Overview of the published standards of care for SMA

A SUPPORT DOCUMENT FOR CLINICAL TRIALS

SMA EUROPE

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SMA Europe is an umbrella organisation, founded in 2006, which includes spinal muscular atrophy (SMA) patient and research organisations from across Europe.

SMA Europe campaigns to improve the quality of life of people who live with SMA, to bring effective therapies to patients in a timely and sustainable way, and to encourage optimal patient care.

SMA Europe is a non-profit umbrella organisation that consists of 23 SMA patients and research organisations from 22 countries across Europe.

AUTHORSHIP & ACKNOWLEDGEMENTS

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INTRODUCTION

The breadth and depth of the treatment landscape for spinal muscular atrophy (SMA) has expanded dramatically over the past decade, with a growing number of therapeutics with multiple targets and routes of administration being tested in clinical trials (CTs). As more of these experimental compounds move from the laboratory into clinical trials, there is an urgent need for clinical sites that are prepared to conduct clinical trials in SMA and that can take on people living with SMA from all over Europe.

Whilst this is very good news for the SMA community, a concern is that clinical trial sites in Europe might not have the capacity or may not be equipped to take on additional trials. SMA Europe, as part of its mission to bring effective therapies to patients in a timely & sustainable way, has joined Cure SMA in the US and the Industry Consortium, in taking on a series of activities to alleviate these challenges and meet the needs of trial sponsors and the SMA community.

These activities include:

1. Identifying SMA clinical trial centres in Europe:
    a. Mapping the spread of these centres across Europe
    b. Assessing their readiness to conduct CTs on SMA
    c. Assessing their capacity to undertake CTs on SMA
2. The provision of educational resources to help sites prepare for SMA Clinical trials, such as these information packs
3. The provision of training opportunities such as workshops, masterclasses and conferences.

This information pack forms part of SMA Europe's broader effort to optimise site readiness for SMA clinical trials. It is based on a document written by Cure SMA in the US, but which has been extensively adapted to fit the European situation and importantly, to reflect the patient's perspective. Its goal is to provide sites with a resource for research teams which addresses major aspects of preparing for and conducting clinical trials.

To this end, SMA Europe has written 2 booklets on the following topics:

1. Spinal Muscular Atrophy: Pathology, diagnosis, clinical presentation, therapeutic strategies & treatments
2. Standards of Care in spinal muscular atrophy

Sites are encouraged to view these packs as a guide, recognising that they are one of many resources that can be helpful and that guidance from clinical trial sponsors, institutional review boards and regulatory authorities should always take precedence when planning for, conducting and closing trials.

THE STANDARDS OF CARE

Background

Spinal muscular atrophy primarily affects voluntary muscle power, but this weakness, which becomes more severe as the disease progresses, leads to complications, of which there are many and which significantly influence everyday life. They do however respond to both approved and potential therapies.

Disease management therefore involves a combination of interventions focused on preserving those functions which are compromised due to muscular weakness and on preserving other organs and systems important for everyday living (breathing, eating, posture and others). Together these complications define the disorder experienced by an affected individual. Management of those complications is a complex process which involves multi-disciplinary teams of health care workers from different fields (medical, psychological and social).

The guidelines for the management of all complications are referred to as the Standards of Care (SoC). Until the approval of the first treatment (Spinraza™/ nusinersen), the management and treatment of SMA relied on supportive care which emphasises quality of life and comfort measures. The Standards of Care have an impact on the everyday clinical care of patients, but also on many aspects of the pathology of the disease and on clinical trials.

Complications are substantial confounders of clinical trials, reducing their statistical power to define the benefit of therapy and increasing their cost. A certain degree of supportive care is expected throughout clinical trials, in order to characterise the participants well and to optimise trial efficiency (Sumner et al. 2017). Supportive care is often listed as a trial inclusion criteria. In some instances, it is important to predefine the condition and criteria and encourage patients and caregivers to initialise supportive care at the start of the trial, especially for SMA type I, whilst respecting the participant's decision on palliative care (Finkel et al. 2017). Clinical Trial Coordinators are often asked to ensure good communication between patients and members of a care team (CURE SMA, 2018). At the Spinal Muscular Atrophy Workshop, held in 2016 by SMA Europe, TREAT NMD and the European Medicines Agency (EMA), it was emphasised that the standards of care should be embedded into clinical trials, dealing with people with SMA upon diagnosis and prior to enrolment. It is important to minimise patient variability, optimise the efficiency of trials and discern between changes attributable to the SoC and the intervention (Finkel et al. 2016).

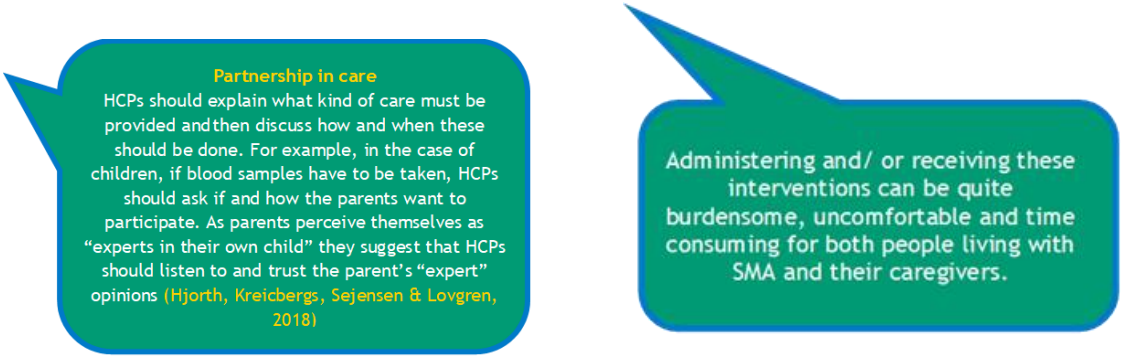
Epidemiological studies of survival in type I SMA have demonstrated that prior to the advent of supportive care opportunities, the median mortality for these infants was approximately 12 months, with 32% survival beyond 2 years (Zerres et al. 1997). The effect of specific care on survival was first identified in data available from a voluntary patient registry, comparing the cohorts of infants born before and after 1995. The survival was improved beyond 2 years of age, with increased dependence upon non-invasive ventilatory (NIV) support (Oskoui et al. 2007).

In an observational prospective study of natural history in SMA type I patients, the median age for reaching the combined endpoint of death or requiring at least 16 hours/day of ventilation support, was 13.5 months (Finkel et al. 2014). The requirement for nutritional support preceded that of ventilation by 3 months (median 8 months). More than 90% of SMA type I patients do not survive or need permanent ventilation support by the age of 2 (Finkel et al. 2016). More recently, pulmonologists have initiated prophylactic NIV ("proactive care") in order to avoid signs of respiratory failure occurring ("reactive care"). The impact of this proactive approach was investigated by Lemoine et al. Those who received proactive care in the form of increased ventilatory support, by both invasive or non-invasive ventilation, as well as feeding support by means of enteral tubes, had a better survival outcome when compared to those who received reactive care (Lemoine et al. 2012).

Advances in care (better nutrition and ventilation) often lead to improved survival, but not in motor function. Infants survive in a very weakened state. Survival depends on the age of presentation, *SMN2* copy number, avoidance of pulmonary infections and the extent of supportive care. For people with SMA types II and III, probability of survival remains comparable across the literature. Improvements in the standards of care resulted in a further improvement in survival rate, also for people with SMA type II (SMA Europe, TREAT-NMD & EMA, 2016).

An international multidisciplinary SMA working group reached consensus on the first guidelines for care standards in SMA in 2007 (Wang et al. 2007). In 2018, patients, academics and healthcare professionals (HCPs) updated these guidelines. The new recommendations address nine topics: diagnosis; rehabilitation; orthopaedic and spinal management; nutritional, swallowing and gastrointestinal management; pulmonary management and acute care issues; other organ involvement; the role of medication; ethical issues and the choice of palliative versus supportive care (Mercuri et al. 2018; Finkel et al. 2018). Care standards for SMA are guidelines meant to be revised to keep up with advances in best care. This document describes the overall optimal practice and is not mandatory for a legal standard of practice.

Although there are many advantages to the Standard of Care for SMA, there are also some concerns over their development. There are no characteristics that predict severity across the broad range of phenotypes so that a change in care can be implemented and compared to a predicted phenotype. A second issue is that SMA patient type and level and quality of care can vary greatly, not only by country or region, but even within institutions. The complexity of modern medicine makes it difficult to evaluate the relative contribution of any one advance against the other, so the change in one aspect of care could influence another aspect of the disease (like orthopaedic management on respiratory function and mobility).



The goal of current SMA care is to limit the negative impact of complications, to focus on SMA research in future investigations to improve the power of clinical trials and variability of care.

The four main areas of the Standards of Care for SMA are: respiratory management, nutritional support, orthopaedic management and physical therapy.

Respiratory management

Introduction

Spinal muscular atrophy has a great impact on the respiratory system, making respiratory care critically important. The natural history of respiratory function is one of declining functions, which corresponds to the initial severity of weakness and roughly parallels the changes in skeletal muscle power over time. In patients with neuromuscular disease, the respiratory load exceeds muscle power. Pulmonary disease is the major cause of morbidity and mortality in people with SMA, particularly for sitters and non-sitters. The degree of respiratory impact is related to the functional status of the patient. Non-sitters have lower baseline lung function compared with patients who are sitters. Walkers initially have normal, stable lung function throughout life with some exceptions (Wijngaarde et al. 2020).

Unlike other neuromuscular disorders, SMA first affects the intercostal muscles in the chest wall, with relative preservation of the diaphragm, which is the primary muscle used to breathe. In the first year of life the chest wall is soft and flexible. Because of the lack of opposition from the weak intercostal muscles and preserved function of the diaphragm, ribs descend, often causing the chest wall to collapse, allowing it to narrow and forming a "bell" shape. This is seen in severely affected children (type I) and somewhat later in SMA type II patients with milder chest wall muscle weakness. This bell shape deformity leads to diminished thoracic volume, lung underdevelopment with hypoplasia, respiratory distress, paradoxical breathing, shallow breathing and hypoventilation due to inspiration not being deep enough for carbon dioxide (CO_2)/ oxygen exchange.

Patients with SMA develop hypoventilation, first at night, then during the day, which leads to chronic respiratory failure. As expiratory function depends on intercostal effort, the dominant functional impairment is the loss of expiratory power with diminished cough pressure, leading to difficulty in airway secretion clearance. The latter contributes to repeated respiratory infections. Bulbar and gastroesophageal weakness lead to a risk of aspiration. Diminished airway clearance, inspiration weakness together with aspiration lead to atelectasis, lobar or segmental collapse and repeated episodes of pneumonia with poor oxygen exchange (Schroth et al. 2009). Contributing factors to respiratory compromise are scoliosis (which alters chest shape wall and efficiency) and interventions aimed at correcting scoliosis, like thoracic lumbar sacral orthosis (TLSO) and spinal fusion (Tangsrud et al. 2001).

Nutritional status also influences respiratory function (suboptimal nutrition increases muscle weakness and excess weight contributes to more difficulty in moving) (Poruk et al. 2012).

Novel therapies for SMA - nusinersen, gene therapy and risdiplam have modified the evolution of respiratory function in patients with SMA. Decreased need for permanent ventilation was observed with all three treatments (Paul, et al. 2020).

New disease trajectory in treated patients may challenge the interventions that are offered in the care of infants and young children with SMA (Fitzgerald, Doumit, Abel, 2018).

It is therefore important to consider the contributing factors that alter the respiratory function and take proper medical care in parallel with primary respiratory care. Recurrent infections that exacerbate muscle weakness and the integrity of the lung parenchyma (more airway secretions, greater difficulty breathing) are very well known as one of the most important triggers to the respiratory failure and progression of the disease, both in type I and type II SMA patients (Sumner et al. 2017). Respiratory manifestations may be preceded by poor feeding and growth, delayed motor milestones, frog-like posture, weak cough, paradoxical breathing, absent peripheral reflexes and tongue fasciculations.

Over the past few years, as respiratory support technologies have improved and new treatments appeared, the approach to respiratory care has shifted from palliative (reactive care) to proactive care. Proactive care is based on the introduction of interventions earlier in the disease course, ideally as soon as diagnosis has been established. With the availability of effective treatments, early assessment and intervention are key to optimal outcomes.

Assessment of pulmonary function

Non-sitter patients with SMA are unable to perform formal lung functional tests. Sitters and walkers over the age of 6 years of age are often able to complete respiratory measures. Lung function is commonly evaluated with measures such as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) through spirometry in outpatient settings. Recommendation for respiratory measurements include peak cough flow (PCF) and vital capacity (VC) (Hull, et al. 2012).

Non-sitters (every 3 months)

- Physical examination assesses respiratory status which include respiratory rate and the presence of paradoxical breathing (chest expansion in quiet breathing and collapse with larger breaths). It also includes assessment of chest wall shape (bell-shaped thoracic cavity or pectus excavatum) and clinical assessment of scoliosis and progression of spine deformity. Careful attention should be given to the medical history (previous respiratory infections and the number, impaired secretion clearance, respiratory decompensation with respiratory failure and admissions in Intensive Care Unit for intensive treatment, documented bacterial infections, radiological consequences as pulmonary atelectasis, surgical interventions) (Hull, et al. 2012).

