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REVIEW ARTICLE

REHABILITATION APPROACH TO SPINAL MUSCULAR ATROPHY

Raquel Lage Araújo[1], Bruna Catarina Ferreira de Melo[2], Ana Margarida Sousa Ribeiro[1], Maria de Lurdes Lopes Palhau Madeira[1], Rosa Maria Almeida Abreu Amorim[1].

[1]Department of Physical Medicine and Rehabilitation, Centro Hospitalar Universitário do Porto - Porto, Portugal
[2]Department of Physical Medicine and Rehabilitation, Hospital Senhora da Oliveira - Guimarães, Portugal.

ABSTRACT

Spinal muscular atrophy is a genetically inherited severe neuromuscular disease due to degeneration of alpha motor neurons in spinal cord and brainstem. SMA is divided into clinical subtypes using the age of onset and achieved development milestones. It is characterized by tetraparesis with a proximal pattern, affecting predominately the lower limbs and hypotonia. Recently, the paradigm of SMA has changed after approval of the first disease-modifying therapy. The pharmacological treatment will have a better outcome if accompanied by a structured rehabilitation care program. In this review, we discuss the management of feeding and swallowing disorders, musculoskeletal deformities, sleep disorders and pulmonary impairment. We will review the therapeutic approaches, including positioning, stretching and exercise, as well as assistive devices prescription.

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Introduction

Spinal muscular atrophy (SMA) is a genetically inherited neuromuscular disease. It is characterized by degeneration of alpha motor neurons in the anterior horn of the spinal cord and brainstem. The result is a progressive weakness of the appendicular, axial, bulbar and respiratory muscles. Cognitive development is not affected, the extraocular muscles are spared, and sensitive examination is normal.[1] A prevalence of approximately 1-2 per 100,000 people and incidence around 1 per 10,000 live births have been estimated.[2]

Five subtypes are described based on symptom onset and maximum motor function achievement. They constitute a continuum from type 0, the most severe form, with the majority of deaths occurring in utero, to the type 4 with adolescent or adult onset, a normal child development and life expectancy.[3]

SMA type 1 is characterized by an onset before six months and an inability to sit unsupported. The onset of SMA type 2 is typically before 18 months, sitting is achieved without support but children are unable to stand or walk independently. SMA type 3 is distinguished by symptom onset after 18 months, generally children can walk independently however their motor function can vary.

The therapeutic approach has been historically purely supportive. However, the emergence of innovative therapies has changed the paradigm in SMA, particularly the most severe form.[4] Physicians are gradually changing their perspectives towards more active management of the disease which should be multidisciplinary and include rehabilitation. The aim of this study was to propose an update on rehabilitation care for this disease.

Address for Correspondance: Raquel Lage Araújo, Largo do Prof. Abel Salazar, Porto, 4099-001, Portugal.
Email: raquel_araujo731@hotmail.com

Development

2.1 Spinal muscular atrophy type 0 (SMA0):

SMA type 0 has an in utero onset. During pregnancy, decrease of fetal movement, intrauterine growth retardation, skeletal deformities and pulmonary hypoplasia can be present. The majority of deaths occur in utero while, if pregnancy concludes, most newborns die of respiratory failure in their first month. No motor milestones are achieved.[5]

2.2 Spinal muscular atrophy type 1 (SMA1):

SMA type 1 is the commonest and most severe form. This type occurs during the first 6 months and is described by global hypotonia, areflexia and tetraparesis with a proximal pattern, affecting predominately the lower limbs.[6] Typically, these children are unable to sit without support and have a poor head control. In the supine position, the lower extremities may be abducted and externally rotated in a "frog-leg" position. The upper extremities tend to be adducted and externally rotated at the shoulders with semi-flexed elbows. Volitional movements of fingers and wrists can persist even when the shoulders and elbows cannot be flexed against gravity.[1] Weakness of intercostal and abdominal muscles with a relative spared diaphragm is common, which results in paradoxical abdominal breathing, creating a bell-shaped thoracic deformity. Sialorrhea, weak sucking, weak cry, labored breathing during feeding and cough impairment are noted by history. Frequent aspiration of food or secretions and poor airway clearance are the reason for recurrent pulmonary infections in these patients.[6]

Three subtypes have been distinguished for SMA type 1:

1A: onset typically during the first month, severe motor impairment is present including no head control;

1B: onset typically between 1 and 3 months, it is characterized by the absence of head control;

1C: onset is typically between 3 and 6 months, children can achieve head control and may be able to roll over from prone position to a supine position.

