Irene L.B. Oude Lansink

Contractures in children with spinal muscular atrophy

Towards better mobility



UMC Utrecht Brain Center

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Contractures in children with spinal muscular atrophy

Towards better mobility

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Op weg naar betere mobiliteit

(met een samenvatting in het Nederlands)

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1

General introduction

Hereditary proximal spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder that causes progressive muscle weakness. Estimates based on incidence figures and survival rates and data from the national Dutch SMA database indicate that there are approximately 500–600 patients in the Netherlands. The incidence rate, defined as the number of new cases within a specified period, is approximately 1 per 10,000 live births[1]. This means that 15 to 20 children who will develop symptoms of SMA in the first years of life are born each year.

The genetic cause of SMA is the loss of function of the *survival motor neuron* (*SMN*) 1 gene on chromosome 5q [2]. More than 95% of patients carry a homozygous deletion of the *SMN1* gene; the remaining 5% of SMA cases is explained by the combination of a heterozygous deletion of one *SMN1* allele and a point-mutation in the second allele. Carrier rates of *SMN1* deletion are approximately 2–3%.

SMA is caused by a significant, although not complete, deficiency of intracellular SMN protein. Animal models have shown that the complete loss of SMN protein expression is embryonically lethal. The fact that SMA is a uniquely human disease (i.e. there are no equivalents in other animals) and its large variation in severity is explained by the fact that only the human SMN locus contains a second *SMN* gene (*SMN2*) that produces residual amounts of SMN protein. *SMN1 and 2* genes show a very high level of homology but differ in one critical nucleotide in exon 7 that alters splicing of mRNA; exon 7 is excluded from most of the SMN2 mRNA copies, which results in the production of a mostly shortened protein. The limited amounts of full length SMN protein are sufficient for early embryonal development, but eventually lead to dysfunction of motor neurons, which cause weakness with onset from the third trimester of pregnancy to early adulthood. This broad range of age at onset and hence severity is explained by the fact that patients with SMA carry between 1 (prenatal onset) and 5 (adult onset) *SMN2* copies. In general, a higher number of *SMN2* copies correlates with milder symptoms[3].

Deficiency of SMN protein causes degeneration of alpha motor neurons in the anterior horns of the spinal cord and disrupts the integrity and function of the neuromuscular junction. This reflected clinically by predominantly axial and proximal muscle weakness (or hypotonia in infants) and muscle atrophy[4]. The clinical phenotypes ranging from severe to relatively mild presentations are captured by the SMA classification system that distinguishes five types (types 0–4) based on age at onset and the highest motor milestones achieved[5–7]. Without disease-modifying treatments (DMTs), children with SMA type 0 typically survive only a few weeks. SMA type 1 presents within the first

six months of life, and affected children never achieve independent sitting. Without intervention, these children develop profound muscle weakness, feeding difficulties, and on average die from respiratory insufficiency before one year of age[8]. SMA type 2 typically begins between 6 and 18 months of age, and children achieve the ability to sit independently. SMA type 3 begins after 18 months of age and is further characterized by the fact that children achieve the ability to walk independently, although they often lose this ability during childhood or adolescence. Children with disease onset after the age of 3 years and in particular those with first symptoms in adolescence may walk far into adulthood. SMA type 4 refers to the very rare adult-onset forms of the disease.

Children with SMA experience progressive muscle weakness that significantly affects their quality of life by limiting physical abilities, independence, and participation. Many children require assistive devices and support for mobility and daily activities, which restricts their participation in self-care, play, and school. Among the many complications associated with SMA, joint contractures stand out because of their frequency and impact. Contractures limit joint range of motion (ROM) and hinder overall movement, thereby intensifying daily functional difficulties. Understanding how contractures develop and how clinicians can manage them in SMA is essential, as these contractures substantially affect children's daily functioning and development.