- Assessment of hypoventilation while awake, by blood gas or transcutaneous CO_2 or end tidal CO_2, is a helpful screen for hypoventilation. Elevated CO_2 levels while awake suggests hypoventilation during sleep and should be further evaluated with sleep study or polysomnography (Hull, et al. 2012).

- Sleep studies are used to identify patients with nocturnal hypoventilation (hypercapnia with hypoxemia during sleep) and whether they may require ventilation during sleep. Oxycapnography during a sleep study is performed using pulse oximetry for transcutaneous oxygen measurements and end tidal or transcutaneous for CO_2 measurements. Polysomnography is a more complex assessment of sleep and monitors sleep state, chest wall movement, movement of extremities, and snoring in addition to monitoring oxygen and CO2 levels. Polysomnography is recommended when more complex sleep disordered breathing is suspected. Obstructive sleep apnea should be referred for evaluation of adenotonsillar hypertrophy.

- Clinical assessment of gastroesophageal reflux.

Sitters (every 6 months)

- Physical examination
- Assessment of hypoventilation (oxycapnography or sleep study)
- Spirometry where possible depending on age and cooperation of the patient (Fitzgerald, Doumit, Abel,2018).
- Clinical assessment of gastroesophageal reflux

Walkers (as needed) – most of them have normal pulmonary function

- Cough effectiveness during upper respiratory infections
- Sleep study and pulmonary testing for symptoms of sleep apnoea (snoring, arousals, daytime somnolence)

Additional assessments may include swallowing evaluation (video-fluoroscopic swallow study) and feeding assessment by speech and language therapist in all non-sitters and sitters. Bulbar dysfunction can lead to aspiration and pulmonary infections.

Chest radiology can be included to identify pulmonary infections and/or atelectasis (Finkel et al. 2018). Nutritional assessment is important to identify malnutrition which negatively impact pulmonary function (Hull, et al. 2012).

Interventions

Interventions for respiratory muscle weakness consequences should focus on:

- Lung expansion (chest wall mobilisation and lung volume recruitment)
- Techniques to improve cough and loosen secretion production (airway clearance)
- Breathing support (ventilation) due to hypoventilation

Physiotherapy/Respiratory therapy should be implemented proactively in non-sitters and sitters (Finkel, et al. 2018).

Lung expansion

Studies have shown that increasing inspiratory volume can improve peak cough flow (PCF) (Fitzgerald, Doumit, Abel, 2018). This can be achieved using bagged manual or mechanical insufflations, a lung volume recruitment bag (LVR bag), Ambu bag or Intermittent positive pressure breathing (IPPB).

The LVR bag is a 1.5 litre self-inflating bag with a one-way valve. The LVR bag can be used with either a face mask or mouthpiece. The aim is to increase inspiratory capacity and improve cough strength. It is an assisted inspiratory technique where the patient has repeated inspirations while not exhaling until they reach their maximum insufflation capacity (MIC) (usually 3 inspirations) followed immediately by a cough (Chatwin, et al. 2018). The LVR bag has shown to maintain or improve maximum passive lung insufflation capacity, improve or stabilise FVC (Fitzgerald, Doumit, Abel, 2018).

The Ambu bag is designed to provide deep lung insufflation via bagging technique. The breath is delivered in a similar way to the LVR or a single insufflation, followed by a cough (Toussaint, et al. 2017). Ambu bag technique can result in abdominal distension and/or pneumothorax and must be used with caution.

Intermittent positive pressure breathing (IPPB) Is a respiratory therapy treatment used to expand the lungs and deliver aerosol medications. It follows the same method as the LVR and Ambu bag. IPPB delivers insufflation to a set pressure at a set flow rate and provides synchronised breath support.

Chest wall mobilisation techniques can be also used prophylactically to increase inspiratory volume and limit chest wall deformity.

Airway clearance

Due to expiratory muscle weakness, people with SMA are often unable to cough and clear their secretions effectively, which results in mucus plugging, impaired mucociliary clearance and eventually lobar and/or lung collapse. Airway clearance is critical to all patients with an ineffective cough. It should be done before eating or at least 30 minutes after eating:

- Manual chest therapy (chest percussion and vibration). Chest percussion is performed by using hand, fin- ger or a face mask. This pressure is transmitted to the lung tissue and assists in dislodging secretion from the airway wall. Chest vibration involves the application of rapid extra thoracic force at the start of expiration, followed by oscillatory compressions. These techniques are widely used in babies and small children and well tolerated (Toussaint, et al. 2017). A more modern version of this is high frequency chest wall oscillation (Vest) therapy with the delivery of repetitive generalised external percussions applied to the entire chest via a specially adapted vest.

- Oral suctioning with a mechanical suction pump and catheter. Oronasal suctioning is essential for airway clearance in patients with dysphagia or ineffective cough, typically non-sitters. Hypopharyngeal pooling of the

secretion can create noisy breathing. The respiratory professional should decide what catheter size is appropriate for use.

- Manually assisted coughs (MAC) with insufflation of the lungs by manual bag inflation followed by abdominal compression. This compression causes a sudden increase in abdominal pressure, which pushes the diaphragm upward and increases expiratory airflow. MAC can be used in all patients with SMA. These techniques have limitations, like patients' cooperation, chest wall rigidity, obesity and difficulty in coordinating such manoeuvre. It is not recommended for patients with severe scoliosis.

- Assisted cough devices, mechanical in-exsufflation cough assist technique, involves the delivery of inflating pressure followed by the immediate transition to negative pressure (expirium). Cough assist devices could be used by mask, mouthpiece, tracheostomy tube or endotracheal tube. Pressures should be high enough to mobilise secretions (in-hale and exhale pressures of at least 30 cm H2O and ideally up to 40 cm H2O). The negative pressure should always be a minimum of 5 mm H2O more negative than the magnitude of positive pressure. The inspiratory and expiratory time will depend on the age and the presentation of the patient. Cough assist is most used on a 1:1 ration of in- spiration and expiration. Occasionally, the patient's preference may lead to 2:1 or 3:1 (2 or 3 breaths in to one cough). Before using a cough assist device, the best way to manage airway clearance is to perform manual or mechanical chest therapy and after finishing using the cough assist device, to suction the upper airway or tracheostomy tube or endotracheal tube. The Cough Assist machine should be used as often as needed (every 10 minutes if needed) in a predefined protocol (Schroth, et al. 2009). Cough assist is a primary mode of airway clearance and a gold standard in patients with SMA. It should be made available for all patients who are non-sitters.

- IPPB - in mildly compromised patients, a cough can also be aided by the use of positive pressure only with intermittent positive pressure breathing. It could be used in combination with inhaled bronchodilators (Dohna-Schwake, et al. 2006).

Parents and carers should be given training and support so that they can follow through with medical advice and use machines effectively (TREAT- NMD, 2017).

Ventilation

For non-sitters, respiratory support should be started prior to signs of respiratory failure in order to manage hypoventilation and avoid progressive to respiratory failure, while for sitters, it should be used in all symptomatic patients (sleep study should be used to determine when a patient has sleep-disordered breathing and needs bilevel NIV, and to titrate settings) (Finkel, et al. 2018). In non-sitters, physicians should not wait for nocturnal hypercapnia, recurrent infections, or signs of respiratory failure. Using NIV early and proactively can prevent or minimise chest deformity, reduce hospitalisation for respiratory exacerbations and palliate dyspnoea.

Respiratory support options include:

- **non-invasive ventilation (NIV) with bi-phasic positive airway pressure (BiPAP).** A BiPAP machine is an external mechanical respiratory assist device that increases inspiratory volume by delivering additional pressure to the upper airways during inspiration.

  Following the pressure-assisted inspiration, pressure drops to a lower value to complete expiration. When used with external facial masks, BiPAP therapy is termed "non-invasive ventilation" (NIV).

  BiPAP support is generally delivered by use of tightfitting facial (mostly nasal) masks. Mask comfort is usually a concern because of nasal bridge discomfort and other skin irritation. Over time, mask pressure may deform the midface region. BiPAP is often used for limited periods, usually during sleep, when a natural respiratory effort is diminished. With the extension of BiPAP support while awake, wearing the facial mask may be more onerous than tracheostomy.

  The indication for BiPAP is nocturnal hypoventilation on sleep studies, with a standard indication with oxygen saturation <90% and end-tidal carbon dioxide (ETCO2) >45. NIV leads to respiratory symptom relief, reduced work for breathing, improved or stabilised gas exchange, good patient-ventilator synchrony while minimising risk and avoiding intubation. A patient receiving BiPAP can re- main stable for years despite the decline in muscle power, with a better quality of sleep, resolution of micro atelectasis, improvement in lung development and reset of the CO_2 levels to normal (Mehta, et al. 2001).

  In the early phase, BiPAP had the ability to correct deformities of the chest if initiated soon after appearance (Bach, Bianchi. 2003). BiPAP therapy at home can reduce hospitalisations (Ottonello, et al. 2011). In case of respiratory insufficiency, many complications associated with intubation can be avoided when using BiPAP (Padman, et al. 1994). Other breathing supports such as 'continuous positive airway pressure' (CPAP), with rare exceptions, are not recommended because they do not facilitate carbon dioxide exchange for oxygen (Finkel, et al. 2018; TREAT-NMD, 2017). Humidification is preferable but not always necessary when patients are only ventilated during sleep. For patients using NIV in the day and at night, adding humidification should be considered. Heated tube humidification systems are most effective. For most patients, NIV is started during hospitalisation, but it can be started at home. NIV should always be managed by a specialised team.

- **invasive ventilation with tracheostomy** is indicated when BiPAP support is insufficient because of greater security or could be chosen if frequent intubation is needed or is difficult, or by patient or family preference. This is generally a long-term solution. The need for tracheostomy ventilation is less frequent in sitters than in non-sitters, but in some cases, it might be needed. The decision to use invasive ventilation should be focused on clinical status, prognosis, and quality of life based on the discussion with the family. Overall, it is controversial in sitters (Schroth, 2009; Finkel, et al. 2018) and in some countries like France and the UK, it is not recommended.

Both invasive and non-invasive ventilator support have associated technical difficulties that require expert support. The options for breathing support should be discussed with the medical team at a time of good health.

Patients with a tracheostomy and their families are often stigmatised in rural areas and under-developed countries, which puts a burden on their social and psychological life. There are differences between countries, as well as social and religious beliefs which lead to the rejection of these patients in the community they live in. It is therefore crucial that decisions are made together with the patient and their family.

Acute respiratory care management

Acute respiratory illness is common with respiratory muscle weakness. Individuals affected by SMA are particularly vulnerable to acute respiratory community-acquired infections. Respiratory illness due to mucus plugging is not so rare, but more serious complications like aspiration, atelectasis and pneumonia could arise very quickly.

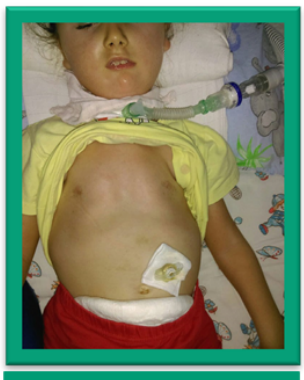
Muscle weakness is exacerbated during illness. In combination with increased airway secretion and diminished power of cough, difficulty in breathing occurs and hypoxemia could appear as a presenting symptom. In acute illness, metabolic demands are increased. A high temperature, high breathing rate, vomiting or diarrhoea lead to loss of fluids and salts. Hypokalaemia could occur due to the loss of potassium. Hypoglycaemia, ketonuria, metabolic acidosis, stupor and coma could happen but are not so frequent. In severe cases, catabolic illness is reported, with a very low muscle mass of about 10% body weight (normal 30-40%) and presenting with respiratory decompensation. Hypoglycaemia is explained by a reduction in muscle proteins, leading to lower availability of amino acids as substrates for gluconeogenesis, which is the major source of glucose production after depletion of liver glycogen, and which usually develops after periods of prolonged fasting. Additional considerations in acute illness should be appropriate nutritional support (good hydration, electrolyte balance and if needed, intravenous glucose). Fasting is not recommended more than 6 hours and if needed, enteral or intravenous caloric feeding should be done to avoid

metabolic decompensation catabolic state and metabolic acidosis, especially in type I patients. Regular meals, late evening meals (carbohydrates and proteins) are suggested in patients with recurrent hypoglycaemia (Bruce, et al. 1995).

Supplemental oxygen is not the first line of treatment in patients with SMA experiencing respiratory distress. Use of oxygen alone can exacerbate alveolar hypoventilation in patient with chronic hypercapnia (chronic CO_2 retention). Therefore, supplemental oxygen should be provided when concurrent with the support of non-invasive positive-pressure ventilation or with the monitoring of CO_2 gas exchange (Wijngaarde, et al. 2020; Finkel, et al. 2017).

After general assessment and review of signs and symptoms in acute respiratory illness, the goal of treatment is to normalise gas exchange and optimise airway clearance to prevent atelectasis with concomitant diagnosis and treatment of the underlying cause of infection (viral or bacterial). Patients will mostly be present with an increased work or rate of breathing or worsening fatigue. Breath sounds might be quiet or absent, with some children presenting with upper airway transmitted sounds or wheezing. Patients will likely have increased secretions, which would contribute to respiratory failure (Chiarini, et al. 2009). On assessment patients are likely to have high CO_2 and/or low oxygen saturations.