2.3 Spinal muscular atrophy type 2:

SMA type 2 is often named an intermediate SMA to indicate the disease severity. Symptom's onset is usually between 6 and 18 months of age. Motor development is frequently normal until the age of 6-8 months, the ability to sit without support is attained but may be delayed, however independent walking is not achieved.[7] Areflexia, global hypotonia and proximally symmetrical muscle weakness affecting predominantly the lower limbs, are common features. Fasciculations may be present as a sign of denervation. Progressive kyphoscoliosis and neuromuscular restrictive lung disease, due to intercostal muscle weakness and spino-pelvic complex disorders, are common in the first decade. Flexor muscle contractures are common in these patients. Hypotonic dislocations of the hip are probable causes of pain in these patients.[1]

Two subtypes have been distinguished for SMA type 2:

2A: children are able to sit without support but are unable to stand or walk even with assistance;

2B: these children, in addition to sitting without support, may stand and take a few steps with assistance.

2.4 Spinal muscular atrophy type 3:

The onset of SMA type 3 occurs usually after the children have acquired independent walk, between 18 months and adulthood. Motor milestones may be delayed in infancy. A proximal weakness pattern further affecting the lower than the upper limbs is also common.[8] There are characteristic changes in gait due to this type of weakness: a lumbar lordosis and an anterior pelvic tilt is often found due to hip extensor weakness, a pelvic drop and a lateral trunk lean in stance phase due to hip abductor weakness, while the foot contact may also be changed from a heel contact to a forefoot or toe contact due to quadriceps femoris weakness. Gower sign may be present therefore climbing stairs and jumping may be difficult for these patients. Due to disease progression, patients may lose the ability to walk independently, and in these, muscles contractures tend to appear. Scoliosis is far less frequent than in the other types and respiratory disease is not common.[1]

Two subtypes have been distinguished for SMA type 3:

3A: onset typically between 18 months to 3 years and the majority of patients lose walk capacity in the following 20 years;

3B: onset typically is after 3 years of age and most patients remain ambulant by the age of 40.

2.5 Spinal muscular atrophy type 4:

Literature defines its onset after the age of 18 years, and it is the mildest type. All motor milestones are achieved, and patients maintain the ability to walk at least to the fifth decade. Lack of respiratory and bulbar involvement is a rule, however tongue fasciculation and hand tremor may be present.[5]

3. Diagnosis

The diagnosis of SMA should be suspected in children with progressive muscle weakness, which typically has a proximal pattern and affects mainly the lower limbs; hypotonia, weak cry or cough and respiratory difficulties may be present.[9] Additional clinical clues are described above for the different types of SMA.

The diagnosis is established by identification of the biallelic pathogenic variant of SMN1 on molecular genetic testing. The gene known to be implicated in SMA is called SMN1 (survival motor neuron 1) which is located on chromosome 5q. SMN1 gene encodes a protein that maintains motor neuron survival in the spinal cord.[10] SMN2 gene, which is located in the same region as SMN1, encodes a similar protein but in much smaller quantities and in a less stable form. In SMA patients, only SMN2 gene is partially functional and therefore these patients produce low levels of the stable SMN protein which results in degeneration of alpha motor neurons in the anterior horn of the spinal cord and brainstem.[11]

An early diagnosis is important since in SMA type 1, 90% of alpha motor neurons, are lost by six months of age. As such, some authors advocate for prenatal diagnosis.[10]

In atypical presentation or in later onsets, a wider investigation should be done depending on clinical findings, which should include a muscle biopsy and a neurophysiological study.