Contractures

The definition of a contracture is a limitation in joint mobility in which a joint cannot achieve its full passive ROM. Contractures represent the most common musculoskeletal complication in SMA and many other neuromuscular diseases. The precise pathogenesis of contractures in SMA is do not yet fully understood, but evidence suggests a multifactorial origin. Prolonged static positioning, imbalances between agonist and antagonist muscle strength around a joint, and the inability to actively move a joint through its full ROM may all contribute[9–12]. In the absence of DMTs, contractures in SMA typically develop during childhood and may progress rapidly[9–15]. The available literature identifies several ways in which contractures affect daily functioning, including pain, functional limitations, and reduced quality of life[9,16,17] and also points out that contractures can limit the beneficial effects of DMTs. Because contractures have a substantial impact, clinicians widely accept early prevention as best practice. International standards of care[13] recommend passive and active stretching, the use of orthoses, and standing tables for children with SMA. However, limited research has examined the patient perspective on the impact of contractures and perceived contracture management.

Disease-modifying treatment

Several pharmacological treatment options are currently available for SMA. In 2017, the European Medicines Agency (EMA) granted market access to nusinersen (Spinraza®), which was the first drug for SMA designed to target the underlying genetic defect. Nusinersen corrects *SMN2* splicing, which results in the production of higher levels of full length SMN protein in cells. The results from two pivotal trials showed positive effects on the survival of children with SMA type 1 and on the motor function of children with SMA types 1 and 2 [18,19]. A growing number of post-marketing studies confirm that nusinersen treatment leads to sustained functional improvement and is well tolerated by a broad spectrum of SMA patients, including subgroups of adults. Zolgensma® (onasemnogene abeparvovec), a one-time form of gene therapy that employs a viral vector for delivery of the *SMN* gene to motor neurons is available in Europe since 2021 and the oral *SMN2* splicing modifying small molecule risdiplam (Evrysdi®) followed in 2023 [20]. Studies have demonstrated that both Zolgensma® and risdiplam significantly improve survival and motor development. However, none of these treatments cure symptomatic SMA, and the long-term effects remain uncertain.

Several studies have shown that pre-symptomatic treatment leads to the best results and often semi-normal gross motor development. The traditional SMA classification system therefore no longer applies to the generation of children with a genetic predisposition for SMA who are now identified by newborn screening programs.

Importantly, while DMTs have transformed the prognosis for children with SMA, contractures remain a common and challenging complication. Even with improved motor function, children with SMA continue to risk developing joint contractures, which can limit their (self) mobility, arm and hand use, and independence. The effectiveness of DMTs varies among patients. Children who begin DMTs earlier, with shorter disease duration, typically respond more favorably, making early intervention a pivotal factor in treatment outcomes. Consequently, experts recommend starting treatment as soon as possible after diagnosis. SMA was added to the Dutch newborn screening program in 2022, enabling diagnosis within the first weeks of life.

As the clinical presentation of SMA evolves with DMTs, understanding how these treatments influence the development and management of contractures becomes increasingly important. Preventing and treating contractures remains a key aspect of rehabilitation care. However, with the introduction of DMTs, little information exists regarding joint ROM in treated patients, creating a critical knowledge gap that needs to be addressed to optimize long-term outcomes for children with SMA[21,22].

Rehabilitation care

Despite the advances of DMTs, SMA remains a chronic condition and clinicians must continue to use proactive, multidisciplinary, and supportive treatment approaches. As SMA phenotypes evolve, rehabilitation goals must focus not just on impairments and motor function but on a broader range of needs. Rehabilitation physicians use the International Classification of Functioning, Disability, and Health (ICF) as framework, developed by the World Health Organization (WHO), to incorporate activity, participation, and contextual (personal and environmental) factors into rehabilitation care[23]. It provides a shared language for understanding disability and functioning and helps set goals within and between multidisciplinary teams. The version for children and youth (ICF-CY) also considers evolving competencies, participation, and independence, encouraging collaborative goal setting with families[24]. However, current SMA care standards do not include the ICF framework.

Clinicians' experience and scientific evidence regarding contractures and rehabilitation strategies for children with SMA receiving DMTs remain limited. There are no studies that focused exclusively on the impact of contracture management in this patient population. The international standards of care, last updated in 2018, provide rehabilitation assessment and intervention recommendations for SMA patients, including both non-sitters and ambulant individuals. However, these guidelines primarily reflect experiences with treatment-naïve patients rather than those receiving DMTs.

