foods, such as ONS, should be thickened as needed. It is also recommended to consume small meals more frequently and to tailor the diet based on individual symptom responses. [49] EN or ONS preparations should prefer whey protein formulation, which alleviates gastroesophageal reflux symptoms. [49] Moreover, patients should avoid lying flat immediately following a meal. For patients unable to maintain an upright position, the head of the bed should be continuously elevated by more than 30°, and they should refrain from eating before sleeping. Foods that can trigger regurgitation, such as chocolate, coffee, high-fat, acidic, and spicy foods, should be avoided.

For patients with constipation, ESPGHAN recommends adequate water and dietary fiber intake. All patients with SMA should undergo an evaluation of their fluid consumption as part of their nutritional and dietary intake assessment. SMA patients with higher mobility often have higher fluid requirements than those with more limited mobility. Adequate fluid intake should be individualized on the patient's metabolic needs and clinical conditions. [55] Regarding dietary fiber intake, children should consume adequate dietary fiber, aligning with the recommended intake levels for their age group. The dietary fiber intake of children (g/d) ≈ age (years) + (5~10) g/d. [49, 56] Adults should also take the region's recommended dietary fiber amount for healthy people. [57]

Recommendation: Texture-modified food and thickened fluids (including ONS liquid formula) should be advised in SMA patients with delayed gastric emptying or gastroesophageal reflux. They are also recommended to eat small meals frequently. Whey protein formula can be preferred to improve regurgitation if EN or ONS preparations are needed. SMA patients with constipation should take adequate water and dietary fiber (Grade II recommendation, Level B evidence).

(This part was written by
Rongrong Li and Wei Chen.)

6.11. Stomatology management

SMA is a hereditary neuromuscular disease in which homozygous deletion or mutation of SMN1 leads to the degeneration of motor neurons in the anterior horn of the spinal cord and the motor nuclei of the lower brainstem, resulting in progressive weakness and atrophy of innervated muscles and the gradual loss of motor function. SMA is divided into five types (type 0, type 1, type 2, type 3, and type 4) based on the age of onset and the maximum motor milestone that can be achieved. [58] With the application of DMT and the promotion of multidisciplinary management, the survival period of SMA patients has been significantly extended, and more and more patients are entering adolescence and adulthood. When the alpha motor neurons in the medulla oblongata are gradually affected, SMA patients will have limited movements such as mouth opening, chewing, and swallowing, leading to steadily reduced food intake, insufficient nutritional intake, difficulty in maintaining oral hygiene, and an increase of oral health problems, which will significantly affect patients' quality of life. Decreased chewing efficiency makes food clumps larger which threatens the patient's life when aspiration pneumonia or airway obstruction occurs. Therefore, regular functional examinations of the stomatognathic system and oral health management should be started early for adolescent and adult SMA patients, changing passive treatment to early active treatment and improving the patient's quality of life.

6.11.1. Stomatognathic problems faced by SMA patients

Studies on the health status of the stomatognathic systems of SMA patients reveal that the strength of the masticatory muscles in SMA patients is approximately 50% lower than that of healthy adolescents of the same age. [59-62] The EMG of the masseter and temporalis muscles revealed that, while the strength of muscle contraction exceeded that observed in the healthy group, muscle fatigue was approximately 30% greater compared to the healthy group. The range of mouth opening and mandibular protrusion movement is about 50% lower than that of healthy peers, with less affected mandibular lateral movement. A Dutch study reported a patient with SMA who had limited mandibular movement since the age of 7 years. [63] Researchers have delved into the potential causes behind these clinical observations. It's believed that affected α motor neurons in the medulla oblongata of SMA patients influence the movements of the innervated masticatory muscles. These muscles are part of a larger functional system that includes neck, shoulders, chest, and psoas muscles. Therefore, any postural changes in the head and neck region can significantly impact the biomechanical dynamics

of the temporomandibular joint and its surrounding structures. The first and second cervical vertebrae are positioned next to the temporomandibular joint, intricately linking the movements of the atlanto-occipital joint and cervical vertebrae with the movements of the jaw. The atlanto-occipital joint stretches when the mouth is opened and flexes when the mouth is closed. The neck muscles of SMA patients gradually atrophy, leading to a forced position of the head and neck, exhibiting scoliosis. Patients gradually experience limited mandibular movement, with the degree of limitation related to the progression of the SMA disease.

In addition to diminishing chewing efficiency, a decrease in the strength of masticatory muscles can adversely impact the growth and development of the craniomaxillofacial bones in patients. SMA patients often exhibit increased vertical bone distance, a high angle, and a steep mandibular plane angle. Common manifestations of poor occlusion include disto-molar positioning, deep anterior overbite, open bite, displacement of posterior teeth, and locked bite. Such disordered occlusion further decreases chewing efficiency. Moreover, progressive limitations in mouth opening hinder effective oral hygiene practices, thereby elevating the risk of dental caries, pulpitis, periapical diseases, periodontal diseases, and other oral health issues.

When the alpha motor neurons of the cranial nerves III, VIII, IX, and XII are compromised, it significantly impairs the patient's swallowing function. As a result, solid food tends to linger in the pharyngeal cavity and just above the esophageal sphincter for a longer duration than liquid food, raising the risk of complications such as aspiration pneumonia or airway obstruction.

6.11.2. Evaluation of the stomatognathic system and oral health status of SMA patients

All SMA patients should receive an evaluation of the stomatognathic system every six months. The specific contents of the review are as follows.

6.11.2.1. The patient's subjective experience

When assessing a patient, it's crucial to inquire about their subjective experience of discomfort or fatigue in the masticatory muscles during activities like opening and closing the mouth, chewing, and swallowing. A visual analogue scale (VAS) can quantify these sensations, ranging from 0 (no pain, or no fatigue) to 10 (maximum pain, or extreme fatigue). Alternatively, the Diagnostic Scale for Dysphagia and Dysarthria in Patients with Neuromuscular Diseases can be considered. This tool consists of 39 yes/no questions and two multiple-choice questions covering aspects such as chewing, swallowing, mandibular movement range, mealtime, food adaptation, weight changes, and the incidence of respiratory infections. This scale is designed to capture patient-reported outcomes.

6.11.2.2. Physical examinations

To enhance the assessment of the craniomaxillofacial growth and development, it's crucial to accurately measure the active and passive mouth opening, mandibular protrusion, lateral mandibular movement, and condylar mobility (refer to Table 2).