4. Treatment

4.1 Pharmacologic treatment

The paradigm of SMA has changed after approval of the first disease-modifying therapy.[12] These genetic therapies work by different mechanisms to restore, at least in part, the SMN protein that is crucial for the development of motor neurons. Until now, there are three molecules available, approved by EMA (European Medicines Agency).

Nusinersen is an antisense oligonucleotide that works by correcting the SMN2 gene splicing, increasing the production of a normal, full-length survival motor neuron protein. Intrathecal administrations, initiated with four loading doses and a subsequent maintenance dose, are given every four months as long as the patient benefits from it. Nusinersen is approved for SMA in pediatric and adult patients.[13]

Risdiplam is a molecule for SMN 2 splicing modifier that boosts the ability of SMN2 to produce a more functional SMN protein. Risdiplam is taken orally once per day and is approved for the treatment of SMA in patients older than 2 months of age.[14]

Zolgensma is an adeno-associated viral vector containing complementary DNA encoding the normal human survival motor neuron protein. This gene therapy involves gene replacement of mutated SMN1 gene for a new working copy. A one-time intravenous administration of Zolgensma results in expression of the SMN protein in alpha motor neurons. This drug is

approved for the treatment of children with less than two years of age with bi-allelic mutations in the SMN1 gene.[15]

4.2 Rehabilitation management

A multidisciplinary approach to evaluation and management includes a strong partnership between physicians (pediatrics, neurology, physical medicine and rehabilitation), therapists (physical therapy, occupation therapy and speech therapy), patients, caregivers and families.[2,16] This will allow to monitor the various aspects that are known to be part of disease progression and when possible, provide anticipatory care.

In Physical Medicine and Rehabilitation, the physical assessment is focused on the functional impairment, which means the ability to cope with activities of daily life. In patients with SMA, the assessment of motor function becomes highly relevant. Nonetheless, a loss of strength does not translate into the same loss of function or autonomy. This assessment can be complemented by a set of scales: functional rating scale, timed test and motor function assessment scale.

C. Vuillerot et al. describe a set of scales that can be used in SMA patients to describe motor function.[17] The functional rating scale describe the stage of motor function. The timed tests describe the time required to do a particular activity, for example the time needed to go from one position to another. The motor function assessment scale evaluates the performance of a series of activities, which can be binary or in a detailed rating approach. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders is a specific scale designed to assess motor skills in children with hypotonia and muscle weakness from birth until 30 months. It contains 16 items rated on a 5-points scale from 0 to 4.[18]

The Revised Upper Limb Module is a specific scale for SMA patients designed to assess the functional capabilities of upper limb function, from 30 months to adulthood. It contains 20 items rated on a 3-points scale from 0 to 2.[19]

The Hammersmith Functional Motor Scale Expanded is another specific scale for SMA patients, intended to assess the overall motor functional capacities, from 30 months to adulthood. It contains 33 items rated on a 3-point scale from 0 to 2.[20]

There are multiple tools to evaluate the functional impairment. It is important to obtain training in the use of these scales to know how to rate each item. The choice of the scale should take into account the type of SMA, the age of the patient, the expected changes and the items evaluated on each scale.

4.2.1 Rehabilitation strategies

We will now describe the rehabilitation strategies for individuals with SMA, including management of feeding and swallowing disorders, musculoskeletal deformities, sleep disorders and pulmonary impairment. We will review the therapeutic approaches, including positioning, stretching and exercising as well as assistive devices prescription.

Recommendations are now based on the current functional status of the patient: non-sitter, sitter and walker.[2,16] The rehabilitation goals for non-sitters include optimization of function, tolerance to various positions and minimization of impairment. The main objectives of rehabilitation in sitters are to prevent contractures, maintain function and mobility. The main objectives for rehabilitation in walkers are to promote function, improve mobility, balance and endurance.[21,22,23] In all patients, determining appropriate mobility aids, adaptive equipment, assistive technology and environmental adaptations will allow the achievement of the highest independence level.