Supplemental oxygen is not the first line of therapy because it does not improve gas exchange and is not the under-lying cause of respiratory illness. Chronic hypoventilation, usually present in type I and some type II patients, leads to increased dependence upon oxygen levels for a respiratory drive; supplemental oxygen may diminish in such cases, spontaneous ventilation and cause more harm than benefit. If airway clearance and respiratory support are maximised and hypoxemia continues, supplemental oxygen should be used whilst monitoring CO_2 gas exchange (Schroth, et al. 2009).



Five year-old non-sitter with a bell-shaped chest, button PEG for feeding and

Parents find tracheotomies very difficult to deal with emotionally. They tend to view this procedure as beginning of the end and persistently resist agreeing to it when first advised. It is therefore advisable to do everything possible before advising for a tracheostomy. The decision should be made with the patient/ carer. On the other hand, some patients may require tracheostomy, to facilitate care and reduce the risk of acute respiratory events. This makes them feel safer in the everyday care of their SMA patient.

Interventions during acute respiratory illness include:

- Airway clearance for 10-20 minutes
- In-exsufflator cough machine/Cough Assist, 4 sets of 5 breaths followed by suctioning mouth
- Postural drainage for 15-30 minutes
- NIV (BiPAP) at home during the day to relieve fatigue and at night (improves gas exchange)

This could be done every 4 hours and Cough Assist, as often as needed. Pulse oximetry should be used for guidance on oxygen saturation. When oxygen saturation is below 94%, a cough machine should be used. If it drops below 90% despite these interventions, the patient should be transported to a hospital for further care.

Assisted coughing techniques are preferred over deep suctioning and bronchoscopy. A Cough Assist machine in combination with BiPAP may decrease the need for intubation. During acute illness, intubation and mechanical ventilation may be needed in a hospital.

Families should be informed about the options for both acute and chronic respiratory care, with written care proto-cols, medical needs and respiratory equipment. Recommended in-home respiratory equipment is:

- Cough Assist machine or resuscitator bag with a mask
- Suction machine
- Spot check pulse oximeter
- Nocturnal respiratory support, if needed (BiPAP)
- Method for secretion mobilisation, e.g. palm cups

Patients should be advised to bring the respiratory equipment they use at home with them to the hospital.

Written resuscitation statements should be available both for the family and for the local emergency services. If hospitalisation is indicated, the patient should be triaged to tertiary care centre with SMA expertise and treated by a multidisciplinary team (neuromuscular, pulmonary, physical, endocrinology, psychosocial, palliative) with the family involved (Finkel, et al. 2018).

Patient-specific protocols (respiratory care, intubation and extubating protocols, discharge protocols) should be created based on community resources, emergency medical services and hospital capacity.

Medications in acute respiratory illness

Medication used to open the airway (nebulised bronchodilators) should be available and used in high suspicion of asthma, or if a clear improvement has been seen after it has been given. They can also be used in conjunction with hypertonic saline or mucolytics to prevent bronchoconstriction.

A respiratory therapist should initiate respiratory management. Physiotherapist and respiratory therapist have an important role in the respiratory care of patients with SMA. This includes providing intensive interventions in an acute care setting, as well as educating patients and caregivers on how to optimise respiratory care in a home environment. However, respiratory care is not standardised and vary globally between different centres and countries.

Anticholinergic agents (Atrovent) should be used carefully in order to avoid secretions drying too much, making it hard to remove.

Nebulised mucolytics (to break down secretions) and hypertonic saline (3% or 7%), or dornase-α, are not recommended for long-term use. There is no evidence to support their use and they can increase secretion burden. Nebulised mucolytics can be used only in the acute setting, if there is evidence of mucous plugging and lobar collapse on the chest x-ray (Loos, et al. 2004).

Gastric protection medications, such as histamine H2 blockers and proton pump inhibitors (PPIs), can be used in cases of gastritis if the patent is not fed enterally. They will not prevent reflux but may help with discomfort and burden in the oesophagus. Long term use may increase risk of aspiration pneumonia (Tilman, et al. 2018).

Prokinetics such as domperidone may be used to improve gastric mobility (Tilman, et al. 2018).

Antibiotics and corticosteroids should be used on an individual basis, after discussion with a medical team and other diagnostic tests done (TREAT-NMD, 2017).

Anaesthesia and preoperative considerations

Sedation and anaesthesia should be planned in a tertiary care centre, with consultations from respiratory specialists to plan the potential need for additional non-invasive or invasive airway support.

Cardiology screening, polysomnogram, nutritional assessment, with standard laboratory analyses and a pulmonary function test where possible, should be done as a part of the pre-anaesthetic evaluation. An assessment of airway status should also be carried out to determine if intubation is possible (limited jaw opening, limited neck mobility and positioning restrictions). Regional analgesia may reduce need for systemic analgesics.

Patients with SMA have a high risk of post-anaesthesia complications, which may lead to prolonged intubation, nosocomial infections, tracheostomy and death. Postoperative management should be based on preoperative respiratory function and type of surgical procedure. An anaesthetic is commonly associated with a loss of lung volume. A delayed extubation in ICU should be considered to facilitate lung recruitment. Cough assist is likely to be necessary (Wang, et al. 2007).

NIV should be implemented as transitional support following extubation in an intensive care unit (Finkel, et al. 2018). Patients should be weaned of NIV when they are able. Opiate-based analgesia should be considered as part of rou- tine post-procedural management with the anticipation of providing NIV and cough assist due to an increased risk of respiratory depression associated with opiate-based analgesia (Damian and Wijdicks, 2019).

Immunisations

Children with SMA are generally immunocompetent. Customary immunisations are usually safely followed in the patient's country.

Pneumococcal vaccine for 13 serotypes should be given prior to 2 years of age (Finkel et al. 2018; Treat-NMD 2017), or as per recommendations of the child's country. 23-valent pneumococcal vaccine should be given to people with SMA older than 2 years of age.

Annual influenza vaccine is recommended for all with SMA over 6 months of age per country guidelines. There should be special efforts made to vaccinate household contacts and caregivers (TREAT-NMD, 2017).

In infants up to 2 years of age, administration of palivizumab injections (a monoclonal antibody directed to respiratory syncytial virus (RSV)) during RSV season is recommended (TREAT-NMD, 2017). RSV commonly infects infants with a cold-like illness, but 25-40% will manifest signs of lower tract infection with pneumonia or bronchitis.

Other organ involvement

Unlike with Duchenne muscular dystrophy and due to the dysfunction in the autonomic nervous system, no cardiac involvement was reported in most cases of SMA type II and III (Bianco, et al. 2015). As a result, no routine investigation of cardiac function is recommended in the revised SMA SoC guideline for these patients. Possible exceptions are the exclusion of cardiac defects in severely affected infants with SMA type I.

Surveillance testing for other organ involvement should generally be based on clinical symptoms and is thus not necessary in most patients. A possible exception is the monitoring of glucose metabolism in all types of SMA.

Nutritional management

Introduction

Adequate nutrition in SMA affected individuals is important at first for maintaining proper muscle function and muscle mass. Nutrition is also critical to fostering:

- **Improved growth (in children)** - gaining weight while growing in height is essential to good health. Having enough energy and proteins keep the body growing by supporting lung tissue and the heart muscle.

- **Better breathing (in children)** - growth in length helps with breathing, providing more room for the chest to expand.

- **Preventing illness** - adequate nutrition helps to prevent and fight against viruses.

- **Bone mass** - diminished bone mineral density (BMD) is highly prevalent in SMA, regardless of disease severity. There is progressively reduction in BMD with worsening of SMA severity (Wasserman, et al. 2017). Low BMD and diminished bone natural remodelling increases the risk of early fractures, which can cause irreversible loss of motor skills. At first, low BMD is a consequence of disuse and muscle weakness. However, calcium or relative Vit D3 (25-OHD3) and vit K deficiency may enhance osteopenia and risk of fractures (Iwamoto, et al. 2003).

Patients with SMA are often thought to be poorly nourished. Children are at risk of malnutrition, altered metabolic status (hypo or hypermetabolic), suboptimal macronutrient (proteins, carbohydrates, lipids) and micronutrients intake (vitamins and minerals), particularly protein intake due to inadequate (usually diminished) nutrition intake because of decreased caloric needs (Martinez, et al. 2015). Needs estimated through inadequate estimated energy requirements often result in either well below or well above the recommended weight parameters for age or height (growth deficiency). It is a consequence of unintended under or over feeding and alteration in body composition (Mehta, 2015). Anthropometrics, nutrition focused physical exam and growth monitoring help to determine adjustments either above or below estimated needs.

In normal infants, muscle mass makes-up about 20% of total body weight; this increases to 30-40% in adults. Individuals with SMA have a low lean body mass (10-50% of normal muscle mass), so they would be expected to be 10-36% lighter than healthy peers. Because of

reduced muscle mass and weakness, resting energy expenditure (REE) and caloric requirements are less (Poruk, et al. 2012). Increased respiratory work, chronic respiratory failure and acute illness increase energy expenditure and caloric requirements, further increasing the risk of malnutrition and failure to gain weight. On the other hand, unintended delivery of excessive energy by overfeeding in patients with SMA results in increased respiratory burden. Energy expenditure and metabolic balance, especially protein imbalance, monitoring fluid and micronutrition intake, requires comprehensive nutritional assessment to guide individualised nutritional therapy by an expert nutritionist. In addition to inadequate energy intake, perorally fed patients have micronutrients intake below recommended standards used in different studies, mostly vitamin C, D and E, calcium, iron, zinc, selenium and folates. Essential fatty acid deficiency is also common. Protein intake is usually adequate or even greater than recommended (1g/kg/day). The needs for protein intake are greater during illness and post-operative care (Martinez, et al. 2018).

There is a tendency for children with SMA to shift from underweight to overweight during school years. This is due to the absolute overall increase in fat mass. It is difficult to know what an ideal body weight should be in the setting of diminished muscle mass. Overweight conditions may limit function due to increased mechanical load and decreased bone health (BMD reduction), while increased fat mass may predispose alterations in glucose metabolism with hyperglycaemia (diabetes), insulin resistance and altered lipid metabolism with hyperlipidaemia. Underweight conditions may predispose to poor tolerance of catabolic disease, hypoglycaemia and wound healing.

Most patients with SMA experience various difficulties which are more or less the reason for inadequate nutrition. Different phenotypes of patients with SMA lead to differences in nutritional status. Patients who are non-sitters tend to be underweight and have difficulty breathing and swallowing, and patients who are sitters are at risk to be overweight and can have weak swallowing function, as well as chewing and respiratory problems. People with SMA who are walkers, rarely have swallowing and feeding problems, but are at risk of being overweight (Bertoli et al. 2017).

Non-sitters and sitters with low functional levels are underweight due to increased energy expenditure (increased respiratory rate and muscular effort) and reduced food intake (dysphagia, delayed gastric emptying, reflux and chronic constipation).

Sitters and walkers are at risk of becoming obese due to a decrease in physical activity, with consequent reduction in energy needs and decrease in energy expenditure with reduction in fat-free mass.

Swallowing coordination and safe swallowing are a primary concern in people with SMA. Chewing can be difficult and swallowing safety compromised due to the size of food bolus or swallowing speed. Oral motor dysfunction correlates with skeletal muscle weakness, so safety and adequacy of feeding are important for all who are unable to sit (Van den Engel-Hoek, et al. 2014). However, safe swallowing is also a concern for patients who are sitters. Patients should be monitored for a history of choking or cough with feeding and assessed when any signs of dysphagia are present (coughing or choking while eating or drinking,

recurrent respiratory infections, long mealtimes, weight loss, fatigue when bottle or breast feeding, lack of energy and endurance while eating, poor secretion management and drooling, sounding wet after feeds, resistance to accept food orally, reports of food "getting stuck"). Detection of dysphagia is important for early diagnosis, treatment and minimising complications such as aspiration and pulmonary infections associated with inability to swallow, which can be life-threatening. Standard assessment to evaluate swallowing function is VFSS (video-fluoroscopic swallow study) or FESS (flexible endoscopic evaluation of the swallow). Shortly after diagnosis, a patient with SMA (non-sitter and sitter) should be regularly referred to a clinician for VFSS. Swallow disfunction is rare for walkers (Audag, et al. 2017; Hiorns and Ryan, 2006). VFFS can identify irregular pharyngeal motility and silent aspiration, but also other parameters associated with dysphagia and impaired feeding such as reduced lip closure, inadequate bolus formation, residue in oral cavity during oral phase of swallowing, delayed triggering of pharyngeal phase, reduced larynx elevation, delayed pharyngeal transit time and multiple swallows. These findings may help guide more effective feeding strategies from a speech and language therapist (Romano, et al. 2017) and identify the type of food and drinks that are safe to eat as well as how these should be prepared (Hiorns and Ryan, 2006).

With new treatments for SMA, little is known about the potential to improve or rehabilitate the swallow function, but there is a hope that patients can continue to eat and drink for longer. Experts now advise to continue to eat and drink small amounts and not to place the patient totally on feeding tube or gastrostomy. Taking small amounts by mouth can protect and retain some bulbar functions.

Limitation of jaw opening and masticatory muscle weakness are common in older individuals with SMA with more subtle developmental deformities, such as malocclusion. Because of these limitations, including fatigue while eating, it is important to carefully select food and allow the patient to eat at his or her speed, ideally in an upright position. If needed, postural support of the head and neck can be given. In non-sitters, jaw contractures can limit a patient's ability to feed orally (Mercuri, et al. 2018).