Items	Normal range
Overbite	Mandibular anterior teeth cover less than 1/3 of labial surface of inferior anterior teeth
Overjet (mm)	3-5
Active maximum mouth opening (mm)	35-40
Passive maximum mouth opening (mm)	35-40
Mandibular protrusion range (mm)	7-12
Mandibular lateral movement (left) (mm)	7-12
Mandibular lateral movement (right) (mm)	7-12
Condylar movement range (mm)	0.5-3.0

Table 2. Examination of the mandibular range of motion.

During palpation examination of the masticatory muscles, the tension and tenderness in both the muscles responsible for opening the mouth (such as the lateral pterygoid muscle, anterior belly of the digastric muscle, geniohyoid muscle) and those for closing it (including the medial pterygoid muscle, masseter muscle, temporalis muscle) should be evaluated. The Fricton index serves to assess the functionality of the temporomandibular joint. The intraoral examination should comprehensively cover oral hygiene, dental health, and periodontal condition. Furthermore, for infants and children unable to undergo CT and MRI scans, ultrasound pre-scanning is a critical evaluation before any puncture interventions.

6.11.2.3. Imaging

To gain insights into the condition of the masticatory and tongue muscles, specifically to detect any atrophy or fatty degeneration, MRI examinations of the temporomandibular joint and masticatory muscles, along with ultrasound examinations of the tongue muscles, are conducted. [64] These tools also help in assessing the structure, morphology, and range of motion of the condyle and articular disc.

6.11.2.4. Electrophysiological examination of masticatory muscles

EMG of each muscle within the masticatory muscle group allows for a thorough and objective assessment of the neurophysiological condition of these muscles.

6.11.2.5. Chewing efficiency test

A solid food chewing and swallowing assessment can be employed, where the patient is tasked with consuming a square biscuit (4.5 cm × 4.5 cm) as quickly as possible but at a safe pace and saying "yes" when finished. Video recording is utilized to count the number of bites, chewing cycles, and swallows, as well as the total time taken to consume the biscuit.

6.11.2.6. Swallowing function test

The functional oral intake scale (FOIS) can quantify the patients' swallowing function (refer to Table 3. [65]

Recommendation: A thorough evaluation of the patient's stomatognathic system allows for an understanding of any limitations in mouth opening, chewing, swallowing, and other essential functions. It can dynamically monitor the patients' oral health status, immediately identify any direct signs of medullary involvement, and formulate prospective management recommendations (Grade II recommendation, Level B evidence).

6.11.3. Health management of the stomatognathic system in SMA patients

6.11.3.1. Management Principles

Early identification of conditions such as restricted mouth opening and aberrant mandibular movements is crucial. Prompt and appropriate interventions, including manual therapy, physical therapy,

Items	Scale (0 = Completely consistent, 4 = Completely inconsistent)				
Grade 1: Nothing by mouth	0	1	2	3	4
Grade 2: Tube dependent with minimal attempts of food or liquid	0	1	2	3	4
Grade 3: Tube dependent with consistent oral take of food or liquid	0	1	2	3	4
Grade 4: Total oral diet of a single consistency	0	1	2	3	4
Grade 5: Total oral diet with multiple consistencies, but requiring special preparation or compensations	0	1	2	3	4
Grade 6: Total oral diet with multiple consistencies without special preparation, but with special food limitations	0	1	2	3	4
Grade 7: Total oral diet with no restrictions	0	1	2	3	4

Table 3. Functional oral intake scale.

and low-energy laser therapy. This approach targets the interconnected systems of the myofascial, joints, and nerves in the head and neck area, decelerating the progression and onset of disorders related to mandibular movements.

6.11.3.2. Rehabilitation

Rehabilitation treatment for oral and maxillofacial weakness and contracture mainly includes manual therapy and auxiliary device therapy.

(1) Manual treatment of the oral and maxillofacial muscle system [66-67]: ① Supine myofascial release. The patient should lie on their back and the practitioner gently plucks the temporalis, masseter, medial pterygoid, lateral pterygoid, and sternocleidomastoid muscles on both sides 2-3 times. ② Sitting myofascial release. The patient is in a seated position and the practitioner puts the little finger deep into the mouth and plucks the muscles around the medial and lateral pterygoids 2-3 times. ③ Cervical spine adjustment. The practitioner gently holds the patient's head with the index fingers around the C2-C3 vertebrae. The head is carefully tilted back and rotated to both sides. After continuous traction for 3 minutes, gently bring the head back to a neutral position. ④ Neck training. The patient actively flexes and extends the head against resistance 12 times (supine forehead resistance and prone occipital resistance), with each isometric contraction lasting 6 seconds.

(2) Auxiliary device treatment.
Passive mouth-opening therapy involves assistive devices like Therabite [68], an adjustable elastic mouth opener. This device is positioned between the upper and lower incisors to maintain maximum mouth opening for 30 minutes and then relax for 10 seconds, with five sets per day and seven times a week. The treatment duration and frequency should be tailored according to the patient's tolerance.

6.11.3.3. Home mandibular functional exercise training

During the homestay, caregivers assist SMA patients in performing active mouth opening, passive mouth opening, mandibular protrusion, lateral movement and swallowing exercise training every day. Through continuous training, the strength of the masticatory muscles can be enhanced and the range of motion of the temporomandibular joint can be improved, improving the ability to eat orally and swallow function. The specific training contents are: ① Perform voluntary and passive maximum mouth opening to tense the muscles for 5 seconds followed by relaxation, with 15 times per set and 3 sets daily. ② Perform maximum mandibular protrusion and maximum lateral mandibular movement to tense the muscles for 5 seconds, and then relax, with 15 per set and 3 sets daily. ③ With lips closed, perform large-scale chewing movements 5 times, in 3 sets each day. ④ Execute rapid tongue extension and retraction movements by extending the tongue out and moving it rapidly up, down, left, and right 5 times, in 3 sets daily. ⑤ Utilize a spoon to apply resistance against the tip of the tongue, repeating this 5 times in 3 sets each day.

6.11.3.4. Oral hygiene maintenance and emergency treatment

With the help of a caregiver, the patient should rinse his mouth after each meal and brush his teeth once in the morning and evening with fluoride toothpaste. Fluoride should be applied every six months at a professional dental institution. When treating dental and periodontal emergencies such as pulpitis and periodontal abscesses in SMA patients with limited mouth opening or temporomandibular joint movement disorders, local anesthetics such as 2% lidocaine can be injected into the bilateral sub pterygoid fossa to relax the masseter muscle, medial pterygoid muscle and other jaw lifting muscles, thereby increasing the mouth opening and enabling the patient to cooperate with the corresponding intraoral treatment.