The published evidence supporting recommended interventions, such as positioning and bracing, seating and mobility, exercise, and stretching, remains limited. More recently, experts have suggested implementing preventive range-of-motion exercises, even in the absence of contractures[25]. However, uncertainty remains about which children will develop contractures, when they might occur, or whether preventive recommendations could lead to unnecessary interventions. Therefore, clinicians should tailor contracture management to each patient's unique needs. The evolving landscape of SMA and the introduction of DMTs have created uncertainty for rehabilitation professionals. To optimize contracture management and rehabilitation strategies, professionals must understand current practices and the factors influencing clinical decision-making in pediatric contracture management. Another crucial aspect of this individualized approach is understanding the underlying course of joint ROM, particularly as new treatments alter SMA's trajectory.

Development of joint range of motion

In treatment-naïve children, SMA causes progressive muscle weakness, which affects the legs more than the arms and is more pronounced proximally than distally. DMTs improve the prognosis, but outcomes depend on factors such as disease progression before starting DMTs and the number of *SMN2* gene copies. While researchers are gaining a better understanding of how DMTs affect survival and motor function, they still largely lack knowledge about the development and patterns of contractures in children with SMA who are receiving DMTs. To provide effective care for children with SMA in the future, it is essential to understand how joint ROM develops.

Gaining deeper insight into the processes that underlie contracture development will enable rehabilitation professionals to manage these complications more effectively and efficiently. Given the variability in outcome of treatment with DMTs, it has become increasingly important to identify the mechanisms underlying contracture risk[17,26]. Moreover, we do not understand how early treatment with DMTs affects children's susceptibility to contracture formation. Experts have suggested that an imbalance between flexor and extensor muscle strength may contribute to contracture risk. Understanding whether a progressive imbalance between flexor and extensor muscle strength leads to a decline in joint ROM could help clinicians make more informed decisions about contracture management. A comprehensive assessment of joint ROM, flexor and extensor muscle strengths, and the flexor-extensor ratio, along with their potential interactions, could provide valuable insights and help determine whether the flexor-extensor ratio could serve as a tool for risk assessment.

Summary of knowledge gaps

- Patient perspective on the impact of contractures and experiences with contracture care.
- Variation in current contracture management by health professionals and what influences clinical decision-making.
- The natural history of joint ROM in children treated with DMTs before and after onset of symptoms.
- The relationship between changes in muscle strength and changes in ROM, i.e. the flexor-extensor imbalance as a potential tool for risk assessment.

AIMS

The studies in this thesis aim to deepen insight into how contractures affect daily activities, variations in their management practices, and the progression of contractures, especially in relation to muscle strength, in children with SMA who are receiving DMT. Specifically, the research in this thesis addresses the following questions:

- How do contractures impact daily functioning and participation of adolescents/young adults with SMA, and what is the impact of received (preventative) treatment of contractures?
- What are the current approaches to managing contractures in the Netherlands, and what factors affect clinical decision-making?
- What are the longitudinal changes in ROM across three important joints in children with SMA receiving DMTs?
- Over time, how do ROM, muscle strength, and the flexor-extensor ratio in the knee and elbow change, and are these variables correlated?

OUTLINE OF THIS THESIS

This thesis focuses on contractures in children with SMA, in particular their impact on daily functioning, contracture management experiences, and implications for future rehabilitation strategies. By placing the patient perspective at the center of inquiry, this work aims to contribute to developing personalized and goal-oriented care strategies for a new generation of children living with SMA.

Part 1: Impact of contractures and contracture management

To study the impact of contractures, we performed a qualitative study (**Chapter 2**) that investigates their impact on the daily functioning of adolescents with SMA. Expanding upon this qualitative insight, **Chapter 3** provides an in-depth analysis of Dutch rehabilitation physicians' perspectives on contracture management in children with spinal muscular atrophy and examines the challenges encountered by clinicians within a continuously evolving therapeutic landscape.

Intermezzo

This thesis started in July 2020, during the COVID-19 pandemic, a period that significantly disrupted both healthcare and research activities. The pandemic impacted patients, caregivers, and scientific studies alike. While it brought numerous challenges,

it also created an opportunity to add an additional section to this thesis. **Chapter 4** explores the experiences, challenges, and needs of parents caring for children with SMA during the early stages of the pandemic, offering insight into their unique circumstances and support requirements under unusual conditions.