Feeding and swallowing care:

Feeding and swallowing difficulties occur because of progressive weakness of bulbar and esophageal muscles.[22] Dysphagia is common in non-sitters and sitters but is rarely a concern in walkers.[24] Physicians should be aware of the signs suggestive of swallowing dysfunctions, as weak suck, difficulty in handling with oral secretions, fatigue, humid voice, respiratory infections, increased mealtimes and sialorrhea.[25] The presence of recurrent pneumonias is also a potential indicator of aspiration.[23]

In the preoral phase, the difficulties are limited mouth opening and getting food to the mouth for self-feeding. In the oral phase, the difficulties include weak bite and increased fatigue of masticatory muscles. Poor coordination of the swallow can lead to penetration and aspiration. Poor head control may also be a factor in the development of feeding impairment.[23]

A feeding history with mealtime observation is desirable. Examination of oral structures that influence feeding efficiency and evaluation of head control are essential.[23] Longitudinal measures of weight and length are recommended to monitor growth of those patients.[2]

A video swallow study (VSS) should be carried out after initial assessment if there are doubts about swallow safety. A VSS study is not simply a diagnostic test of aspiration but is an opportunity to evaluate therapeutic strategies, such as adapted food texture and positioning.[23] Non-sitters, close monitorization is recommend to detect early signs of feeding difficulties. For sitters, evaluation is recommended after diagnosis and periodically, every 3-6 months for younger children and annual evaluations afterwards.[2]

Treatment should aim to reduce the risk of aspiration during swallow and optimize the efficiency of feeding and promote enjoyable mealtimes. Changing food and liquid consistency are appropriate treatment strategies. A semisolid diet can be used to compensate poor chewing and reduce the duration of mealtimes. Thickened liquids may protect against aspiration of fluids.[36]

Seating alterations and orthotic devices to promote proper positioning may improve swallow safety and efficiency.[23]

The dysphagia working group did not reach consensus about the indications for gastrostomy tube placement.[23] Some studies recommend early gastrotomy in non-sitters' patients while the infant is healthy, whereas others believe that exposing such patients to the risk of surgery is inappropriate prior to the onset of symptoms.[22,23] Gastrostomy tube feeding is the optimal method of feeding when insufficient caloric intake or unsafe oral feeding is of concern.

Whether a gastrostomy tube is placed often requires a discussion with caregivers and family.[23] Placement of a short-term nasogastric tube is recommended until long term gastrostomy tube can not be done.[23] Although there was no consensus, many experts advocate Nissen fundoplication in conjunction with gastrostomy tube placement for the treatment of gastrointestinal reflux.[26]

Pulmonary care:

Pulmonary disease is a cause of morbidity and mortality in SMA patients. The compromised respiratory muscle function results in impaired cough leading to poor clearance of lower airway secretions, hypoventilation during sleep progressing to daytime, chest wall and lung underdevelopment, as well as recurrent infections that exacerbate muscle weakness.[27]

The parameter to monitor respiratory muscle function, in cooperative patient with SMA, is forced vital capacity (FVC). The risk of pulmonary complications increases as FVC decreases.[28] The suggested frequency of evaluation is after diagnosis and every 3 to 6 months in non-sitters and sitter patients and less often in walkers.[23]

Chest physiotherapy is an important part of the management in these patients and includes techniques that promote airway clearance and improve ventilation. Manual techniques include percussion, vibration and positioning to promote postural drainage. It is particularly important to implement during respiratory disease exacerbation, perioperative periods and as prophylactic pulmonary management.[2]

Volume recruitment techniques are helpful for patients with diminished forced vital capacity, which can be performed by air stacking using a manual ventilation bag.[29] Strengthening the inspiratory muscles is equally useful outside the periods of clinical exacerbation.[30]

Airway clearance techniques should be introduced in patients based on clinical assessment of cough effectiveness or by measuring the peak cough flow.[16] Daily assisted cough is recommended for patients with more severe disease.[2] For sitters it is recommended to perform airway clearance as needed and walker patients may need airway clearance postoperatively and during respiratory disease exacerbation.[31]