Recommendation: An individualized oral-mandibular rehabilitation treatment plan is recommended for SMA patients at different stages of the disease. Dental and periodontal examinations and maintenance should be conducted every six months to improve patients' quality of life and prognosis (Grade II recommendation, Level D evidence).

6.11.4. Summary

The human body is an organic whole, with heads, spine, pelvis, and lower limbs functionally interrelated. The abnormal muscle state and body posture of SMA patients are closely related to the limited

mandibular movement function. Studies of oral and maxillary disease management in adolescent and adult SMA patients have just started, lacking high-quality evidence. It is necessary to dynamically evaluate the oral health status of patients early, providing prospective recommendations to formulate individualized rehabilitation treatment plans and improve the quality of life and prognosis of patients.

(This part was written by Chunlan Guo.)

6.12. Drug use and monitoring in the pharmacy department

6.12.1. Nusinersen

In December 2016, nusinersen was heralded as the first antisense oligonucleotide (ASO) drug approved by the US FDA for treating SMA in children and adults. In November 2018, nusinersen was included in the first batch of new overseas medicines urgently needed for clinical use released by the Center for Drug Evaluation (CDE) of the State Drug Administration. In February 2019, it was approved for marketing in China. On January 1, 2022, the drug was officially included in the national medical insurance reimbursement list significantly alleviating the financial burden on families of children with SMA in China. Currently, nusinersen is marketed in many countries and regions worldwide, including Canada, Brazil, Europe, Australia, Japan, and Russia.

Nusinersen has a large molecular weight and cannot pass through the blood-brain barrier, so it is administered by intrathecal injection [69], with a recommended dose of 12 mg. Treatment begins with four loading doses, with the first three loading doses given 14 days apart and the fourth loading dose given 30 days after the third loading dose, followed by maintenance doses every 4 months. [70] If a loading dose is delayed or missed, it should be given as soon as possible, with at least 14 days between doses, and continued at the prescribed frequency. If a maintenance dose is delayed or missed, it should be given as soon as possible and continued every 4 months. [70] After multiple loading and maintenance doses, the mean CSF trough concentration of nusinersen can increase cumulatively by 1.4- to 3-fold and reach steady-state in approximately 24 months. After intrathecal injection, plasma trough concentrations are relatively lower than CSFs, with a median plasma peak Tmax range of 1.7 to 6.0 h. After the drug enters the CSF, the blood concentration decreases rapidly within 20 hours. The rate of decrease slows significantly within 7 days and further slows from 7 to 14 days. After 15 days, the blood concentration is relatively stable. After multiple doses, no accumulation was found in the plasma exposure indicators (peak concentration Cmax and area under the concentration-time curve AUC). The half-life of 12 mg of nusinersen in the CSF is 135 to 177 days. [71] Nusinersen and its metabolites are excreted from the body through urine. [70]

Nusinersen's metabolism is primarily slow, mainly through hydrolysis mediated by nucleases (3′ and 5′), rather than as a substrate, inhibitor, or inducer of cytochrome P450 enzymes. In vitro studies have shown that nusinersen is not a substrate or inhibitor of human BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP transporters. Therefore, nusinersen is less likely to interact with other drugs. [70]

The clinical manifestations of SMA vary greatly. Several critical studies have been conducted for different types of SMA on nusinersen, including the ENDEAR study for type 1 SMA [72], the CHERISH study for types 2 and 3 SMA [73], the NURTURE study for presymptomatic SMA [74] and the long-term extension study SHINE. [75] These studies have demonstrated that nusinersen has clinical benefits and good tolerance in different subtypes, age groups, and stages. No severe adverse reactions related to the drug were found, showing an excellent benefit-risk ratio.

In infantile SMA, most adverse reactions are respiratory problems related to SMA, including lower respiratory tract infection, constipation, and severe atelectasis. [70] Because SMA infants are nonverbal, adverse reactions reported by patients may not be collected in studies —especially those related to post-lumbar puncture (LP) syndrome, such as back pain and headache. The frequency of post-LP syndrome increases with age. [72] In late-onset SMA patients, most adverse reactions are related to LP, such as headache, back pain, and post-LP headache, and most of these events occur within 5 days after LP. [70]

Furthermore, patients treated with nusinersen need to be regularly monitored for coagulopathy, thrombocytopenia, and proteinuria. Although the incidence of clinically significant thrombocytopenia, platelet dysfunction, or nephrotoxicity was

very low in trials using similarly modified ASOs, a study of patients with familial amyloid polyneuropathy has reported a death with inotersen due to thrombocytopenia-related intracranial hemorrhage. [76] Therefore, when clinically indicated, platelet and coagulation laboratory testing is recommended before the administration of nusinersen. In addition, there have been reports of communicating hydrocephalus irrespective of meningitis or hemorrhage in patients treated with nusinersen in postmarketing use, with ventriculoperitoneal shunt devices implanted in some patients. Evaluation for hydrocephalus should be considered in patients with decreased consciousness. The benefits and risks of nusinersen in patients with ventriculoperitoneal shunts are unclear, and maintenance therapy requires careful consideration. [70]

A study of nusinersen based on the U.S. FDA Open Data Project (Open FDA) showed [77] that the top five adverse events were headache, post-LP syndrome, fever, infectious pneumonia, and vomiting. The top five adverse reaction risk signal strengths were post-LP syndrome, CSF leakage, rhinovirus infection, urine protein detection, and respiratory syncytial virus infection. This study suggests adverse reactions that require high attention in clinical applications.