Part 2: Development of joint range of motion in the era of DMTs

Transitioning from the qualitative and focus on impact of part 1, part 2 turns to quantitative research on joint ROM and muscle strength in children with SMA receiving disease-modifying treatments. **Chapter 5** is a prospective cohort study that examined how joint ROM changed over time in three functionally important joints among young children. Extending these findings, **Chapter 6** is a longitudinal analysis of changes in joint ROM, muscle strength, and flexor-extensor ratio of the knee and elbow, to examine whether changes in muscle strength precede changes in joint ROM in children with SMA receiving DMTs.

A general discussion of the main findings of this thesis can be found in **Chapter 7** and a summary in Dutch in **Chapter 8**.

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PART 1

Impact of contractures and contracture management



2

Impact of contractures on daily functioning in adolescents with spinal muscular atrophy: a qualitative study

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ABSTRACT

Purpose: Exploring impact of contractures in adolescents and young adults (AYA) with spinal muscular atrophy (SMA) on daily functioning and participation and impact of received contracture management.

Methods: We included 14, non-ambulant AYA with SMA types 2/3 (10 females and 4 males), aged 16–30 years. Interviews focused on two topics: perceived impact of contractures on daily functioning and of previous contracture management. We used inductive thematic analysis for interview analysis.

Results: In general, participants experienced muscle weakness to be more of a hindrance than contractures; they had adapted to their contractures over time. Participants considered contracture treatment useful when goals were meaningful and realistic. Participants mentioned that their perspective on contracture management would change in the light of a promise of improved motor function due to disease modifying treatment.

Conclusion: Despite the relatively low impact of contractures in comparison to loss of muscle strength, non-ambulant AYA with SMA should be informed on the potential impact of contractures and benefits and potential adverse effects of their management. This information can support the shared decision-making process. While respecting individual choices, it allows for incorporating interventions into daily life and promotion of daily functioning and participation when children with SMA are growing up.

Keywords: spinal muscular atrophy, contractures, treatment, adolescents and young adults, daily functioning

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease, caused by the homozygous loss of function of the survival motor neuron (*SMN*) *1* gene[1]. It demonstrates a considerable variability in severity. The SMA classification system uses age at onset in combination with achieved motor milestones to distinguish types 1 to 4 [2].

Muscle weakness is a common feature in children with SMA, a disorder associated with secondary musculoskeletal impairments, in particular loss of joint mobility and the development of contractures[3]. Currently, nearly all children and adults with SMA develop contractures at some stage in life. Prevalence of contractures in SMA vary with age, SMA type, walking ability (ambulatory vs non-ambulatory) and joints affected, with a reported range from 22% to 100%[3]. The introduction of SMN2 splicing modifying therapies, such as nusinersen (Spinraza®) and risdiplam (Evrysdi®) and *SMN1*-gene therapy (Zolgensma®/onasemnogene abeparvovec), has changed the natural history of SMA, characterized by progressive muscle weakness[4,5], into one of prolonged motor development in young children to improved muscle strength in older individuals[6]. This has made pro-active contracture management even more important than before[7], since sufficient joint range of motion is necessary to benefit from the increase in muscle strength. Prevention of contractures has, therefore, become a central goal of rehabilitative management[7].

Contractures are assumed to have a large impact on daily functioning and comfort in SMA[8]. Contractures in the arms and hands can limit activities such as eating, wheelchair use and computer/smartphone use, while contractures in the legs may interfere with standing[9] and foot deformities may lead to difficulties with fitting shoes. However, data on the perceived impact of contractures on daily functioning in children and young people are scarce, and several systematic reviews challenge the efficacy of interventions aimed at contracture treatment in neuromuscular and neurological disorders[10–17].

In order to rationalize supportive treatment, we require greater insight into the perceived impact of contractures on daily life with SMA and in the perceptions of received contracture management. The aim of this study was to document experiences of adolescents and young adults (AYA) with SMA with contractures (both the impact of contractures and the impact of contracture management), with the overarching goal of improving the care for a new generation of children with SMA treated with disease modifying treatment (DMT). More specifically, we explored the opinions and ideas of AYA with SMA on the perceived impact of contractures on their daily functioning and

on their participation, as well as how they experienced interventions to prevent and treat contractures during childhood.