Constipation and distension are multifactorial in origin. The main causes are immobility itself and diminished abdominal pressure and abdominal wall laxity. Many individuals use various laxatives chronically to regulate constipation as well as probiotics.

Gastroesophageal reflux disease (GERD) is important because of the silent aspiration of gastric content.

Secretion management: profound dysphagia can lead to an inability to swallow oral secretions. People with SMA, particularly non-sitters, often have difficulties in managing secretions and often drool. They may benefit from medication, such as glycopyrronium bromide or hyoscine patches depending on the person's respiratory status and following direction from the respiratory team.

Assessment of nutritional status

Regular nutritional assessments are important to identify signs and symptoms of malnutrition. Nutritional problems may result from different causes and require different assessments and interventions, thus a multidisciplinary team (MDT) approach is mandatory (Romano, et al. 2017).

Comprehensive nutritional assessments are important for both non-sitters and sitters. In both types of patients, swallowing problems should also be evaluated, as well as feeding difficulties (e.g. dysphagia, increased meal times, cough or choke whilst eating, chewing difficulty, feeding fatigue), jaw contracture, breathing problems and acute illness. For all SMA types, it is important to enquire about and document gastrointestinal (GI) symptoms such as GERD, constipation, vomiting, use of bowel regulatory agents or drugs for GERD relief.

Nutritional status assessment in SMA patients is hampered in several ways:

Anthropometry assessments

Anthropometry is the most commonly used method in the clinic which can be used to assess the growth and nutritional status in people with SMA. Growth in children can be assessed using standard WHO growth charts for boys and girls, for both height and weight. WHO growth charts may be helpful to monitor trends and changes over time. However, there is controversy around the use of standard growth charts for children with neurological disease. Growth charts for healthy children do not take into consideration the progressive change in body composition that occurs in muscle diseases (Wang, et al. 2007). The absence of specific growth charts for neuromuscular disorders such as SMA, makes the interpretation of anthropometric measures complex. Patients with SMA have altered body composition, so the use of anthropometrics and standard growth charts is challenging. For example, low BMI or weight for height does not mean a low body fatty mass. It may imply a high fatty mass and low muscle mass in people with SMA. Fat mass in adipose tissue is increased and fat-free mass (water ~73%, protein ~19%, mineral ~8%, including osseous and non-osseous mineral and glycogen ~0.1%) is decreased in people with SMA, when compared to healthy individuals (Bertoli, et al. 2017). Anthropometric measurements are also difficult to make due to frequent contractures and scoliosis. Interestingly, to overcome this, a group of nutritional scientists implemented a standardisation process for such measurements and developed a procedural manual specific for SMA patients (Bertoli, et al. 2019). It measures:

- Weight in kg
- Standing height in cm
- Segmental height in the recumbent position in patients who cannot stand independently or have spine deformity in cm
- Segmental length (arm length, ulna length, femur length and tibia length) in cm
- Circumference (arm, head, wrist, waist, thigh and calf) in cm

- Skinfold thickness in mm (triceps, biceps, suprailiac, subscapular and anterior thigh) using skinfold caliper
- Body Mass Index (BMI) calculated by the following formula: BW (Kg)/SL2 (m2)
- BMI-Z-scores: for children under two, using the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts. According to CDC guidelines a child with BMI-Z-scores value below the -2, between -2 and +2, between +2 and +3 or above +3 was considered underweight, normal weight, overweight or obese, respectively.
- Weight/length (kg/cm)

Body composition assessment

Height/length and weight are often not enough when assessing nutritional status. The absence of specific growth charts leads to misinterpretation, which might result in inappropriate nutrition in patients (over- feeding or underfeeding). A body composition assessment including skinfold measurements, muscle circumference, or bioelectric impedance analysis is therefore essential for nutritional status assessments (Wang, et al. 2007).

Body composition (BC) can be performed using Dual-energy X-ray absorptiometry (DEXA) equipped with a paediatrics software application. The scanning of children is done with them lying supine on the table, their feet in a neutral position with arms resting along their sides, palms facing upwards. DEXA scans are performed by well- trained staff, for an average measuring time of 10 minutes. DEXA provides measurements of soft tissue and bone for the total body and the sub regions (arm, trunk, leg), including fat mass (FM (g)), lean body mass (LBM (g)) and bone mineral content (BMC (g)). The fat free mass (FFM) is calculated by adding BMC to LBM. It is also possible to calculate the proportion between FFM and FM and their ratio. Total body bone mineral density (BMD) can also be calculated as the amount of mineral matter per square centimetre of bone (g/cm3). **Dual-energy X-ray absorptiometry (DEXA) is a gold standard method for body composition assessment.**

Non-sitters and sitters have a high FM percentage compared to the respective reference values for sex and age, while total BMC percentages did not differ. Non-sitters showed less BMC in the arms than sitters. Total body water (TBW) and extracellular water (ECW) are lower in non-sitters and sitters than reference values for sex and age with no differences between the groups. Non-sitters have significantly low FFM and LBM compared to sitters, specifically in the trunk and arms. Non-sitters tended to have lower BMD compared to sitters (Bertoli, et al. 2017).

Nutritional laboratory analyses

Nutritional analyses are recommended, but there is no single marker representing good or poor nutritional status (Romano, et al. 2017). Blood laboratory variables which should be included in assessment of patients with SMA are:

- Urea and electrolytes
- Creatinine
- Glucose
- Insulin
- Full blood count
- Haemoglobin, ferritin and iron
- Sodium, potassium, calcium, magnesium, phosphate, zinc
- Albumin and total protein levels
- Liver enzymes (AST, ALT, LDH)
- Vitamins (A, B12, E, 25-hydroxy vitamin D, folic acid)
- Parathyroid hormone (PTH)
- Lipid profile (total cholesterol, high-density lipoprotein-HDl, low-density lipoprotein-LDL and triglycerides)

Bone status

Patients with SMA have altered bone metabolism (bone remodelling and impaired mineralization) and low vitamin D levels, which together with lack of exercise and muscle weakness may lead to fragility fractures (Baranello, et al. 2019). Most fractures are due to low impact trauma. About half of the most severe cases have at least one fragility fracture by the age of 10 years. Low BMD is common in children with SMA, due to low vitamin D levels and consequent increased secretion of parathyroid hormone (PTH). High levels of PTH further increase bone resorption and fragility. To support bone health, it is recommended to optimise calcium and vitamin D intake and promote physical activity. Intravenous bisphosphonates (IV BP) are used when osteoporosis and fragility fractures are present. IV BP are safe and effective in reducing the fracture rate in patients with SMA (Nasomyont, Hornung & Wasser-man, 2020). Annual assessment of BMD using DEXA and Vit 25-OHD3 are recommended yearly.

Energy needs – resting energy expenditure (REE)

Resting energy expenditure represents the amount of calories required for a 24-hour period by the body, during a non-active period. Measuring REE is very important to start nutritional support. Unless using indirect calorimetry (IC), predictive equations should be used as a starting point with adjustments based on growth and body composition.

The gold standard to measure REE is indirect calorimetry, to assess mREE (measured REE). IC measures oxygen consumption and carbon-dioxide production and is strongly recommended in all patients with SMA. However, indirect calorimetry devices are rarely available in clinical settings as they are expensive and require personnel with expertise.

An easier way to assess and calculate energy needs is to use predictive REE equations. There are several equations developed for calculating pREE (predictive REE) and they are all for healthy persons. The most used are WHO, Schofield and Culley and Middleton. The last is

generally used in all patients with neurological impairments. General Guide- lines for SMA children use 9-11kCal/SL (supine length in cm). The overall precision of this commonly used equations is very low in SMA patients.

To improve pREE, a group of scientists from the International Center for the Assessment of Nutritional Status (ICANS) in Italy, developed pREE equations for SMA non-sitter patients in order to assess their nutritional needs. Using iC, they concluded that mREE is directly correlated with age, weight and length. They further investigated the ventilator status in relation to mREE and concluded that ventilator status had a critical role in mREE in SMA non-sitter patients. They compared mREE with SMA patients without respiratory support and found that all ventilated patients had lower mREE compared to non-ventilated patients, which is independent of all other variables (age, weight and length). REE was lower in ventilated patients on average -305kcal/day. They also investigated mREE in patients treated with Nusinersen and concluded that treated patients have higher mREE. From this observation, the authors generated 2 sets of pREE equations: for spontaneously breathing SMA patients and for ventilated patients. They also introduced the treatment variable (treated vs untreated). By using these equations, it is possible to assess pREE through simple antropometrics measurements (weight, supine length and tibial length in cm) taking into account ventilatory and treatment status. These equations are available in the literature and may be used in clinical practice to assess REE in kcal/day (Bertoli, et al. 2020).

Non-sitters

Anthropometry assessments
There are no specific growth charts for children with SMA. WHO standardised growth charts should be used (https://www.who.int/childgrowth/standards/en/)

Body composition assessment
This should be done annually and include BMD.

Macronutrient and micronutrient intake

- 3-day food record prior to the visit, reviewed by a dietician
- Actual energy intake (AEI kcal/day)
- Protein intake (g/kg/day)
- Carbohydrate intake (%)
- Fat intake (%)
- Vitamins
- Energy intake adequacy - by comparing AEI to measured resting energy expenditure (MREE) and defined as underfed when AEI:MREE <80% and overfed when AEI:MREE >120% (Martinez, et al. 2015).

Resting energy expenditure (REE)

Video Fluoroscopic Swallow Study - is recommended shortly after diagnosis and, if the initial test is normal, only further testing is carried out if there is evidence of progression, increased symptoms, or concerns.

Nutritional laboratory analyses

Evaluation of dietician every 3-6 months (for older children and adult, once a year)

Sitters (every 3-6 months for younger children and after, once a year)

Assessment is the same as for non-sitters, with special considerations in case of obesity (Mercuri, et al. 2018; TREAT- NMD, 2017).

As their ability to move around is reduced and their body composition is altered, sitters are at risk of becoming over-weight. If they are showing signs of this, they should be evaluated for obesity as well as glucose metabolism.

Some experts suggest that sitters with SMA should be evaluated for the possibility of obesity/overfat at BMI greater than the 25th percentile.

Walkers

It is rare for walkers to have swallowing and feeding difficulties. Nutritional assessment should be undertaken if there are concerns of obesity and or being overweight, as this can reduce mobility and may increase the risk for metabolic syndrome, high blood pressure and diabetes:

- Dietician/nutritional visit
- Anthropometric assessment
- Glucose laboratory
- Annually assessment of BMD and Vit 25-OHD3

Interventions and management of nutritional status

To start nutritional support in patients with SMA, it is necessary for the patient to be evaluated by a nutritionist and gastroenterologist.

The clinician can assess dysphagia (weak suck, fatigue, humid voice, pneumonia) and difficulties with feeding (pocketing, jaw contractures, increased time taken for meals). Once the swallow has been evaluated, then the patient with SMA can continue to feed orally. The patient may require some modifications to their diet and swallow techniques. The management of dysphagic patients with SMA should involve multidisciplinary team (MDT) to support the strategies specific to each patient. Clear recommendations should be given in terms of which sorts of food and drinks are safe, their consistency and structure,

how to prepare it, how the patient should be fed (position and techniques), adjust feeding time, assess strong and weak points in patient's swallowing abilities and how to clear the oropharyngeal area to prevent aspiration. Occupational therapy can be used to help swallow safely and eat effectively. General recommendations in case of dysphagia are to take small but frequent calorie rich meals to reduce the time spent on meals and patient effort and to consume purred food and drinking water during and after the meal to improve swallowing and help to clear oropharyngeal residue. In the case that swallowing is unsafe (residual food bolus, prolonged passage or aspiration) or there is a growth failure, there are two temporary (short term) ways of providing food through the nose for both non-sitters and sitters:

- Nasogastric tube (NJ) - the feeding tube goes into the stomach
- Nasojejunal tube (NJ) - feeding tube goes to the small intestine

A long-term option is a gastrostomy tube (G-tube) or with Nissen fundoplication, due to decreased GI motility, reflux and increased pressure related to respiratory treatments. G-tube is surgically put through the skin and into the stomach. A G-tube can also be placed endoscopically and is called a percutaneous endoscopic gastrostomy (PEG). Most clinicians recommend G-tube placement in those patients receiving BiPAP, but specific indications are not established. The potential for aspiration due to GERD with BiPAP therapy is high. In that case, fundoplication with G-tube or jejunal placement or enteral tubes are worth considering (Yuan, et al. 2007). G-tube permits continuous feeding, in favour of greater muscle mass.

In non-sitters, a G-tube is regularly used for total nutrition, while in sitters, it is used for supplementary nutrition in case of growth failure. If they can still swallow safely, they should also be encouraged to have some food by mouth (TREAT-NMD, 2017).

Careful MDT management is needed to balance the benefits and risk of oral versus enteral feeding in the best interest of patient in terms of health, growth and nutrition.