Respiratory support options include noninvasive ventilation (NIV) with bilevel positive airway pressure.[32] Noninvasive ventilation in infants with spinal muscular atrophy can prevent alterations in the shape of the chest wall, increase lung growth, slow the loss of chest wall compliance, decrease the rate of infection and hospital admission.[22] Usual indications for NIV include hypoventilation or obstructive sleep apnea.[16,23] The limitations of NIV are difficulty in identifying a well-fitting interface and the complications of applying an interface for long periods of time (>16 hours/day), including skin irritation, breakdown, midface hypoplasia, gastric distention and emesis.[31]

Sleeping disorders care:

Patients with neuromuscular disease are vulnerable to sleeping disorders mostly due to hypoventilation, apnea or both. Hypoventilation is caused by a reduction in the tidal volume leading to worsening of gas exchanges. Obstructive events during sleep have also been reported in patients with SMA due to bulbar muscle weakness, predisposing to upper airway collapse. Oximetry alone is usually considered an acceptable method of screening for nocturnal hypoventilation in asymptomatic children with neuromuscular disorders. All children with abnormal overnight oximetry should undergo more detailed sleep monitoring with transcutaneous PCO2.[32] Further investigations should include blood gas analysis and chest radiograph.[23] Nocturnal hypoxemia and hypercapnia should be diagnosed at an early stage to prevent the onset of daytime symptoms as well as deleterious neurocognitive and cardiac consequences.[33]

Musculoskeletal disorders care:

Scoliosis is common in non-sitter and sitter patients. The hypotonic spinal curves and thoracic kyphosis can progress through childhood. Inspection of the spine should be done routinely in the clinical examination.[34] If scoliosis is suspected, spine radiographs should be performed in the most upright position independently attainable by the patient. Cobb angle may be used for management assessment. If the Cobb angle is less than 15-20°, vigilance is recommended, whereas if the Cobb angle is greater than 15-20°, in addition to vigilance, a brace is recommended, especially in children with significant growth remaining. To this moment, there is no consensus on the type of brace to be used.[2] The decision to surgically instrument the spine is predicated mainly on curve magnitude (Cobb angle ≥50°) and rate of progression (≥10° per year). In patients with extensive scoliosis, restrictive lung disease may be present which can also affect respiratory function.[35]

Hip instability is common in non-sitter and sitter patients. Unilateral and bilateral hip instability should be surgically managed only in patients with significant pain. However, treated hips tend to re-subluxate or dislocate.[36]

Stretching:

Modalities for stretching include active-assistive and passive techniques, the use of orthoses, splints and serial casting. Stretching techniques should be performed by physical therapists. Parents and caregivers should also be instructed in daily stretching activities. Session duration for effective stretching depends on specific patient needs, joints, and rehabilitation aims. Supported standing is important to facilitate lower extremity stretching, and promote spine and trunk posture.[2]

Positioning:

Seating systems and postural supports may include positioning with rolls, beanbags, molded pillows and wedges. Customized wheelchair is recommended. To promote mobility and transfers, the use of strollers and power wheelchairs with recline options and adapted seating systems are also advised. Cervical bracing is often used for head support. Thoraco-lumbar sacral orthoses are recommended for posture and to promote function. Upper and lower limb orthoses are used to promote function, maintain flexibility and posture.[2]

Orthoses and adaptative equipment:

In neuromuscular disorders, spinal bracing improves postural control in sitting position and supports upper limb functionality.[37] Some studies have analyzed the consequences of spinal bracing on respiratory function

in neuromuscular diseases and their results showed a statistically significant reduction of forced vital capacity in pulmonary function tests performed while wearing a brace.[38,39,40] For this reason, braces can be used, provided that they do not compromise pulmonary function. Spinal orthoses should be fabricated with an abdominal cutout to allow appropriate diaphragmatic excursion and access for gastrostomy tubes. Currently, there is no consensus on the type of brace to be used, as both rigid and soft spinal thoracolumbar orthoses may be recommended.[16]