Precautions: ① Adverse reactions. There have been reports of thrombocytopenia, coagulation abnormalities, and nephrotoxicity after subcutaneous or intravenous injection of other ASO drugs. If clinical indications occur, it is recommended to perform platelet and coagulation function and urine protein tests before administration. A post-marketing study has reported that patients treated with nusinersen developed communicating hydrocephalus unrelated to meningitis or bleeding. Therefore, patients with decreased consciousness should be considered for evaluation of hydrocephalus. The benefits and risks of nusinersen in patients with ventriculoperitoneal shunts are unclear, and maintenance therapy requires careful consideration. ② Drugs. Store in a refrigerator at two °C ~ 8 °C; keep in the original carton away from light and avoid freezing. If refrigeration is not possible, nusinersen in the original carton away from sunlight can be kept at 30 °C or lower for up to 14 days. Unopened vials of nusinersen can be taken out of the refrigerator and then returned if necessary before administration; if taken out of the original carton, the total time out of the refrigeration environment should not exceed 30 hours at a temperature not exceeding 25 °C. When using, the drug should be placed at room temperature (25 °C), and do not use an external heat source to heat it. The particulate matter and color in the bottle should be checked before use. If visible particles are observed or the liquid in the bottle changes color, it should not be used. The drug must be used within 6 hours after being taken out of the bottle. [70]

Recommendation: When treating SMA patients with nusinersen, attention should be paid to not only common side effects such as respiratory infections, post-LP syndrome, nausea, and vomiting but also examination, including platelet count, coagulation, and kidney function. The risk of meningitis and hydrocephalus should be noted (Grade I recommendation, Level A evidence).

6.12.2. Risdiplam

In August 2020, the FDA approved the world's first oral drug for treating SMA, risdiplam. Risdiplam is an SMN2 splicing modifier for treating SMA patients aged 2 months and above. Risdiplam powder for oral solution passed the priority review and approval procedure of the State Drug Administration as a Class I innovative drug. It was marketed on June 17, 2021, with the trade name Evrysdi, providing a new treatment option for SMA patients and their families.

In June 2022, the US FDA extended the applicable population of risdiplam to SMA children under 2 months old. On June 13, 2023, the State Drug Administration of China approved the expansion of the relevant population of risdiplam to SMA patients aged 16 days and above. The drug was included in the national medical insurance reimbursement list on March 1, 2023, significantly increasing the accessibility of medicines for patients.

Risdiplam is a powder for oral solution, with each bottle containing 60 mg of risdiplam. It should be used with the reusable oral syringe that comes with the drug. The medication can be formulated into an oral solution with a concentration of 0.75 mg/mL using either purified water or water for injections. It should be taken once daily after meals or breastfeeding and cannot be mixed with formula milk or milk. The recommended daily dose is 0.2 mg/kg for children aged 2 months to under 2 years, 0.25 mg/kg for children aged 2 years or older (<20 kg), 5mg for children aged 2 years or older (>20 kg). Risdiplam has rapid oral absorption and can cross the blood-brain barrier, ensuring

its widespread distribution throughout the central nervous system and the entire body. Its pharmacokinetic profile is linear, achieving a steady-state concentration after continuous administration for 7 to 14 days. The peak plasma concentration (Tmax) ranges from 1 to 4 hours. The intake of food does not impact its absorption process. Risdiplam displays a mean terminal half-life of about 50 hours and is predominantly eliminated through feces or urine. [78]

Risdiplam is metabolized through flavin monooxygenases 1 and 3, alongside CYP1A1, CYP2J2, CYP3A4, and CYP3A7 enzymes. The coadministration of a potent CYP3A inhibitor, itraconazole (200 mg twice daily), alongside a single 6 mg dose of risdiplam, did not markedly impact risdiplam's pharmacokinetic properties. Consequently, it is suggested that no dosage adjustment of risdiplam is necessary when coadministered with CYP3A inhibitors. [79] Further research, utilizing a physiological pharmacokinetic model, has extrapolated the risk of drug interactions in healthy adults to SMA children. [80] It found that primary CYP3A inhibition by risdiplam occurs in the intestine rather than the liver, and risdiplam CYP3A inhibition risk predicted by pharmacodynamics in pediatric patients with SMA aged 2 months to 18 years was negligible.

Risdiplam has also been studied in many different types of SMA patients. On July 29, 2021, the New England Journal of Medicine published a clinical trial of risdiplam for infants with type 1 SMA (FIREFISH). [81] The results showed that risdiplam for infants with type 1 SMA can improve motor function and achieve motor milestones, with the proportion higher than that of previous cohorts. In the SUNFISH part 1 study of patients with type 2 and type 3 SMA, [82] risdiplam effectively and sustainably increased the SMN protein level of patients by more than 2-fold. In the SUNFISH part 2 study of risdiplam in patients with type 2 and non-ambulatory type 3 SMA [83], the primary outcome was the change from baseline in the total MFM-32 score in neuromuscular disease. At month 12, the score in the trial group (1.36 points) was significantly increased compared with the placebo group (-0.19 points), with 38.3% of the patients in the trial group having a significant improvement in the MFM-32 score (≥3 points). The study revealed that compared with placebo, risdiplam significantly improved the motor function of patients with type 2 or non-ambulatory type 3 SMA aged 2 to 25 years. Exploratory subgroup analysis showed that the motor function of young individuals can generally be improved, and the motor function of the elderly can also remain stable for a long time. The current research is still ongoing.

For late-onset SMA patients taking risdiplam, typical side effects are fever, nausea, vomiting, diarrhea, and rash. For infantile-onset SMA patients, frequent side effects include upper respiratory infections, pneumonia, constipation, and vomiting. [84] In the SUNFISH part 2 study [83], common adverse events reported by patients on risdiplam compared with the placebo group were: fever [25 of 120 patients on risdiplam (21%) vs. 10 (17%)], diarrhea [20 (17%) vs. 5 (8%)], rash [20 (17%) vs. 1 (2%)], oral and aphthous ulcers [8 (7%) vs. 0], urinary tract infections [8 (7%) vs. 0], and arthralgia [6 (5%) vs. 0]. An animal study [85] has revealed that risdiplam is teratogenic and may lead to sperm degeneration and decreased sperm count among male animals. However, these effects on sperm cells are reversible and not hereditary after the medication discontinuation.

Precautions [85]: Risdiplam should be taken at the same time every day. In instances where a dose is missed, make sure to take it within 6 hours of the scheduled time. Should the 6-hour window be missed, skip the missed dose and restart it at the scheduled time the following day. In situations where you either fail to swallow the entire dose or experience vomiting post-dose, there's no need to take an additional dose. Simply proceed with your next scheduled dose the following day. Inhaling risdiplam powder should be avoided. Use purified water or water for injection to prepare the solution, valid for 64 days after preparation (with the preparation day counted as day 0; for instance, a solution prepared on April 1 would expire on June 4). Remember to mark the solution's expiration date clearly on the bottle label. Store the prepared solution upright in its original glass bottle in the refrigerator, maintaining a temperature range of 2 °C to 8 °C, and ensure it is kept away from light. Do not freeze the solution.