METHOD(S)

We conducted a qualitative interview study with AYA with SMA in whom contractures were present. This study was reported in accordance with the guidelines of the Standards for Reporting Qualitative Research (SRQR) checklist[18].

Our questions during the interviews with adolescents and young adults focused on two major topics:

1. Their opinions and ideas on the perceived impact of contractures on their physical and psychosocial functioning and on their participation in society;
2. Their experiences with received interventions to prevent and treat contractures during childhood.

Participants

A research nurse contacted adolescents and young adults, aged 16–30 years, with SMA types 1, 2 and 3 and persisting contractures, registered on the Dutch SMA database. We recruited a purposive sample of AYA (age, SMA type and gender) until data saturation was reached, i.e. no new codes emerged from the interviews. Interviews 11 to 14 did not add any new codes, which indicated that saturation had been reached.

In the Netherlands, care for individuals with SMA consists of supportive multidisciplinary care, provided by a regional rehabilitation center and local physiotherapists, in addition to treatment with DMT that is centralized and provided by the SMA Center at the UMC Utrecht.

The Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands classified this study as exempt from the Medical Research Involving Human Subjects Act (19-668); all participants gave signed informed consent.

Research team and reflexivity

The research team was led by AB, a senior researcher with background in human movement sciences, trained in qualitative methodology and experience in rehabilitation research on neuromuscular/motor neuron diseases. IOL is an experienced pediatric physiatrist working in a university hospital and expert center for SMA. As a medical

doctor her focus is on neuromuscular diagnoses; BBo is a master student in medicine performing her research internship in this project. She was not involved in the treatment of AYA with SMA and had no working experience in rehabilitation. She was specifically trained in qualitative research methodology for this project. JWG is professor of pediatric rehabilitation medicine and head of a pediatric rehabilitation department at a university hospital with expertise in brain-based developmental disabilities and neuromuscular diseases; WLvdP is professor of neurology specialized in (pediatric) neuromuscular diseases and director of the Netherlands SMA Center; BBa is an experienced pediatric physical therapist, researcher and head of Child Development and Exercise Center of a university hospital. IOL performed all the interviews. She was not involved in the rehabilitation care of the participants.

Data collection

A semi-structured interview guide was developed by the multidisciplinary research team following a review of literature[9,19,20] and the clinical experience of the team members. Topics included daily functioning with contractures (using the International Classification of Functioning, Disability and Health (ICF) framework[21] as a structure to explore the impact on various activity and participation domains, including social functioning and relationships, self-care, work/spare time/school) and experiences with perceived interventions (Appendix 2.1). All interviews were performed by one interviewer (IOL) who conducted the interviews either face-to-face (before the COVID-19 pandemic) or screen-to-screen (during the COVID-19 pandemic) in the period Nov 2019 – Jan 2021. The interviews were audio-recorded and transcribed verbatim.

Data analysis

Data collection and data analysis were carried out simultaneously in an iterative process. The transcripts were analyzed according to the three phases of directed content analysis as described by Braun and Clark[22]. Trustworthiness was ensured through adhering to each of the following criteria: credibility, transferability, dependability and conformability. Credibility (the extent to which an interpretation of data is representative of the experiences of participants) was enhanced through purposive sampling (to ensure that a range of views were available to create rich data for interpretation) and discussion of themes and data interpretation within the research team and with peers in the SMA expert center through research meetings. Two researchers (IOL and BBo) prepared by reading several transcripts and familiarizing themselves with the data.

To facilitate judgements about transferability (the extent to which findings might be applied or generalized to other participants in similar contexts), relevant contextual information about participants was reported in the findings.

Dependability (the extent to which a researcher's interpretation of data would be consistent if repeated) was enhanced through the use of NVivo software (QRS NVivo 12), which facilitated a clear audit trail of the decisions about analysis from initial coding to final themes. In the organizing phase, analysis began with a first set of codes, based on the topic list of the interview. Hence, the first step in the process of coding was inductive. The directed content analysis started with two researchers (IOL and BBo) independently analyzing the first 6 interviews by assigning codes to fragments relevant to the research questions. They compared and discussed the codes and developed a preliminary codebook using their definitions. A third researcher (AB) helped by commenting on the coding and discussing discrepancies.