Parents of patients with SMA state that the decision to place a gastrostomy is a difficult one, and patients with SMA report grief when traditional oral feeding becomes unsafe for them. Placement of a gastrostomy tube improves caregiver reported quality of life (Qian, McGraw, Henne, Jarecki, Hobby K & Yeh, 2015; Roper& Quinlivan, 2010)

The nutritionist can assess nutritional analysis of food records/feeding regimen, longitudinal anthropometrics, body composition and bone density, energy needs and laboratory nutritional status, especially vitamin D labs, with the aim to provide adequate energy, fluid, macro/micronutrient intake, avoiding underweight and obesity and pre- venting hypo/hyperglycemia (Mercury, et al. 2018).

What kind of diet should be prescribed?

According to the consensus statement the concept of a tailored dietary approach is recommended with respect to specific dietary needs in each patient with SMA (Mercuri, et al. 2018). It is important to do a nutritional status analysis by 24 hours recall or 7-day food diary record data taking into consideration other aspects as gastrointestinal symptoms and possible metabolic abnormalities (metabolic acidosis, abnormal fatty acid metabolism, hyperlipidemia, hyper/hypoglycaemia). Around 20% of all patients with SMA have some metabolic abnormalities.

Concerning energy needs when a patient has unintentional weight loss of less than 10%/per year or impairment or growth pattern, high caloric diet is recommended. It is important to introduce a progressive increase of calories intake up to 10% for energy need mEE by IC or calculated pREE and maintain a 10% increase until an improvement in body weight and growth pattern. Then a normocaloric diet can be set with respect to energy needs. It is recommended to use high-protein and energy food fortification strategies that are possible to provide maximum calories in a minimal volume of food and drink. A full nutritional assessment should be completed every month to see if dietary intake is appropriate or there is a need to change the strategy. For overweight and obese patients with SMA it is suggested to normalise caloric intake with respect to energy needs by providing a balance diet. Patients need to be monitored during several months to see improvement of nutritional status (Wang, et al. 2007). In acute care situations it is important to avoid fasting because of the risk of metabolic abnormalities, especially hypoglycaemia. Nutrition including protein sources should be provided within 6 hours during an acute episode with good hydration and electrolyte intake. Adequate fluid and fibre intake is recommended for frequent constipation.

One popular diet in the American community is the administration of an elemental amino-acid based formula for type I and some type II patients (http://www.aadietinfo.com/about/). It is developed by Mary Bodzo, a mother of a young adult with SMA who is a sitter. Amino acid diet has been generally formulated for infants and children with severe protein allergies, short-bowel syndrome and other special gastrointestinal conditions. An elemental or semi-elemental formula in the diets of longer surviving children with SMA type I are widely used among families and caregivers. These are extensively included with other nutritional supplements including L-carnitine and Q10 enzyme in liquid form, which makes conclusions about a beneficial effect of this type of diet challenging (Davis, et al. 2014). There is no data to support the benefits of elemental formula diets apart from parents' testimonials, in terms of the number of potential benefits and observed improvements in their child with spinal muscular atrophy, after switching to an elemental or semi-elemental formula. Using elemental formulas, rapid uptake of individual amino acids could limit muscles to buffer surge levels which might be dangerous. There is no data to support the use of synthetic amino acids as opposed to intact protein in patients with SMA. Use of elemental formulas should be undertaken under the control registered dietician. Additional research is needed to evaluate the use of elemental formulas, including

optimal macro and micronutrient intake, as well as creating evidence-based nutrition guidelines.

New treatments for patients with SMA have created different disease trajectories, so nutritional assessment and care may need to be revised in the future and adapted to each individual patient with SMA.

Supplements and alternative therapeutics

Calcium and vitamin D supplements should be given when levels of these vitamins are inadequate or in the presence of low BMD. Patients with SMA may require supplementation with micronutrients and electrolytes, especially during illness (Bassano, et al. 2018).

To date, clinical trials have not found evidence to support the use of certain supplements or therapeutics in patients with SMA, which include creatine, phelylbutyrate, gabapentin, hydroxyurea and combination therapy with valproate, acetyl-L-carnitine and Q10. However, the use of albuterol (Salbutamol) (a beta-adrenergic agonist) has shown some improvements in open-label studies (Sonia, et al. 2017).

Orthopaedic management

Introduction

Individuals affected by SMA, especially children, are prone to a number of spine, joint and bone complications due to progressive muscle weakness, that confound the function further and could be painful. Deformities can also impact other functions as respiration, gastrointestinal motility, sitting and walking ability. These can include:

- Spine deformity, chest and thorax deformity
- Pelvic obliquity and hip deformity
- Joint contractures
- Bone fractures

Of greatest impact is collapsing scoliosis that can at once be painful.

Irrespective of drug or other treatments all SMA patients (sitters, non-sitters and walkers), should have regular assessments and reviews by trained team members such as an orthopaedic consultant, physiotherapist (PT) or occupational therapist (OT) (TREAT-NMD, 2017).

Proactive management is more effective than a reactive approach, despite that the ability to correct deformities or slow down progression is limited and it is unlikely that

interventions will stop complications entirely. A proactive approach in children is particularly important to allow growth, skeletal maturation and for them to develop as functionally as possible (Mercuri, et al. 2018). As a part of multidisciplinary team (MDT) orthopaedics work closely with physical therapists with the aim to address the patient's current state and functional needs, assess the complications and slow the progression of deformities.

Management of orthopaedic complications ranges from conservative to surgical and depend on functional status and disease progression (Obid, et al. 2020). Surgical management should be considered when conservative methods are ineffective, or when pain, positioning and functionality have substantial impact on patient's quality of life (Mercuri, et al. 2018).

Indeed, as there is a disconnect between motor function and perceived quality of life in SMA, the goal with every SMA patient should be ensuring the best quality of intervention for each patient regardless of where in the disease severity spectrum they might fall (de Oliveira & Araujo, 2011; Wang, et al. 2007; Finkel RS, et al. 2018)

Spine deformity

Scoliosis is the curvature of the spine to the side, out of the normal plane. In SMA, this curvature most likely develops because of a lack of muscular support of the bones of the spinal column and imbalance in muscle tonus. Children who use wheelchairs are at higher risk for developing a spinal curve than children who walk. When bones, discs and ligaments of the spinal column lack normal muscular support, there's a tendency for them to bend further, either to the side, forward or backward. As the muscular weakness progresses along with growth, there is a tendency for the curvature to develop and over time, for it to become more severe. Scoliosis in SMA is of a collapsing type, with curvature advancing quickly after early slow progression to about 45-60 degrees.

Right side scoliosis in a 7 year-old sitter

The spine can curve in several directions. A bend to the side is described as "scoliosis". A bending of the spine towards the backward (or hunchback) is called kyphosis. Finally, a curve forward, or inward, is called lordosis. These may be described in combination, such as kyphoscoliosis (backwards and to the side).

Thoracic hyperkyphosis has been observed in clinical practice in patients who are newly able to sit, or transtioning from a non-sitter
to a sitter phenotype.

While the numbers vary, a very high percentage of people with SMA will develop scoliosis. It is very common in those with severe early-onset of weakness who sit upright due to gravity, but can also arise in infants with severe SMA before upright posture is regularly maintained.

More mildly affected patients who can walk are also at risk for progressive scoliosis, but to a much lesser extent and after the loss of independent ambulation. Walking in orthoses is difficult to assess, but it seems to slow or at least delay progressive scoliosis (Fujak, et al. 2013).

Scoliosis is often diagnosed between the ages of 4 and 6, although it can start as early as eight or nine months of age. In children, scoliosis often arises well before growth is complete, and severity correlates with the age of presentation.

Scoliosis has a negative effect on pulmonary function and other activities. Scoliosis can alter respiratory mechanics, by changing the orientation of the muscles and joints of the respiratory system. In severe forms it can put a patient at risk of severe respiratory morbidity or respiratory failure (Mayer, 2015). Scoliosis leads to postural asymmetry, loss of function, strength and functional asymmetry, difficulty in positioning and pain. It is important to maintain the patient's ability to sit, as this is imperative to allow them to go out of their homes and participate in social activities. Bed-ridden patients can develop strabismus, which can influence negatively on visual – perceptual abilities.

Intercostal muscles that are unable to oppose the stronger diaphragm cause changes in the shape of the chest cavity and distortion of the rib cage. Inward rib collapse, rib cage distortion with progressive verticalisation of the ribs, thorax constriction and scoliosis reduce the space available for the lungs to grow and allow breathing. This leads to the development of thoracic insufficiency, with the thorax unable to support normal lung growth and respiration (Livingston, et al. 2015). The spinal curve can also make it more difficult to be sit. The patient may lean to the side, requiring support of the arms, which can lead to decreased freedom for the upper extremities to function or perform other daily activities. Spine curve can also cause pain (TREAT-NMD, 2017).

Assessment

- Inspection of the spine as part of routine clinical examinations (scoliosis, kyphosis, lordosis, pelvis, spinal mobility/rigidity and shoulder levels and scapulae)

- When kyphoscoliosis is suspected on clinical examination, anterior posterior (AP) and lateral projection (LL) spine radiographs are indicated for the best functional level maintained by the patient (sitting position in children who can sit independently, standing in walkers and lying down for non-sitters) to define and quantify the extent of spinal deformity. The measurement used is called the Cobb angle, which is measured by determining the most tilted spinal bones (vertebrae) in each curve. Radiation exposure due to repetitive x-rays should not be ignored and radiation should be kept to a minimum.

- For non-sitters and sitters, scoliosis >20° (Cobb angle) should be monitored every 6 months by X-ray, until skeletal maturity and once a year after

skeletal maturity. This is because spinal curvature can still progress into adulthood. The flexibility of the spine should also be monitored. For angles more than 20°, bracing may be used along with routine monitoring. If the Cobb angle progresses more than 40-50 degrees and the patient is not able to wear a brace, surgery should be considered. If the Cobb angle progresses more than 10 degrees per year, surgery could be indicated (Mercuri, et al. 2018).

Interventions

The overall goal of interventions focusing on the spine are:

- To slow progression and delay definitive treatment
- Straight spine over a level of the pelvis
- Maximise comfort, positioning, and ease of care
- Maximise lung growth and trunk height
- Maintain flexibility

In attempting to treat scoliosis, conservative (non-operative) or operative methods are possible. For orthopaedic surgeons, the timing of surgery is crucial to allow maximal growth and prevent deterioration of pulmonary function.

Non-operative methods

There are no known, well-researched, non-surgical ways to prevent the spine from developing scoliosis.

In younger patients, when scoliosis arises before skeletal maturity and end of linear growth, a major therapy is to control positional curve, for both non-sitters and sitters, and should be practiced from an early age.

Bracing is ineffective in halting curve progression in non-sitters and sitters and can cause the constriction of chest wall and impact negatively on pulmonary function, so the impact should be considered in patients with respiratory weakness. A patient-centric approach is important when choosing the type of brace that will be used (Mesfin, et al. 2012). Bracing does not halt curve progression, and surgical intervention becomes necessary after several years of evolution. On the other hand, bracing will lend support to the trunk and spine of the child to better perform activities of daily living and slow the curve progression. Braces can be beneficial also for the patient when transitioning from non-sitter to sitter phenotype, in patients who are able to sit only with the support and to maintain a comfortable and straight seating position (Mesfin, et al. 2012). The limited success has been achieved in walkers and indications for use should be discussed individually.

Goals of “positional curve control” are to correct positioning and balance while sitting, permit the arms to move more, keep the spine straight, relieve pain and delay definitive treatment.

Positional curve control could be done by:

- **Special seating devices**: can be added to a wheelchair or specialised stroller, such as a custom seat back, lateral chest supports, and shoulder or chest straps. Special, individual moulds can be helpful in this regard also. A special orthopaedic chair might be used.

- **Wheelchair modifications** – wheelchairs should be fitted individually in order to prevent abnormal posture, scoliosis and pelvic obliqui-ty. This could happen when the seat width is too wide, back support height is too low, only one leg rest is being used, footplates are set at unequal heights, armrest height is too high or too low. For further information about proper seating and positioning for long term care see the following link: https://hub.permobil.com/blog/pelvic-obliquity-understand-what-you-are-looking-at-and-how-to-position-a-resi-dent-with-an-obliquity

- **External bracing** - has been a major therapy in children who still have lots of growing to do. A brace or body jacket is meant to support the trunk to allow for better activities of daily living and better seating. It is hoped that it will delay the progression of the curvature, allowing the child to grow more, but almost certainly has no effect on the early development or eventual progression of the curvature, and may even interfere with the respiratory function. External bracing has a potential for worsening pulmonary function, although the effect of different designs of the brace itself is still unexplored (Tangsrud, et al. 2001).

  There are many variations in favoured bracing techniques. The hard-shell thoraco-lumbo-sacral orthosis (TLSO) refers to a general category of brace that moulds the trunk from below the arm to the level of the pelvis. A TLSO can be used to help keep the flexible spine straight and keep the child upright. A soft or semi-rigid spinal orthosis is recommended for sitters, despite there being no consensus on the type of brace that should be used (TREAT-NMD, 2017). Specific rigid braces that secure the head and neck as well, allowing a stable sitting position may be used in non-sitters if they do not compromise pulmonary function and nutrition (in children with PEG). The brace should be custom-made based on the characteristics of the patient, functional and respiratory status and fitted by a specialist (an orthotist) (Mercuri, et al. 2018; TREAT-NMD, 2017). Comparison between one bracing technique and another is difficult because of differences in method, measurements and population between institutions and internationally.