Recommendation: No dose adjustment is required when risdiplam is used with CYP3A inhibitors. In addition to monitoring common adverse reactions of risdiplam (respiratory tract infection, fever, diarrhea, rash, vomiting, constipation, etc.), attention should also be paid to its possible reproductive toxicity (Grade I recommendation, Level B evidence).

6.12.3. Onasemnogene abeparvovecxioi

In May 2019, the US FDA approved the first gene therapy, onasemnogene abeparvovecxioi, for treating SMA patients under 2 years old. This gene therapy uses a self-complementary adeno-associated virus 9 vector to introduce the normal SMN1 gene into the patient's body through intravenous infusion, producing normal SMN1 protein, thereby improving the function of affected cells such as motor neurons. Patients only need to receive a single intravenous injection with long-term expression of SMN protein in cells, achieving long-term remission or even cure. [86] The recommended dose is 1.1 × 1014 vectorgenomes (VG)/kg with an infusion time of over 60 min. Systemic corticosteroids are given the day before the onasemnogene abeparvovecxioi infusion for 30 days, with a dose equivalent to 1 mg/(kg·d) of oral prednisone, and reduced over 28 days. Before taking the drug, the patient's infection status should be assessed, including liver function, creatinine, complete blood count, and troponin. Patients with concurrent infection should postpone using the drug until the infection improves. If liver function abnormalities persist, systemic corticosteroids should be continued until the AST and ALT levels are both lower, with 2 times the upper standard limit (UNL). If oral corticosteroids are not tolerated, intravenous corticosteroids can be considered according to clinical indications. The drug has not yet been approved for marketing in China.

The clinical trials have established the effectiveness of onasemnogene abeparvovecxioi in treating patients with type 1 SMA. The START trial, which included 15 participants, demonstrated the drug's potential in extending survival and enhancing motor abilities. Notably, younger patients and those with better baseline function experienced more significant benefits when treated with a higher dose. [87] Moreover, the STR1VE study, an open-label, single-arm, single-dose Phase III clinical trial, further affirmed its safety and efficacy, particularly in younger patients with type 1 SMA. [88] The trials reported that the most common side effects, occurring in 5% or more of the participants, were elevated liver enzymes and vomiting. Ongoing efforts to gather real-world data continue to monitor its performance and safety profile.

The biodistribution of onasemnogene abeparvovecxioi was evaluated in two patients who died after an infusion dose of 1.1 × 1014 vg/kg, showing that the highest level of vector DNA was found in the liver. Vector DNA was also detected in the spleen, heart, pancreas, inguinal lymph nodes, skeletal muscle, peripheral nerves, kidneys, lungs, intestines, gonads, spinal cord, brain, and thymus. SMN protein is ubiquitously expressed in spinal motor neurons, brain neurons, and glial cells, as well as the heart, liver, skeletal muscle, and other tissues. [89]

Precautions: ① Adverse reactions. Onasemnogene abeparvovecxioi can elevate liver enzyme levels, leading to severe liver injury or failure. To mitigate this, patients are given oral corticosteroids before and after the onasemnogene abeparvovecxioi infusion and undergo liver function monitoring. Onasemnogene abeparvovecxioi may reduce platelet and red blood cell counts, potentially causing acute kidney injuries and increasing the risk of bruising or bleeding, alerting of the possibility of thrombotic microangiopathy (TMA), which may occur approximately 1 week after the infusion. Onasemnogene abeparvovecxioi may increase cardiac troponin I levels, with cardiac toxicity found in animal experiments. ② Vaccination schedule. It's advisable to adjust the vaccination schedule to accommodate the corticosteroid treatment. Respiratory syncytial virus infection should be prevented. ③ Concurrent infection. Serious complications can arise after the infusion, such as coughing, wheezing, sneezing, a runny nose, sore throat, or fever. ④ Drugs. Onasemnogene abeparvovecxioi remains stable for 14 days when stored between 2° C to 8° C. Before infusion, inspecting the vial for any respirable particulate matter or discoloration is important. If these conditions are observed, the vial should not be used. [86]

6.12.4. Other drugs

6.12.4.1. Fast skeletal muscle troponin activators (FSTAs)

FSTAs slow down the release of calcium from the regulatory troponin complex of skeletal muscle fibers, thereby making the sarcomere sensitive to calcium and increasing skeletal muscle contractility. They are expected to become a new treatment option for diseases related to skeletal muscle weakness and fatigue.

Reldesemtiv is a new generation of FSTAs developed by Cytokinetics and Astellas. In 2017, the US FDA granted a designation for reldesemtiv orphan drugs for the potential treatment of SMA.

Reldesemtiv is an oral small-molecule drug. Phase I clinical trial data showed [90] that reldesemtiv was well tolerated when administered to healthy subjects at 30-4000 mg once a day and 300 mg or 500 mg twice daily. The main adverse reactions included headache, dizziness, nausea, vomiting, and visual fatigue. All adverse reactions were mild or moderate. The half-life is 8 to 12 hours, and there are no significant differences in pharmacokinetic parameters between young and elderly subjects. In a pharmacodynamic study [90], the frequency response of dorsiflexion of the foot was evaluated after stimulating the deep peroneal nerve to activate the tibialis anterior muscle. The response of the tibialis anterior muscle on reldesemtiv correlated with the dose and blood concentration and was frequency-dependent with peak force amplification of 60% at 10 Hz. Compared with tirasemtiv, reldesemtiv can produce more than 2 times the peak force at a lower blood concentration under the same stimulation, indicating that reldesemtiv is more effective in improving muscle function than tirasemtiv.

In a double-blind, placebo-controlled phase II clinical trial [91], the efficacy of oral reldesemtiv in patients with SMA was evaluated. Patients with type II, III, or IV SMA older than 12 years were randomized into two dose groups (150 and 450 mg orally, twice a day). The study showed that the patients' 6-min walk test was improved, and the degree of improvement was dose-related. In the 450 mg group, compared with placebo, the patients' 6-min walk distance increased by 35.63m (4 weeks, P=0.0037) and 24.89m (8 weeks, P=0.0584). In addition, the patients' maximum respiratory pressure also increased. Both doses of reldesemtiv were well tolerated, indicating that reldesemtiv can provide clinical benefits and support for the SMA patient population.