While coding the subsequent 4 interviews, new codes and subcodes were added to the list of codes. This resulted in a final codebook.

We then used this to adjust the coding of the first 10 interviews and to code the remaining interviews. Interviews 11 to 14 did not add any new codes, which indicates that saturation was reached. Analysis of coded data (searching for themes, reviewing themes and defining/naming themes) was discussed by the researchers (AB, IOL, BBo and JWG). The last phase, reporting, consisted of describing the results, using clarifying quotes and highlighting the most important findings (AB, IOL, BB, WLvdP, JWG).

Confirmability (the extent to which the findings of the study are free from bias) was maximized through line-by-line coding of the data (which helped the researcher to stay 'close' to participants experiences). The researchers also kept a reflexive log to consider their influence on the collection and interpretation of the data.

RESULTS

Participants

We conducted interviews with a total of 14 participants (10 women and 4 men) with a median age of 24 years (range 16–30 years). Two non-ambulant participants with SMA type 3 and 12 non-ambulant participants with SMA type 2 participated. None of the participants were able to make a transfer to standing. All participants reported contractures in various joints in the upper and lower extremities. The contractures were located in nearly all their joints (Table 2.1).

Table 2.1. Personal characteristics

	Gender	Age, yrs	SMA type	Level of ambulation	Joints affected by contractures (self-report)
P1	M	28	2	Non-ambulant	Hip, knees, ankles, feet and elbows.
P2	F	29	2	Non-ambulant	Back, elbow, knees and mouth.
P3	F	24	2	Non-ambulant	Knees and elbows, possibly the hips too.
P4	M	16	2	Non-ambulant	Every joint has a contracture, but the most difficult are hands and arms.
P5	F	26	2	Non-ambulant	All joints: shoulder, elbow, wrists, hips, knees, feet and ankles.
P6	F	27	2	Non-ambulant	Knees, hips, feet and arms.
P7	M	27	2	Non-ambulant	Hips, elbows, shoulders, fingers, knees and almost every joint.
P8	F	20	3	Non-ambulant	Knees, hips, one elbow and ankles, so just about everywhere.
P9	F	18	2	Non-ambulant	Knees and hips. And a little bit my elbows.
P10	F	30	2	Non-ambulant	Wrists, ankles, neck, shoulders, in every joint there is a contracture, the ones you use the most are your knees, elbows and then your hips.
P11	F	18	2	Non-ambulant	Wrists, elbows, shoulders, hips, knees and feet, almost all joints.
P12	M	24	2	Non-ambulant	Elbows, knees and hips.
P13	F	20	2	Non-ambulant	Legs: feet, ankles, knees, hips. Arms almost no contractures.
P14	F	28	3	Non-ambulant	Hips and legs (knees) and hands.

The qualitative analysis of the perceived impact of contractures on daily functioning revealed two main themes: 1) ongoing adaptation/acceptation, and 2) normalization. Regarding the experience with received interventions to prevent and treat contractures during childhood, we identified three main themes: 1) considerations in regard to contracture management, 2) prevention of contractures and future uncertainties, and 3) DMT and future impact. The findings will be presented in more detail below.

Perceived impact of contractures on daily functioning

In general, participants' perception was that their contractures did not hinder them in their daily functioning, nor did they mention pain or stiffness associated with the contractures. *'I know that I have contractures, but I'm not hindered by the contractures' (P3)*. Participants mentioned that the impact of the contractures was more significant in the upper than in the lower extremities. Various participants mentioned that contractures of the legs were less impactful as they were completely wheelchair dependent.

'I mainly have contractures in my lower extremities, which I don't really use, so the contractures don't bother me' (P13) and *'To me, there is no need to extend my legs, why should I?' (P8)*

For the following activities, participants reflected on the impact of contractures in everyday life and shared some of the strategies they used to adapt.