  Another commonly used spinal orthosis is Garches brace (GBs). This type of

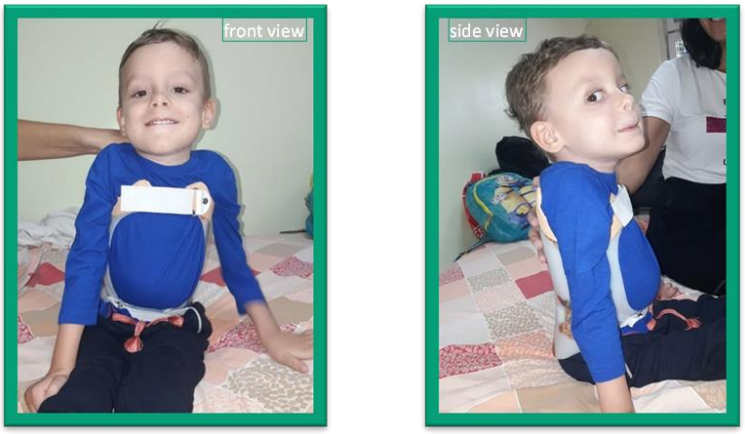
brace has been used in France for many years. It is multi modular, allows for setting adjustments, avoids thoracic compression and facilitates transfers and sitting position in hypotonic patients (Catteruccia, et al. 2015).

External bracing tends to work best in patients with broad "C" curve deformities characteristic of SMA, when less than 45 degrees. The literature and recommendations (Mercuri, et al. 2018) support the use of a brace after a curve reaches about 20 degrees. If the scoliosis is less than 20 degrees, it is recommended to monitor the spine and be proactive in terms of proper sitting and positioning of the child.

Many factors affect the success of bracing, including age, height, obesity, degree of skeletal maturation, residual spinal flexibility, presence of G-tube and tolerance to bracing, which may become even worse as muscular weakness worsens.

In summary, there is no study which shows whether a brace or special seating is more effective in delaying progression in the long-term. However, they are the best as a temporary therapy intended to permit more growth before definitive spinal surgery intervention (Fujak, et al. 2013).

Some authors suggest that early onset of scoliosis in SMA could be treated with growing rods successfully, while posterior spinal fusion should be done in older patients (Mesfin, et al. 2012).



Operative methods

The goal of surgery is to provide a stable, corrected spine above the pelvic level and maintain balance. Surgery can also give the lungs and internal organs room to grow and fully develop, improve breathing and quality of life overall. Patients can be free of braces which improves their comfort and functionality (Modi, et al. 2011).

The need and the timing of an operation for scoliosis in SMA is based on number of factors. If surgery is being considered, the aspects of interventions should be discussed at great length with families and their doctors. If one has chosen to proceed with surgical intervention “at some point”, it remains optimal to proceed while the spine is still flexible and pulmonary function is still adequate. Delaying surgical intervention can result in inadequate pulmonary function to support surgery, poor outcome and increased surgical risk. The patient should begin to prepare 3 months prior to surgery with rehabilitation to increase spine flexibility and soothe soft tissues and nutritional and respiratory care to allow the best surgical result and avoid complications.

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The most important factors to be considered in making the decision to proceed with spinal surgery are (Mercuri, et al. 2018; TREAT-NMD, 2017):

- Skeletal maturity and the age - since these two usually do not match, skeletal maturity can be established by taking X-ray of the bones in the left wrist.
- Spinal curve Cobb angle (if the major angle is >50 degree)
- Rate of progression of the curve (>10 degrees/year)
- Respiratory function (if the curve interferes with pulmonary function)
- Unbalanced sitting (hips and pelvis are positioned unevenly)
- Chest wall shape and rib cage collapse
- If the curve is causing problems with day-to-day activities, pain in the back or in the hip
- Hyperkyphosis

The surgical approach depends on clinical variables, but the most important ones are skeletal maturity (after 5 years of age), degree of spine curvature and rate of progression as main indicators (Cunin, 2015). New recommendations are based on different approaches in spinal surgery, mostly according to age (Figure 1).

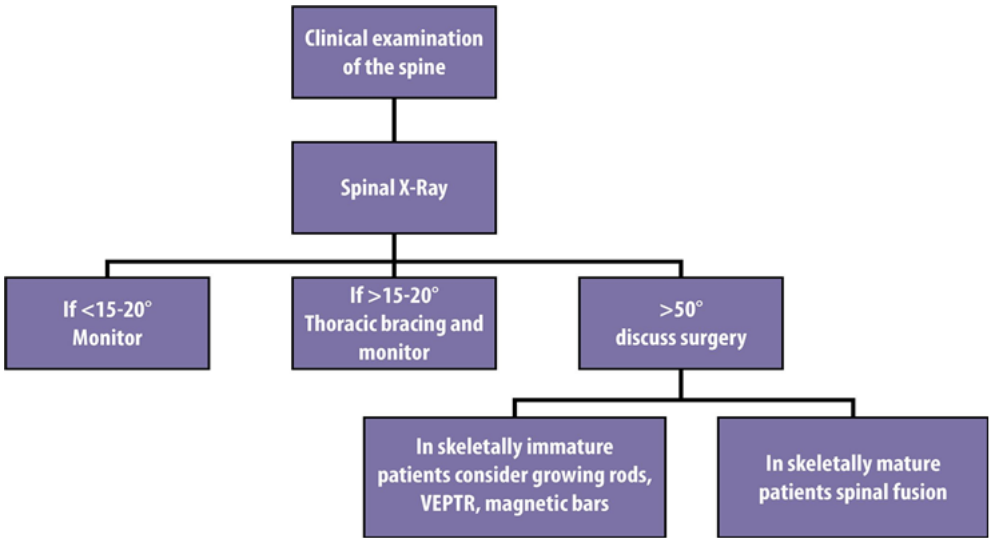


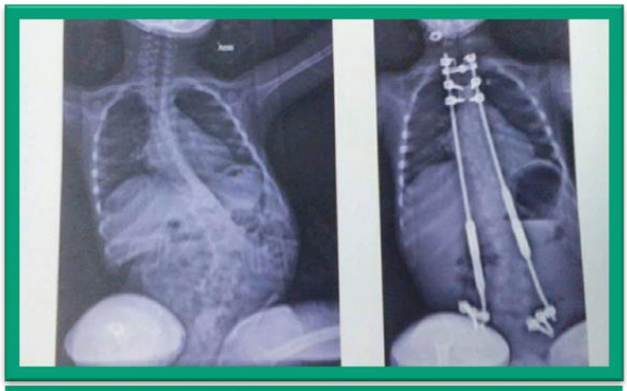
FIGURE 1: Management of scoliosis in spinal muscular atrophy

There was consensus that one or two mid-lumbar levels should be left unexposed in the midline to accommodate intrathecal access for the new drugs. Conversion of growth-friendly instrumentation to definitive posterior spine fusion should be decided on a case-by-case basis (Mercuri, et al. 2018).

The two general types of scoliosis surgeries are:

- **growing constructs** – these are growth-enabling spinal stabilising technologies that have emerged since 2000. Placement of "growing rods" (GRs) that are anchored at the ends with telescoping connectors midshaft, can be extended periodically to accommodate spinal growth. The spinal curve is straightened as much as possible when the rods are placed, then every six to nine months the rods supporting the spine are gradually lengthened with repeated surgery. GRs improve trunk height and the space-available-for-lung ratio while controlling curve and pelvic obliquity in young patients with SMA with severe scoliosis, but they do not halt rib collapse. Despite many advantages, repeated surgery has a substantial risk for surgical and anaesthetic complications. Before any operation, the multidisciplinary medical team should carry out a full evaluation of health, especially respiratory function (McElroy, et al. 2011).

  Magnetic growing rods (MAGEC), novel, non-invasive devices that extend the rods midshaft with an external magnetic device. These were introduced first in 2013 and allow lengthening without the need for repeated surgery (Akbarnia, et al. 2013).



X-Ray of the spine before and after magnetic rod surgery

Vertical expandable prosthetic titanium rib (VEPTR) - a device which expands the thorax as well as stabilises the spine. This device is attached superiorly to the ribs, and the spine or pelvis inferiorly, propping up the descended ribs associated with SMA (Abol Oyoun, Stucker. 2014). A retrospective study of children treated with either rib or spine-based growth-friendly instrumentation systems have shown poor efficacy in ameliorating chest deformity or increasing thoracic volume and therefore are not recommended. There is a concern that over time it may lead to stiffening of the chest wall, complications of repeated surgeries and weakness of the patient (Livingston, et al. 2015).

- **definitive spine fusion -** Spine fusion surgery permanently fuses the vertebra. The fusion of the vertebra takes place between the individual segments or parts of the spine, much as it would between the two ends of a broken bone in one's forearm. Standard posterior (from the back) fusion with instrumentation (rods, hooks, screws and wires) is usually undertaken. Spinal fusion technology encompasses unit rod technology or pedicle screws plus unit rods. The rod is fixed to the spine at frequent levels by hooks or latter screws, inserted into spinal pedicles. This permits much greater corrective forces and eliminates the need for onerous postoperative immobilisation. This technology remains favoured for individuals who have finished or nearly finished growing.

  The most significant concerns with this surgery include pulmonary or ventilation concerns, blood loss, infection, and the impact on nerves.

  There is also concern about the progression of curvature after spinal fusion if there is the continued growth of the spine; this is more of a concern in younger children and when only short segments of the spine are fused (Zebala, et al. 2011).

  No motion or growth can occur over the levels where the spine is fused. Patients lose their pre-surgical abilities to leverage movements of the trunk to facilitate that of the limb, which is important in those with severe weakness (Granata, et al. 1993).

Postoperative care

Most children stay home anywhere from two to five weeks following this surgery, to regain their strength. Gradual progression of activities is warranted. Certain activities, such as bending and lifting, must be done in a cautionary manner, until the bone has fused in completely around the metal rods (six to twelve months). Sometimes, a post-operative brace may also be helpful to protect this area. Adjustments in the chair will be necessary. Physical therapy helps to maintain thoracic expansion and flexibility. Daily respiratory rehabilitation exercises are strongly recommended.

Pelvic obliquity and hip deformity

Classic triadic deformity with prominent thoracolumbar (TL) scoliosis curve, which continues into the sacrum, are pelvic obliquity and hip subluxation on the high side of the pelvis. Simultaneous progression patterns of scoliosis, pelvic obliquity, and hip subluxation/dislocation in non-ambulatory neuromuscular patients was investigated in 211 patients (Patel, Shapiro, 2015). Of 211 patients, 49 had an SMA diagnosis. Most of them were type II (non-ambulatory), with only few type I patients (either supine or semi-sitting as their maximal functional level) and type III patients, which became non-ambulatory towards the end of the first decade of life. In 10 SMA patients, spine deformities developed more rapidly than hip deformities, in 15 patients, scoliosis and hip deformity developed at the same time. In one patient, hip deformity developed more rapidly than spine deformity. In the weakest patients (SMA type I and some type II) both hips may dislocate very early. Another SMA patients had TL scoliosis with or without pelvic obliquity greater than 2 degrees. In Type III patients, 10% had minimal scoliosis.

The underlying causes of these three inter-related deformities are asymmetric muscle function due to weakness and positional deformity that worsened as irregular growth of soft tissues and skeleton is superimposed on the abnormal position. Deformity of each component tends to develop early in the first decade (2-5 years) in type II patients. The earlier the triad develops, the worse the deformity.

Severe lumbosacral scoliosis (LS) contributes to pelvic obliquity - scoliosis invariably extends beyond L5 vertebra to the sacrum. Scoliosis leads to an associated pelvic tilt or obliquity since there is no space for a compensatory scoliosis correction at the lowermost spinal levels. As the pelvis tilts, the hip on the high side begins to sublux (the acetabulum that tilts away from its normal coverage of the femoral head). The entire pelvis tilts with the low side adjacent to the convexity and the high side to the concavity of the scoliosis curve.

The triad deformities are flexible early in development and passively correctable, then partially rigid and eventually markedly rigid due to soft tissue contractures and bone deformity. Pelvic obliquity and early flexibility are recognised in the scoliosis literature and when obliquity becomes rigid, its correction is one of the reasons why spinal fusion is extended into the pelvis (Bui, Shapiro. 2014).

Orthopaedic surgeons, together with the multidisciplinary team, have to determine the frequency of radiologic assessments to outline deformity status, maximal functional level, progression, flexibility/rigidity of each of spine, pelvis and hips and show a close relationship between these deformities.

Hip development in SMA is affected by weakness, including significant gluteal weakness, looseness of ligaments and absence of weight bearing (standing) (Sporer & Smith, 2003; Zenios, et al. 2005).

In children with SMA, several changes can occur:

- Dislocation: the top of the femur bone is out of the hip socket
- Dysplasia: shallow hip socket (acetabulum)
- Subluxation: the femoral head is not covered completely by the hip socket

A pelvic tilt (obliquity) can lead to an increasing hip deformity. Subluxation and dislocation of the hips are common in patients with intermediate forms of SMA (Zenios, et al. 2005). In milder forms migration percentage of the femoral head (dislocation) is in positive correlation with the age of the patient and scoliosis (Granata, et al. 1990).