6.12.4.2. Myostatin inhibitors

Apitegromab (SRK-015) is a fully human monoclonal antibody under study developed by Scholar Rock. Apitegromab can specifically bind to the precursors of myostatin (including pro myostatin and latent myostatin), inhibiting myostatin's activation and improving the motor function of SMA patients. It has been granted the designation of orphan drug and pediatric rare disease designation for treating SMA by the US FDA. Myostatin is a transforming growth factor β superfamily member, a critical negative regulator of skeletal muscle, and a therapeutic target for muscular dystrophy. In vitro studies and animal experiments have shown [92-94] that apitegromab directly inhibits myostatin activation in target tissues, significantly increasing muscle strength and function.

The Phase I clinical study of apitegromab was conducted in two parts. [95] Part A was a single ascending dose phase, and Part B was a multiple ascending dose phase. The results showed that intravenous apitegromab was safe and well tolerated. No dose-limiting toxicity was found at the highest evaluated dose of 30 mg/kg. The single ascending dose study found that the mean serum concentration, Cmax, and AUC values of apitegromab were dose-dependent, and the concentration-time curve showed an obvious biphasic elimination pattern. The half-life of the drug was 24-31 days. The drug clearance rate was low (6.05-7.69 mL/h), and the mean distribution volume was dose-independent, ranging from 5.40 to 6.85 L, indicating the distribution in the vascular and extravascular spaces. The multiple ascending dose study revealed that after apitegromab was given, Cmax increased in a dose-related manner. Both single and multiple ascending dose studies showed that serum latent myostatin was dose-dependent and continued to grow, indicating strong target engagement and no anti-drug antibodies were found in the trial. Apitegromab is safe, with no difference from basal lines of the subjects' vital signs, electrocardiograms, and laboratory data. The main adverse reactions included ligament sprain, viral infection, gingival abscess, and upper respiratory tract infection.

The Phase II TOPAZ clinical trial was conducted to assess the efficacy and safety of apitegromab in managing types 2 and 3 SMA. [96] This 52-week study enrolled 58 non-ambulatory patients across these SMA types. Participants received an intravenous dose of apitegromab every 4 weeks, and the study was organized into three distinct cohorts. Cohort 1 focused on patients aged 5 to 21 with type 2 SMA who could walk independently. This group explored the effectiveness of 20 mg/kg apitegromab as a monotherapy and in combination with nusinersen. Cohort 2 included type 2 and 3 SMA patients aged 5 to 21 years who were not able to walk independently and had initiated nusinersen treatment at or after the age of 5. The efficacy of combining 20 mg/kg apitegromab with nusinersen was evaluated for this group. Cohort 3 comprised type 3 SMA patients aged 2 years and older who began nusinersen treatment before the age of 5.

This cohort compared the outcomes of high-dose (20 mg/kg) apitegromab combined with nusinersen against a lower-dose (2 mg/kg) regimen. Key findings at the 6-month included motor function improvements across all three treatment groups. Notably, 67% of participants saw at least a 1-point increase in their HFMS scores, while 35% experienced a ≥ 3-point surge. In Cohort 3, those in the high-dose group averaged a 5.6-point rise in their HFMS scores, surpassing the 2.4-point average increase of the low-dose group, with a 7.1-point surge by 12 months. Approximately one-third of the low and high-dose groups achieved a ≥ 10-point enhancement in motor function at 12 months, with around 60% demonstrating a ≥ 5-point improvement. Further results are anticipated.

Apitegromab is now advancing into a Phase III clinical trial, signifying its potential as the inaugural monoclonal antibody treatment targeting muscle function for SMA.

6.12.4.3. Salbutamol

Salbutamol has been used in clinical practice in some countries to treat SMA patients and has achieved good clinical results. Salbutamol, a β2-adrenoceptor agonist, can significantly increase full-length SMN2 transcript levels in peripheral blood cells of SMA patients. [97-98] These data may support salbutamol as a candidate drug for the treatment of SMA. In 2001, an open-label study evaluated the efficacy of salbutamol. [99] This study included 13 children with SMA types 2 to 3 who had a deletion of exon 7 of the SMN1 gene. The results showed that salbutamol could increase the muscle strength of the children. After 3 months of using salbutamol, the children's MRC score and FVC improved. Subsequently, the results of two other studies also confirmed that salbutamol can improve motor function in children and adults with type 2 SMA. [100-101] In addition, a clinical trial showed [102] that the maximum inspiratory pressure, nasal inspiratory pressure, and slow vital capacity of the salbutamol group were significantly better than those of the placebo control group. These preliminary studies suggest that salbutamol may be beneficial and well tolerated in SMA patients across different disease subtypes and at various ages, with no serious adverse effects noted. Future prospective randomized, double-blinded, placebo-controlled trials are needed to confirm these preliminary findings.

7. TRANSITION OF PEDIATRIC PATIENTS FROM CHILDREN'S HOSPITALS TO ADULT HOSPITALS

The comprehension of SMA has significantly deepened over the years, with the enhancement of multidisciplinary management and the adoption of DMTs. This has enabled early diagnosis and treatment of SMA, considerably improving the prognosis for many affected children. As these children age into adolescence and adulthood, transitioning from pediatric to adult healthcare services becomes critical because pediatric specialty hospitals or general pediatric departments may not be equipped to continue managing older patients with SMA. How to address this issue has become another practical problem in the management of SMA.

In 2019, the National Health Commission of China took a significant step by selecting 324 hospitals known for their capabilities in diagnosing and treating rare diseases to create a national network. This initiative aimed to centralize the management of rare diseases and facilitate two-way referrals, enhancing care for patients with rare conditions like SMA. By June 2022, the National Rare Disease Registry System in China had registered over 60,000 cases of 172 rare diseases, showcasing the country's commitment to improving the management of rare conditions.

Based on the distribution of specialties and department structures of domestic third-class hospitals, establishing an integrated electronic medical record (EMR) system has been recommended. The pediatrician can fill in a unified patient case registration form on the unified rare disease registration platform at the initial diagnosis of SMA and then regularly fill in the patient's management condition during follow-up. When the child needs to be referred to a general hospital or other provincial and municipal hospitals due to age or other family reasons, the neurologist of the receiving hospital can access the patient's previous medical records and continue to fill in the patient's subsequent electronic medical records. This relay of clinical management will form a complete SMA electronic medical record database, which will also become a valuable exploration of the Chinese SMA diagnosis and treatment team for referrals, follow-up treatment, and clinical data accumulation.

Recommendation: The transition of SMA children to adolescents and adults is a new issue worldwide. China's establishment of a unified electronic

medical record for SMA patients to achieve management linkage is beneficial (Grade III recommendation, Level D evidence).