Supported standing has been advocated in non-ambulatory children with SMA to provide an upright weight-bearing experience that models standing activities. Standing frame improves bone density, spinal alignment, muscle length, gastrointestinal and pulmonary function, and cognitive and social engagement. The Rehabilitation team must ensure that child can attain and maintain a supported standing position that protects the airway, with close supervision during standing.[41] Recently updated care standards recommend that supported standing should be considered for children with both SMA types 1 and 2, with an optimal frequency of 5 to 7 times per week.[2,16]

Adaptative equipment improves mobility, activities of daily living performance, independence, participation and quality of life. The use of dynamic arm supports facilitate limb motion against gravity and support important tasks such as eating, drinking and touching their head.[42] Studies have shown that most users seem satisfied with dynamic arm supports, with continuous use reported up to 17 hours per day however, over time, most stop using them. Experts believe that disease progression difficult the operation of dynamic arm supports.[43,44]

In non-sitters, the patient's posture should guide the choice of equipment and devices that augment overall function. Upper extremity orthoses include the use of mobile arm supports and slings that increase augment range of motion and functional abilities. Splints to preserve range of motion and prevent pain may be indicated. Playing and occupational support should include lightweight toys and assistive technology with variable controls and different activation systems.

In sitters, weight-bearing ischial orthoses, knee-ankle-foot and walking orthotics should be considered for standing or assisted ambulation with a walker, in patients with sufficient strength. When this is not possible, a standing frame or mobile stander with ankle-foot orthoses should be considered.

In all patients, equipment related to activities of daily living and assistive technology may be useful to enhance the abilities for independent work and play. Environmental controls and home modifications to allow safe accessibility and highest independence should be explored.[23]

Mobility:

Only a small fraction of patients with SMA are ambulatory throughout life.[22] Power mobility is an intervention that allows independent exploration of their surroundings. Self-initiated locomotion in children has been linked to the development of emotional skills, spatial cognition, increased independence, positive interactions with external stimuli, emergence of new capacities to cope with environmental stressors and a sense of competence.[45]

The decision to recommend wheelchair use depends on several factors, namely patient falls and fatigue. If the child is too weak to self-propel or becomes easily fatigued operating the chair, then an electric chair should be recommended.

Children with SMA are ideal candidates to introduce power mobility at an early age. Their normal intellectual ability should enable this success.[45] Children as young as 24 months can learn to drive motorized power wheelchairs with basic wheelchair skills competently.[46]

Non-sitter and sitter patients should have electric wheelchairs with custom postural support and seating systems. In walkers, lightweight manual wheelchairs or power assisted wheels are recommended when endurance is limited. Similarly, electric or power wheelchairs or scooters may also be considered to facilitate independent mobility over longer distances.[2]

Exercise:

Recently, the evidence favoring exercise in patients with lower motor neuron disease has increased substantially but there is no agreement about type, frequency and intensity of exercise.[47]

About aerobic exercise, low to moderate intensity and interval training could be a safer exercise modality in SMA patients, as it has been shown in Spinal Bulbar Muscular Atrophy.[48] Combined aerobic and strength exercise in moderate intensity was well tolerated among SMA type 3 patients participating in a single blind randomized controlled clinical. The most notable change was an increase in oxidative capacity, with no harmful impact.[49]

Regarding strength exercise, submaximal resistance training is found to be well tolerated, by SMA type 2 and 3 patients, with some strength improvements and no adverse events.[46]

However, in a recent Cochrane review, the authors conclude that it is uncertain whether combined strength and aerobic exercise is beneficial or harmful in people with SMA type 3.[50]

Non-sitter' patients can participate in aquatic exercise with proper head and neck support and constant supervision. Recommendations for sitters include aquatic therapy and general conditioning exercise with and without resistance. For walkers, balance training should also be a part of the exercise program.[2] Fatigue and muscle pain, during or after exercise is indicative of excessive exercise, and intensity and frequency should be reconsidered.[47]

Conclusion

We are currently moving towards a new era in SMA management thanks to the advent of genetic treatment. The pharmacological treatment will have better outcomes if accompanied by a structured rehabilitation care program. Rehabilitation strategies can improve motor function, performance, activities of daily life and quality of life of patients with SMA. Further studies are required to evaluate the effectiveness of these strategies.

Compliance with Ethical Standards

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