A hip deformity can be shown by a loss of motion. There may be decreased abduction, the muscles in front of the hips may develop tightness, and the legs may both point to the same side (windblown). Feeling or hearing a “click” or “clunk” of the hip may mean that it is moving in and out of the socket. A dislocated hip can become painful and make sitting difficult, but it is in the most cases not painful because of the patient’s hypotonia. Due to the muscle weakness, the dislocated femoral head generates little tension against surrounding muscles (Mesfin, et al. 2012; Sporer & Smith, 2003).

Assessment of the hips Interventions

- Physical examination during every visit by an orthopaedic surgeon (neurologist or physiotherapist)

- An x-ray of the hips can be taken if there is a concern for a hip problem (pain during mobilisation of the hip or limitation of hip abduction).

Intervention

The goal is to keep the hips in the socket. The long-term focus is to have minimal or no pain and to keep activities, such as going to the toilet, dressing or sitting less difficult.

There are no known, well-researched, non-surgical ways to prevent the hip from subluxation or dislocation. Some actions can be taken in order to prevent hip deformities in all types of SMA severity:

- Correct positioning in the stroller or wheelchair with adaptation as the child grows

- Standing with support as long as it is tolerated, to promote weight bearing

- Walking with or without orthoses
- Maintain flexibility and range of motion by physical and aqua therapy (motion exercises)

- Positioning the legs in an abducted position using a pillow, brace or foam wedge in non-sitters

Surgical treatment of hip deformities - a lot of controversy surrounds the management of hip disorders by surgical interventions in children with SMA. Older studies usually recommend against surgical repair (Mesfin, et al. 2012; Zenios, et al. 2005; Granata, et al. 1990; Sporer, Smith. 2003).

The goal of treatment for hip subluxation or dislocation is reducing symptoms as pain, which can be achieved with assistance of a pain therapy specialist.

If the patient is experiencing any pain, surgery is not recommended due to a high rate of recurrent dislocation with surgical intervention (Mesfin, et al. 2012). The long-term follow up of hip deformities in a cohort of SMA patients with natural history, showed that pain and functional difficulties (positioning, skin and perineal care) were not significant or even present. The authors suggested observation rather than surgical intervention in SMA patients with hip dislocation (Sporer, Smith, 2003).

Unilateral and bilateral hip instability should be managed with other interventions only in patients with significant, chronic pain with sitting or threatens independent ambulation, despite physiotherapy and positioning treatment:

- Intra-articular injections of corticosteroids and anaesthetics (Tangtiphaiboontan, et al. 2018).

- Femoral head and neck resection in case that all other interventions fail, to relieve hip pain.

Total hip arthroplasty is not recommended because of poor quality of the bone.

Joint contractures

Joint contractures are common in SMA. A contracture is a fixed tightness around the joints caused by shortening of muscles due to decreased movement. They contribute to increase disability by reducing the functional range of motion (ROM), loss of function for activities of everyday living and can cause pain in the joints. Pathogenesis of contractures is

multifactorial and due to extrinsic and intrinsic factors. Extrinsic factors responsible for contractures development are:

- Decreased ability to move a limb through its full range of motion
- Static positioning for a prolonged period of time, which results in shortness of muscle length
- Asymmetrical strength between flexor and extensor muscles in major muscle groups (agonist-antagonist muscle imbalance).

Intrinsic factors which contribute to contracture development, are infiltration of muscles by connective tissue (collagen) and adipose tissue. Fibrosis and fatty tissues replace chronically shortened resting muscle length. Contractures arise and resistance of the joint to passive stretch.

Lower limb contractures are more prevalent than upper limb contractures. They usually rapidly develop in SMA patients after the loss of ambulation and transition to a wheelchair. They can appear at any age and stage of the disease, they can occur in any joint, on one side or both and can progress rapidly or slowly.

The range of motion is reduced by 20 degrees among 22% to 50% of SMA type II patients, depending on the joint. The most prevalent are knee, ankle and hip contractures respectively. Lower extremity contractures are rare in SMA type II and ambulatory type III patients (Skalsky, McDonald. 2012). The upper limbs are less affected by contractures, and if they are, it is more commonly proximally. Limitation in shoulder elevation is most prevalent and important, due to the great discomfort in performing daily activities. Extension and supination of elbows and wrists are less common, but still occur (Fujak, et al. 2010) and increase progressively with age. Among those who use a wheelchair, knee and hip contractures are almost universal.

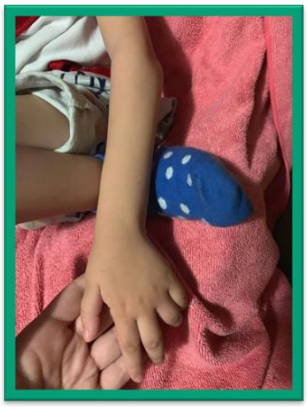
Finger flexion contractures on the hand are not common in SMA, like in dystrophies (Skalsky, McDonald. 2012)

Flexion contractures of the fingers

Chronic foot deformity is very common, which directs the foot in a planovalgus position. The deformity itself is not painful and should not additionally impair ambulation in those who have limited ability to walk. Those with milder SMA develop an equinus deformity with hindfoot varus, which may make them be unstable for walking. Prospective passive stretching in the early years is found to be beneficial to anticipate severity. Operative management may be helpful for ones who are able to walk with or without assistance. Foot surgery in those who are not walking is not justified and could just be a cosmetic concern.

Ulnar deviation of the hands and wrists is a common finding in SMA. It does not contribute much to hand dysfunction unless severe. Bracing is of little values and operative correction

is not so successful in restoring normal configuration of the wrist without disrupting residual function.



Ulnar deviation, left arm in a 4 year old sitter

Assessment

Contractures can be assessed by determining the range of motion (ROM) of the child's limbs.

ROM is the measurement of movement around a specific joint or body part. It is measured by moving the limbs to see how much flexibility they have, using a goniometer, an instrument that measures the angle at joint. Goniometers show the degree of an angle from 0 to 180 or 360 degrees. It is available in different shapes and sizes for the joints. Another tool that measures a joint angle at extension and flexion is an inclinometer, for measuring the spinal angle. Clinical examination with ROM evaluation should be performed by physiotherapists every 6 months.

This will include:

- Hip and knee flexion contractures, ankle and hind foot movement, knee valgus if severe, elbow flexion contractures, loss of supination and wrist and finger tightness including wrist deviation
- Neck range of movement (flexion/extension, rotation, side flexion and neck contours)
- Joint hypermobility as well as contractures (Main, 2019)

Management of contractures

The overall goals are to:

- Prevent the development of contractures and anticipate them where possible
- Keep the present contractures from getting worse

Interventions are directed to non-invasive approaches. Surgical interventions might be required for fixed, advanced contractures. Conservative management of joint contractures is based on prevention using orthotics and physiotherapy exercises.

Prevention: early diagnosis and initiation of a physical medicine approach are most important, before or while the contractures are mild. This includes ROM exercises and stretching, positioning of the limb, standing and/or walking and splinting/bracing.

ROM exercises and stretching are mandatory for all of the joints in the arms and legs, done at a gym, in water or stretching at home, with educated physiotherapists, including education of patients and families. Stretching can be passive (performed by someone else), active assistive or active. The amount of stretch in a muscle depends on many factors, including how long the contracture has been present. Stretching should always be in the line of muscle pull, done slowly, never trying to do more than the patient can do and never causing pain. All joints should be stretched, including neck and vertebra. A stretching programme should be done on a daily basis, for a minimum of 30 minutes (Main, 2019). Passive (performed by someone else), active assistive or active stretching of the elbow flexors are recommended and may be combined with a stretch into forearm supinators. Occupational therapist (OT) management of wrists and hands range of motion is recommended to slow the development of contractures and to maintain fine motor skills (Skalsky, McDonald. 2012).

Whether or not and to what degree development or worsening of established contractures can be prevented by stretching exercises, is more the provenance of strongly held opinion than that of evidence-based data. Once developed, anything more severe than a minor contracture is not correctable by even vigorous passive stretching (Skalsky, McDonald. 2012).

The positioning of the limbs to promote extension and oppose flexion implies lower limb positioning in a rest position that opposes or minimalises flexion. Positioning the feet in a wheelchair is important too (footplates and legs rests should be properly positioned). Prone lying position is an effective method to stretch the hip flexors. Appropriate seating is important to maintain good posture, reduce Iliotibial (ITB) tightness and reduce fatigue (Skalsky, McDonald. 2012).

Standing and/or walking should be regularly done, in addition to stretching. A stander could be used to provide a stretch in lower limbs joints. Orthoses could be used also to maintain the flexibility of the hips, knees and ankles (Skalsky, McDonald. 2012).

Splinting/bracing is another adjunctive measure used to slow the development of contractures, maintain and pro- mote a range of motion and function. Splints support or immobilise a limb. Braces which are similar to splints are used to support part of the body to help stabilise and promote movement. To be effective in improving flexibility, splints should be used on a daily basis (Mercuri, et al. 2018).

Ankle-foot-orthoses (AFOs) during the day and night-time as resting splints have been used to maintain a good angle of the foot relative to the tibia together with flexibility at these ankles, especially in walkers. These are also recommended in sitters. Long leg knee-ankle-foot orthoses (KAFO) which immobilise the knee in extension may be worn for ambulation, for standing, or as a night resting brace (Skalsky, McDonald. 2012).

Ankle contractures on a non-sitter, with taping and proper positioning in bed

Night-time resting splints which promote wrist extension and finger extension (hand splints) should be advised: daytime positioning splints should also be worn to emphasise wrist and finger extension. Mobile arm supports are an option for shoulder weakness, but are rarely accepted by patients.

Serial casting which puts the limb into a series of plaster casts over a period of time, slowly correcting the position with each recasting, could be applied and changed frequently with taping under the cast (Main, 2019).

Bracing of a stiff deformity is often painful and may cause pressure sores and is not recommended.

Surgical management of joint contractures

Despite all preventive measures, surgery might be necessary. Surgical management of lower limb contractures should be considered when they cause pain or impair function (most often on the ankle). Splints or orthoses should be applied after the surgery (Mercuri, et al. 2018; Main, 2019).

Upper limb contractures rarely require surgical intervention, only when reduced upper limb range of motion is impending care and hygiene (Skalsky, McDonald. 2012).

Bone fractures

Broken bone (fracture) in children with SMA, is due to the reduced measured bone mass (osteoporosis), especially in non-sitters and sitters. For more about bone mineral density, see Nutritional management. Fractures of the long bones (femur, lower leg and upper arm) occur relatively frequently. Vertebral fractures can be frequent and are of- ten undiagnosed. The only symptom can be back pain (Baranello, 2019). Fractures could be caused by minimal or no trauma (fragile fractures) and are more common on the legs. Fractures can cause irreversible loss of motor skills (Vestergaard, et al. 2001). Osteopenia and osteoporosis are a consequence of immobility, but also due to low SMN proteins levels which plays role in bone metabolism through interactions with osteoclast stimulatory factor. Low vitamin D levels may also lead to an increased risk of fragility fractures in non-sitters

and sitters. In patients who are a walkers, fractures may occur accidentally, especially during puberty which may lead to loss of ambulation (Mercuri, et al. 2018).

Assessment

Bone health is assessed by checking Vit D3 level and calcium levels in the blood and by DEXA scanning.

DEXA scans of lumbar vertebrae are the most suitable method for measuring BMD because it is accurate, take shorttime, ease of examination, reproducible and has low dose of radiation. The frequency of examinations will depend on clinical symptoms and risk factors but are recommended yearly (Vai, et al. 2015).

Fractures are assessed by X-ray in case of clinical signs of fractures or pain or oedema.

Prevention

There are several different ways to try to prevent fractures from occurring:

Active weight-bearing exercise (standing in a stander or without support may improve bone strength). It is recommended to stand for more than 7 hours a week (2 hours per day, 5 days a week). For walkers, maintaining the child's ability to walk as long as possible will help maintain bone strength. Standing in a stander may be very difficult because of severe weakness in non-sitters.

Supplementation with Vit D3 and calcium in the event of insufficient dietary intake.

Caregivers should be cautious when moving the patients' arms and legs

Interventions

If a fracture does occur, it could be treated in two ways:

Casting or soft splints are recommended for non-ambulatory patients. As fractures are rarely displaced, children treated with splinting until the pain resolves should be followed by rapid return to activity. Cast immobilisation should not be prolonged (>4 weeks) because it aggravates muscle wasting and osteoporosis (Vai, et al. 2015).

Surgery is recommended for walkers. Surgical stabilisation using intramedullary rods or bridging fracture are often used. If a child who walks is put in a leg cast or has been operated on, it is important to get them back up and walking as soon as possible.

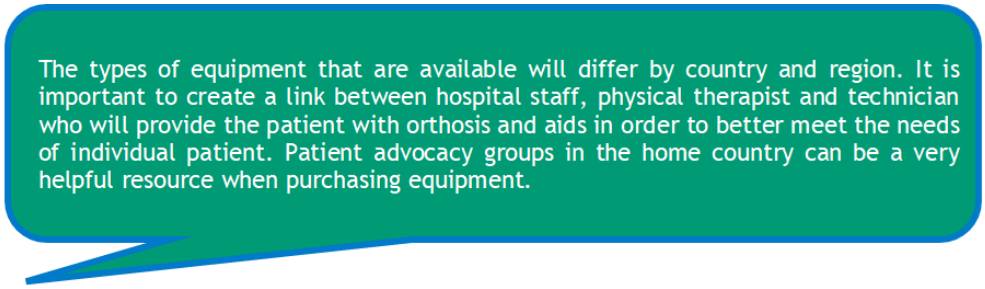
Bisphosphonate therapy as prevention to bone fractures is not recommended. A Cochrane review from 2007, suggests that while short-term (less than 3 years) bisphosphonate therapy is well tolerated, the sum of evidence does not support bisphosphonate as standard therapy to prevent fractures (Ward, et al. 2007).