- Use of arms and hands: participants reported a loss in range of motion of the wrist (ulnar deviation combined with palmar flexion), but not of the fingers, which were mainly described as hypermobile.
- Personal care: changing tight clothes sometimes caused problems, but most of the participants reported that they did not adapt their clothing. *'It is mostly the problem of the caregiver in my opinion' (P6)*, one of them stated.
- Personal hygiene: one participant addressed the problem of abducting her legs for keeping clean her private parts.
- Social-emotional well-being: In general, participants did not feel contractures had an impact on their self-esteem.
- Sexual activities: two of the participants mentioned that contractures complicated positioning. It required more coordination with their partners to find the correct position.
- Study/work/leisure: participants did not mention any specific problem due to contractures in relation to study/work/leisure time.

Although, on the whole, participants did not feel impaired by contractures in daily life, they mentioned situations in which this did happen. Two participants described negative experiences during surgery due to awkward and painful positioning (quotes X and Y).

> *Quote X: 'they cast my ankle at a 90 degree angle. The following day I was in so much pain because my muscles were not used to this position – due to the contracture. They removed the cast and the pain was gone immediately. They cast it again in a comfortable position. When I broke my knee a couple of years later, I knew how to advise the doctors to cast it in a comfortable position for me.' (P5)*

> *Quote Y: 'I had to undergo surgery in a supine positioning, but I am not able to extend my hips completely. They positioned me in a supine position and my hips were overstretched. After surgery, the pain due to my hips was worse than from the operation. The second time I had to undergo surgery, I asked for a different position, i.e. on my side.' (P1)*

Other examples of perceived impact of contractures were on sexual (Quote X) and reproductive functioning (Quote Y).

Quote X: 'Positioning with your partner is quite difficult'. (P6)

Quote Y: 'I was stressed during my pregnancy about whether I would be able to spread my legs enough to give birth' (P14) and 'I had to terminate my pregnancy due to my body posture. Because there was too little space, the fetus would not survive. If contractures influence this, which I believe they do, they have a great impact.' (P10)

Ongoing adaptation/acceptation. As described above, many participants stated they usually did not feel impaired by their contractures in their daily activities or social participation. The participants' explanation was that they had become used to the contractures, as they developed slowly and gradually, at the same time as a decline in muscle strength, during childhood and adolescence. Participants mentioned they had learned how to adapt their daily activities gradually. Also, they stated that they found it difficult to distinguish the impact of contractures from the impact of reduced muscle strength.

'I am used to moving my arm only in a reduced range, because my muscles don't have the strength to move in the complete range of motion'. (P1)

Normalization. Participants frequently mentioned they wanted to live their life as normally as possible. Although they stated contractures did not have a negative influence on their self-esteem, they did mention that a normal appearance was important. In particular, nearly all participants said they did not want to wear orthopedic shoes as they felt they stood out too much. One of the most important goals the participants mentioned in contracture management was the ability to wear normal shoes during adulthood: *'For me the most important thing is that I can just keep wearing normal shoes and as long as that's the case, it's fine with me.' (P7)*

Participants stated appearance was important when choosing different aids, for example arm support. Some participants explained arm support or a wheelchair are very ugly. To look as normal as possible, they avoided various aids as much as possible. In relation to contractures, participants also found it important that aids were not too noticeable.

One participant said she did not want the contractures to be visible when taking pictures: *'I am aware of them, for example when I take a picture: how do my hands*

look, are they in their contracture position or are they turned correctly so that they look normal. Are my feet straight?'. (P10)

Perceived impact of received interventions to prevent and treat contractures during childhood

Participants were positive about physiotherapy which they perceived as additional comfort.

Considerations in regard to contracture management. Most participants felt strongly that contracture treatment should provide a clear benefit. They did not feel the necessity to try everything to prevent contractures or limit worsening of contractures when these did not significantly impair their daily functioning.

Some participants felt that contracture management was not a matter of shared decision- making, but that it was rather decided for them in their childhood years without clear benefit for them. Most participants did not feel it necessary to preserve the range of motion of their joints, when their strength prevented them from using the joint fully. None of the participants had the strength to stand independently and, therefore, most of them did not see the need to be able to straighten their legs. To prevent further contractures of the knees, some participants had used a stander during their childhood. Most of them were very explicit about their dislike of this treatment and complained about the stander being painful and uncomfortable.