8. SUMMARY

With the advancement of genetic diagnosis technology, the popularization of multidisciplinary management models, and the application of DMTs, more and more SMA patients are entering the adolescent and adult stages. The standardization of management of these adolescent and adult patients has become a common problem faced by the global medical community in recent years. After the efforts of various specialties, this version of the diagnosis and treatment guidelines has been released. This was only the first step to standardized diagnosis and treatment of adolescent and adult SMA. Many issues must be continuously improved and optimized in future practice and further summarized and revised based on evidence-based medicine. We hope this guideline can contribute to diagnosing and treating SMA in China.

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.

Experts involved in the development of this guideline

Neurology: Peking Union Medical College Hospital (Liying Cui, Yi Dai, Xunzhe Yang); Qilu Hospital of Shandong University (Yuying Zhao); The Second Hospital of Hebei Medical University (Yaling Liu); The First Affiliated Hospital of Harbin Medical University (Honglin Feng); The First Hospital of Jilin University (Xuefan Yu); West China Hospital, Sichuan University (Huifang Shang); The First Affiliated Hospital of Chongqing Medical University (Fei Xiao); The First People's Hospital of Yunnan Province (Qiang Meng); Tongji Hospital (Min Zhang); Huashan Hospital Affiliated to Fudan University (Wenhua Zhu); The Second Affiliated Hospital of Zhejiang University School of Medicine (Zhiying Wu); The First Affiliated Hospital of Nanchang University (Daojun Hong); Jiangsu Provincial People's Hospital (Qi Niu); The First Affiliated Hospital of Sun Yat-sen University (Xiaoli Yao); The First Affiliated Hospital of Fujian Medical University (Wanjin Chen); Xiangya Hospital of Central South University (Lu Shen); The First Affiliated Hospital of Xi'an Jiaotong University (Jingxia Dang); The First Hospital of Shanxi Medical University (Junhong Guo); Tianjin Third Central Hospital (Zhecheng Zhang); Peking University Shenzhen Hospital (Juanjuan Chen); Nanfang Hospital of Southern Medical University (Haishan Jiang); Chinese PLA General Hospital (Chuanqiang Pu); Xuanwu Hospital, Capital Medical University (Yuwei Da); Beijing Tiantan Hospital, Capital Medical University (Zaiqiang Zhang) ; Peking University First Hospital (Zhaoxia Wang); The First Affiliated Hospital of Soochow University (Liqiang Yu); Henan Provincial People's Hospital (Mingming Ma); The First Affiliated Hospital of Zhengzhou University (Jingtao Wang).

Radiology: Peking Union Medical College Hospital (Feng Feng, Fengdan Wang, Lan Song, Hui You); Qilu Hospital of Shandong University (Xiaofeng Ma); The Second Hospital of Hebei Medical University (Zuojun Geng); The First Affiliated Hospital of Harbin Medical University (Changjun Wu); The First Hospital of Jilin University (Hongwei Zhou); West China Hospital, Sichuan University (Lei Li); The First People's Hospital of Yunnan Province (Gang Wang); Tongji Hospital (Jing Zhang); The Second Affiliated Hospital of Zhejiang University School of Medicine (Yanbin Tan); The First Affiliated Hospital of Nanchang University (Dechang Peng); Jiangsu Provincial People's Hospital (Shanshan Lu); The First Affiliated Hospital of Sun Yat-sen University (Zhiyun Yang); The First Affiliated Hospital of Fujian Medical University: (Dejun She); Xiangya Hospital of Central South University (Xiaoping Yi); The First Affiliated Hospital of Xi'an Jiaotong University (Qiuli Zhang); The First Affiliated Hospital of Shanxi Medical University (Lei Zhang); The First Affiliated Hospital of Soochow University (Ximing Wang).

Psychiatry: Peking Union Medical College Hospital (Xia Hong, Yinan Jiang); Qilu Hospital of Shandong University (Xueqin Mao); The Second Hospital of Hebei Medical University (Lina Yan); West China Hospital, Sichuan University: (Jiajun Xu); Tongji Hospital (Yuan Yang); The Second Affiliated Hospital of Zhejiang University School of Medicine (Bin Gao); Jiangsu Provincial People's Hospital (Yong Li); The First Affiliated Hospital of Sun Yat-sen University (Liqian Cui); The First Affiliated Hospital of Fujian Medical University (Zisen Zhuang); Xiangya Hospital of Central South University (Qian Xiao); The First Affiliated Hospital of Xi'an Jiaotong University (Xiaobo Yang); The First Affiliated Hospital of Shanxi Medical University (Zhifen Liu); Nanfang Hospital of Southern Medical University (Zhihong Lü).

Rehabilitation Medicine: Peking Union Medical College Hospital (Guangyu Zhang); Qilu Hospital of Shandong University (Yonghui Wang); The Second Hospital of Hebei Medical University (Hongling Li); The First Affiliated Hospital of Harbin Medical University (Chunlei Li) The First Hospital of Jilin University (Zhenlan Li); West China Hospital, Sichuan University (Cheng Li); The First People's Hospital of Yunnan Province (Xuesong Gai); Tongji Hospital (Min Lu); Huashan Hospital Affiliated to Fudan University (Yulian Zhu); The Second Affiliated Hospital of Zhejiang University School of Medicine (Bing Xiong); Jiangsu Provincial People's Hospital (Guangxu Xu); The First Affiliated Hospital of Sun Yat-sen University (Peng Liu); The First Affiliated Hospital of Fujian Medical University (Jun Ni); Xiangya Hospital of Central South University (Suixin Liu); Nanfang Hospital of Southern Medical University (Ruixue Yin); The First Affiliated Hospital of Soochow University (Liying Han).

Orthopedics: Peking Union Medical College Hospital (Jianxiong Shen); Qilu Hospital of Shandong University (Xinyu Liu); The Second Hospital of Hebei Medical University (Wei Ma); West China Hospital, Sichuan University (Xin Rong); The First People's Hospital of Yunnan Province (Sheng Lu); Tongji Hospital (Huang Fang); Huashan Hospital Affiliated to Fudan University (Hongli Wang); The Second Affiliated Hospital of Zhejiang University School of Medicine (Zhiwei Wang); The First Affiliated Hospital of Nanchang University (Bin Zhang); Jiangsu Provincial People's Hospital (Jin Fan); The First Affiliated Hospital of Sun Yat-sen University (Peiqiang Su); The First Affiliated Hospital of Fujian Medical University (Zida Huang); Xiangya Hospital of Central South University (Qile Gao); The First Affiliated Hospital of Shanxi Medical University (Yanrong Liu); Nanfang Hospital of Southern Medical University (Zhongmin Zhang).