Many orthopaedic specialists confine bisphosphonates use to those with SMA who have had a pathological long bone fracture that can strengthen the bones.

Physical therapy

Complications of spinal muscular atrophy can be alleviated by regular physiotherapy (PT). Physiotherapy is one of the key components in the management of patients with SMA. It helps to minimise the complications of the disease and maintain functional ability of patients (ability to perform daily activities), so they can have a good quality of life. Early intervention is the most effective approach for patients with SMA.

The choice of assessment of functionality, support and equipment are individual and reflect the aspect that are more relevant for the level of severity (e.g. in non-sitters and sitters more important are muscle weakness, postural control, contractures, chest wall deformities, pulmonary function, fractures and pain, while in walkers more important are mobility, asymmetry, fatigue, contractures and inflexibility).



Physical therapy management is not based on the classification of SMA severity; it is based on the individual with specific difficulties and problems. Physical therapy programs must reflect current functional status of the patient and support the patient's goal. Daily physical therapy is necessary to maintain motor function and optimise muscle condition and force (Arnold, Kassar & Kissel, 2015). The aim of physical therapy is to promote function by maintaining/ improving power, preventing/reducing contractures, promoting/ maintaining mobility and reducing postural asymmetry. Priorities should be prevention of secondary consequences of the disease, maintenance or improvement of motor skills and function, pain free function, and, overall, reduced burden of care and independency as much as functional status permits (Mercuri, et al. 2018).

An important principle of physiotherapy is to promote education of the patient and family, promote a global approach, maintain the patient's motivation and help patient and the family to manage at home.

Assessment

Regular physical therapy assessments provide the information required to adjust individual physical therapy programmes and improve quality of life. Assessments should be patient centric and aligned with the patient's functional status and age, as well as their clinical progression over the time (Trabacca, 2020). Assessments should be routinely done every 6 months by trained examiners, unless there are some circumstances that require a different

follow-up. Regular monitoring by examination is recommended in order to identify changes over the time, identify complications and assess response to intervention (Mercuri, et al. 2018). Substantial loss of functional activities correlates with an increase in joint contractures, sudden scoliosis and excessive weight gain.

Clinical examination is the same for all patients with SMA regardless of functional status and allows identification of clinical features (Mercuri, et al. 2018):

- Postural asymmetries - scoliosis, chest deformity and hip dislocation (in sitting, standing if possible, even in orthosis, and lying if necessary - position of head in relation to body, shoulder heights and scapulae, waist contours, level of pelvis, knee heights, foot posture, weight bearing and non-weight bearing, contractures, sitting ability, sitting tolerance)
- Range of motion (ROM)
- Strength and Power - strength is assessed in all patients and myometry is used for most sitters and walkers, but could be used in non-sitters in upper extremity muscles
- Pain
- Positioning and braces
- Communication skills

Functional examination identifies specific limitations in the function of daily activities and can be used to track or describe disease trajectory (Arnold, Kassar & Kissel, 2015). For the functional assessment physical therapists use functional scales. Which functional scale will be used, depends on patient's functional status and age. Recommended functional scales in the assessment of non-sitters, sitters and walkers are:

- For all patients with SMA (ambulatory and non-ambulatory), from 2 years of age and older – Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM) and Motor Function Measure-32 (MFM-32). It can also be used to track or describe disease trajectory

- For patients with SMA who are under 2 years of age – Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and Hammersmith Infant Neurological Exam Section 2 (HINE-2).

- For patients with SMA who are non-sitters and over 2 years of age – there is currently no validated scale sensitive enough to assess motor skills. For these reasons, many centres use CHOP-INTEND or HINE-2 to track trajectories. Recently, a new scale has been developed to assess older patients who are non-sitters (Adult Test of Neuromuscular Disorder – ATEND), which is still in the validation process and will be used to assess older, weaker patients with SMA (Duong, et al. 2020).

- For patients who are walkers – the 6-minute walk test (6MWT) is a specific functional test which measures maximal distance an individual can walk in 6 minutes over a 25-meter linear course. It is a reliable measure of fatigue and walking ability. Other functional assessments in patients with SMA that can walk are mobility and gait pattern (speed, symmetry, distance) and timed tests (10-meter walk or run test, time to rise from the floor, timed up and go (TUG), timed dexterity tests, timed writing test).

Rehabilitation

PT treatments which are fun, engage the whole family and are part of everyday life, are more likely to get done and be more effective.

The primary rehabilitation goals for non-sitters are to reduce the impact of tight joints, optimise function and help people tolerate different positions such as sitting with assistance. Consequences of impaired movement in patients with SMA who are non-sitters are reduced perceptual, visuomotor and language development and compromised emotional and cognitive development.

For sitters, the main objectives are to reduce the impact of tight joints keeping them flexible and to prevent curving of the spine (scoliosis), as well as maintaining a range of movement and promoting function.

For walkers, the aim is to maintain, restore and promote maximum mobility and function, overall range of movement, improve balance and stability, and as much independence as possible with day-to-day activities.

Positioning

Non-sitters

- Daily use of a seating system and postural support (rolls, beanbags, moulded pillow and wedges to support supine positioning)
- Custom and moulded wheelchair seating system and sleeping systems
- Thoracic bracing with abdominal cut outs for respiratory support
- Cervical bracing for head support
- Strollers and power wheelchairs with a recline or tilt option and adapted sitting systems

Sitters

- Thoracic bracing for posture and functionality (TLSOs)
- Cervical bracing for safety and to support patient during transportation
- Static, dynamic, and functional orthoses for positioning, supported standing and supported ambulation (KAFOs, AFOs hip (H)-KAFOs). Supported standing will help with stretching of the lower limbs, promote

spine and trunk posture, decelerate contractures, reduce scoliosis, improve respiratory function and enable social participation (Mercui, et al. 2018).

Walkers

Braces worn around the chest and spine can be used if needed. Dynamic ankle braces (AFOs) can be used for flexibility during rest and shoe inserts, or SMOs to maintain foot alignment when walking.

Stretching

Non-sitters and sitters

- Active-assistive and passive stretching (pain-free manual stretching) as the easiest way to prevent contractures
- Splints for upper and lower limbs for stretching and promoting range of motion and function (arm splints, knee immobilisers, hand splints, AFOs, KAFOs)
- Thoracic bracing (TLSOs)
- Cervical bracing
- Serial casting
- Supported standing with specific adaptation in some cases (gait trainers and walkers, KAFOs, AFOs, H-KAFOs)
- Standing frames helps maintain bone health, digestion, blood circulation, respiration, promote good trunk posture and good posture of lower limbs.
- Supported standing should be up to 60 minutes with minimal frequency of 3-5 times/week, optimal 5-7 times/week. Standing for more than 1-hour bouts is not recommended (Mercuri, et al. 2018)

Session duration for effective stretching will depend on the specific needs of the patient and rehabilitation goals (Mercuri, et al. 2018).

Walkers

- Passive stretching – the focus should be on the ankle and hamstrings for ambulant or transitioning patients
- Active-assisted techniques
- Supported standing (ankle-foot orthoses – AFOs, knee-ankle-foot orthoses - KAFOs) to maintain flexibility, posture and the function of the knee and ankle

Maintaining the range of motion is critical, because even the smallest deviations from a normal range of motion may put patients who can walk in a risk of becoming non-ambulatory (Salazar, et al. 2018

Mobility and exercise

Non-sitters

- Assistive technology and adaptive equipment are recommended (eye movement tracking devices, upper extremity actuators, mobile arm supports to assist upper extremity function, bath equipment, adapted beds, strollers with recline and the ability to lay flat, power wheelchairs should have recline/tilt, adapted seating systems).

- Complementary approaches to increase mobility and assist with contractures are hydrotherapy with head and neck support, taping and massage therapy. It is important to keep moving through mobilisation, play time that incorporates lightweight rattles and switches and specific exercises.

Standing frame with arms suspension for non-sitters

(at the back is a BiPAP machine connected to a tracheostomy tube)

Stander for sitters (1,5 years old) with good control of the trunk and head

(aimed for forward anchor in contrast to stander for type I which is backward)

Sitters

- Submaximal aerobic exercises (swimming, hippo-therapy, wheelchair sports, aerobic and general conditioning exercises with or without resistance) are strongly recommended for maintaining and improving function, pain management, caloric expenditure and psychological impact. During every exercise, it is important to promote symmetry between sides and muscle groups in terms of postural symmetry, frequency and intensity of the exercises.
- All sitters should have electric/power wheelchairs with custom postural support and seating systems (for children as young as 3 years old)
- Lightweight manual wheelchairs or power assist wheels are ideal to promote self-propulsion in stronger patients
- Use of seating and mobility systems
- Use of gait training devices and mobility devices to promote supported ambulation
- Mobile arm supports to assist upper extremity function.
- Any type of activity, hobby or sport that the patient enjoys

Walkers

- For ambulatory patients, exercises are similar to those for patients with SMA that are sitters. Recommended aerobic and general conditioning exercise (swimming, walking, cycling, yoga, hippo-therapy, rowing, elliptical/ cross-trainers). Exercise programmes should be designed and monitored by a physical therapist familiar with SMA. Fatigue is an important factor, and the therapy sessions must be concluded before the patient becomes exhausted.
- Lightweight manual wheelchairs or ones with power-assisted wheels may be useful due to the tiring effort it takes to walk (for longer distances).
- Any type of activity, hobby or sport that the patient enjoys

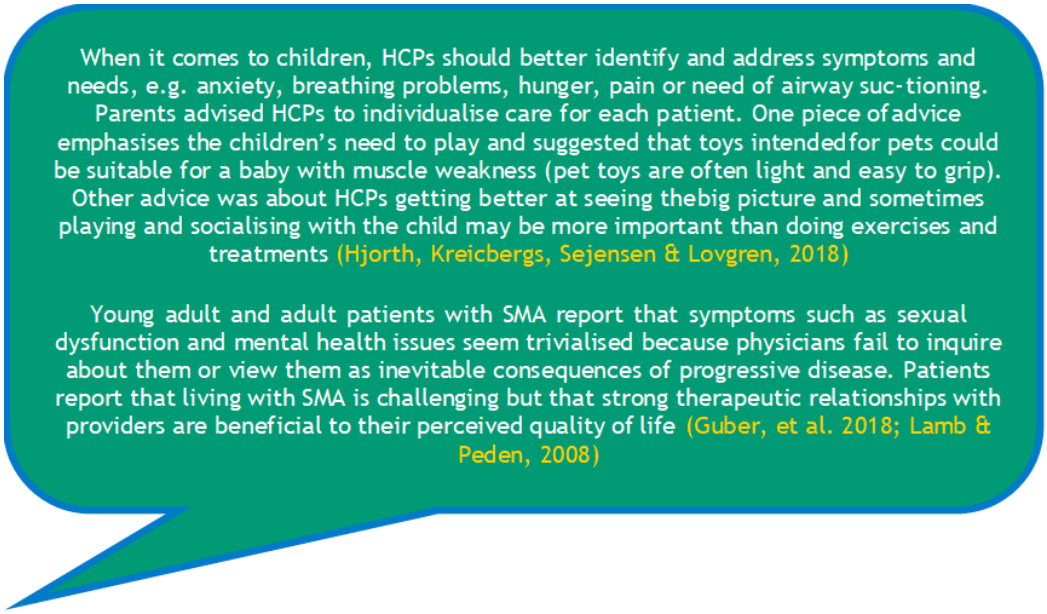
Overall, there is inadequate information to support a specific regime as best, though low resistance, high repetition exercises are generally favoured over specific strength-building regimes. Many individuals with SMA experience fatigue as a limiting factor for both exercise and daily functioning. The Cochrane review from 2019 suggests that it is uncertain whether combined strength and aerobic exercise training is beneficial or harmful to people with SMA type III, as the quality of evidence is very low (Bartels, et al. 2019). Well-designed and adequately powered studies are lacking, using protocols that meet international standards for the development of training interventions, in order to develop exercise guidelines for SMA.

Key takeaways

SMA is a complex disorder which requires a multidisciplinary approach, with a team of various specialists to manage the different aspects of care. A multidisciplinary team (MDT) should consist of a neurologist, an orthopaedic doctor, physical therapists and occupational therapists, pulmonologist, acute care specialist, anaesthesiologists, nutrition and swallowing specialists and primary care physicians. Other specialists should be consulted according to individual health concerns in patients with SMA. The MDT should be coordinated by the neurologist who is familiar with the disease, its course and complications.

Exchange of information between members of the MDT are crucial to ensure the best quality of treatment and follow-up of patients with SMA.

It is necessary to have a patient-centric approach to any complications and not to apply the same approach for all patients with SMA.



Conclusion

While there have been rapid advances in new therapies which change the natural history of the disease, the reality is that the best therapies will only be partially effective. Effective management of the complications of weakness remains important, along with research at all levels of impairments.

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NOTE: The quotes in green bubbles represent comments by patient advocates.