Respiratory: Peking Union Medical College Hospital (Yi Xiao, Jinmei Luo); Qilu Hospital of Shandong University (Yuwen Xue); The Second Hospital of Hebei Medical University (Yadong Yuan); The First Affiliated Hospital of Harbin Medical University (Shihuan Yu); The First Hospital of Jilin University (Yue Gu); West China Hospital, Sichuan University (Jiajia Dong); The First People's Hospital of Yunnan Province (Yunhui Zhang); Tongji Hospital (Shuyun Xu); The Second Affiliated Hospital of Zhejiang University School of Medicine (Pingli Wang); Jiangsu Provincial People's Hospital (Xin Yao); The First Affiliated Hospital of Sun Yat-sen University (Jianqiang Huang); The First Affiliated Hospital of Fujian Medical University (Jianchai Huang); Xiangya Hospital of Central South University (Juntao Feng); The First Affiliated Hospital of Xi'an Jiaotong University (Bai Zhu); The First Hospital of Shanxi Medical University (Yiwei Shi); The First Affiliated Hospital of Suzhou University (Tao Chen); Weifang No.2 People's Hospital (Lina Chen).

Endocrinology: Peking Union Medical College Hospital (Mei Li); Qilu Hospital of Shandong University (Xiaoli Zhang); The Second Hospital of Hebei Medical University (Songyun Zhang); The First Affiliated Hospital of Harbin Medical University (Hongyu Kuang); Tongji Hospital (Yan Yang); Jiangsu Provincial People's Hospital (Dai Cui); The First Affiliated Hospital of Sun Yat-sen University (Hai Li); The First Affiliated Hospital of Fujian Medical University (Linjing Huang); Xiangya Hospital of Central South University (Min Wang); The First Hospital of Shanxi Medical University (Yunfeng Liu); The First Affiliated Hospital of Soochow University (Chao Chen).

Anesthesiology: Peking Union Medical College Hospital (Xulei Cui, Weiyun Chen); Qilu Hospital of Shandong University (Dongliang Li); The Second Hospital of Hebei Medical University (Rongtian Kang); The First Affiliated Hospital of Harbin Medical University (Lei Guo); The First Hospital of Jilin University (Xuesong Song, Zhiwen Li); West China Hospital, Sichuan University (Yusi Hua, Hong Xiao); The First Affiliated Hospital of Chongqing Medical University (Ping Li); The

First People's Hospital of Yunnan Province (Huajin Jin); Tongji Hospital (Xijian Ke); Huashan Hospital Affiliated to Fudan University (Xuehua Che); The Second Affiliated Hospital of Zhejiang University School of Medicine (Fengjiang Zhang); The First Affiliated Hospital of Nanchang University (Xian Ma); Jiangsu Provincial People's Hospital (Yinbing Pan); The First Affiliated Hospital of Sun Yat-sen University (Ying Xiao); The First Affiliated Hospital of Fujian Medical University (Qing Huang); Xiangya Hospital of Central South University (E Wang); The First Affiliated Hospital of Xi'an Jiaotong University (Fei Yan); The First Hospital of Shanxi Medical University (Wenjie Zhang, Ziye Jing); Nanfang Hospital of Southern Medical University (Weifeng Liu); The First Affiliated Hospital of Soochow University (Xiaohong Jin).

Dentistry: Peking Union Medical College Hospital (Chunlan Guo); Qilu Hospital of Shandong University (Chunling Jia); The Second Hospital of Hebei Medical University (Lihua Shan); The First Affiliated Hospital of Harbin Medical University (Su Ma); West China Hospital, Sichuan University Dental Hospital (Bo Yang); The Affiliated Stomatology Hospital of Nanjing Medical University (Zheng Zhu); The First Affiliated Hospital of Sun Yat-sen University (Anxun Wang); The First Affiliated Hospital of Fujian Medical University (Yun Wu); The First Affiliated Hospital of Xi'an Jiaotong University (Long Zhang); The First Hospital of Shanxi Medical University (Xiaojun Sun); The First Affiliated Hospital of Soochow University (Lifang Zhu).

Gastroenterology: Peking Union Medical College Hospital (Xiaoqing Li); Qilu Hospital of Shandong University (Tao Zhou); The Second Hospital of Hebei Medical University (Li Liu); The First Hospital of Jilin University (Yuqin Li); Tongji Hospital (Li Cao); Jiangsu Provincial People's Hospital (Hong Zhu); The First Affiliated Hospital of Sun Yat-sen University (Baili Chen); Xiangya Hospital of Central South University (Guanghui Lian); The First Affiliated Hospital of Xi'an Jiaotong University (Li Ren); The First Hospital of Shanxi Medical University (Junjie Ren).

Nutrition: Peking Union Medical College Hospital (Wei Chen, Rongrong Li); Qilu Hospital of Shandong University (Xiaoli Huang); The Second Hospital of Hebei Medical University (Yan Wang); Tongji Hospital (Ting Ye); Huashan Hospital Affiliated to Fudan University (Jiaying Zhang); The Second Affiliated Hospital of Zhejiang University School of Medicine (Fang He); Jiangsu Provincial People's Hospital (Hemei Bu); The First Affiliated Hospital of Sun Yat-sen University (Yi Sui); The First Affiliated Hospital of Fujian Medical University (Bei Lin); Xiangya Hospital of Central South University (Juying Liu); The First Hospital of Shanxi Medical University (Ping Sun); The First Affiliated Hospital of Soochow University (Jing Yang).

Pharmacy: Peking Union Medical College Hospital (Bo Zhang, Jinghan Qu, Tingting Xu); Qilu Hospital of Shandong University (Rui Zhang); The Second Hospital of Hebei Medical University (Zhiqing Zhang); The First People's Hospital of Yunnan Province (Yanlin Ma); Tongji Hospital (Juan Li); The Second Affiliated Hospital of Zhejiang University School of Medicine (Donghang Xu); Jiangsu Provincial People's Hospital (Yongqing Wang); The First Affiliated Hospital of Sun Yat-sen University (Pan Chen); The First Affiliated Hospital of Fujian Medical University (Wei Wu); Xiangya Hospital of Central South University (Shao Liu); The First Hospital of Shanxi Medical University (Yueping Jin); Nanfang Hospital of Southern Medical University (Chunping Gu).

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