> *'I always thought, I can't walk so why bother.' (P3)*

> *'I didn't see the need to stand. I sit all day, so why in god's name would I want to stand in a stander?' (P7)*

Also one participant indicated that the stander took away his ability to move independently: *'I lose my freedom and control, that has always been important to me. To be able to decide where I want to go and when I want to go there. And not having to be moved by someone else.' (P7)*

Splints were often used to try to maintain muscle length. Several participants strongly disliked their splints as they were painful, ugly or bothered them while sleeping. Most participants were not, therefore, compliant in wearing them. A reason for using the splints was the belief that they were helping, especially if the participant thought it was important to preserve the function of specific joints. One participant, for example, felt ankle-foot orthoses were unnecessary, but a splint for the wrist was worn every night.

Participants did feel physiotherapy had a positive impact in relation to contractures and noted it helped reduce the feeling of stiffness in their joints. Several participants stated that going to therapy as a child was not much of a burden given the perceived benefits and most continued to see a physiotherapist as an adult.

'Afterwards, it's always pleasant to stretch it all.' (P12)

'When I was young, I always said that after being away for holidays for 3 weeks, without having physiotherapy, I noticed that I felt stiffer.' (P9)

Views about contracture management strongly depend on participants' own understanding/knowledge about the development of contractures and previous experience. Most participants had noticed that contractures did not often develop in the joints they used regularly. Participants tended to associate aids that limit movement, such as a wheelchair tray, with a decline in function and increase of contractures; hence they did not want to use it.

Prevention and future uncertainties. Most participants were not convinced that management could prevent contractures, but were clear about their hope that their contractures would not worsen over time. Some participants found the sight of fellow individuals with SMA with severe hand contractures to be frightening. *'I think I would be upset if the contractures worsened. Because my hands and arms, they are the only extremities I can still use. So I would hate it if the contractures would become as bad as in my knees.' (P9)*

Disease-Modifying Treatment and future impact. Although participants were very clear about their negative feelings toward contracture management, they were also clear about the relevance of contracture management in the light of DMT. Currently, in the Netherlands, various DMTs are available for children with SMA. Participants stressed the importance of contracture management in the case of motor function improvement with the use of DMT. *'If children are able to stand with the help of DMT, I would definitely advise using contracture management. There is a different goal with contracture management now in comparison to myself, since I can't stand.'* And, *'I think it is different now in children with DMT. In my case it did not matter, I wouldn´t use my legs anyway. But now I think it is more important to prevent contractures instead of trying to influence them while contractures progress'. (P3)* And *'Now that nusinersen is more and more available, a stand-up chair may be useful for some people, if it helps to keep their legs more flexible, but yes, at the time it was not really something that had priority.' (P10)*

DISCUSSION

Our study shows that non-ambulant adolescents and young adults with SMA and existing joint contractures do not experience a major impact on daily life of these contractures. Even though all participants are affected by contractures in multiple joints, they do not experience their contractures as a constant hindrance in their everyday functioning. This might be due to slow adaptation and acceptance over time and/or the decline in muscle strength which also impacts functioning. They did not experience pain and stiffness. Most participants specifically felt physiotherapy, in particular the passive stretching of their joints, had a positive influence. However, additional contracture management, such as orthoses, standers, casting etc., were not considered a positive addition to their treatment plan. In various interviews, the desire to wear normal shoes was the most important subject regarding contracture management. Participants' negative experiences regarding orthotic management of contractures was mainly because they felt, in their situation (without DMT), there was no clear goal: they would never be able to stand or walk.

Multidisciplinary rehabilitation interventions aim at optimizing independence, physical functioning, and psychosocial functioning[23]. Most participants indicated that they considered their situation to be acceptable, but that they would mind if their hand function deteriorated due to contractures. They also indicated that they found end-stage contractures difficult to look at. Apparently, AYA adapt gradually to the slow decline of hand function[4] and also learn to accept accumulating disability. The impact of contractures is most apparent in specific situations, such as during surgical interventions or during intimacy. Increasing awareness of the impact of contractures among affected individuals and healthcare professionals is, therefore, important. SMA experts should increase awareness, amongst surgeons and anesthesiologists to whom affected individuals are referred, of contractures pre-surgery and to better accommodate for them during procedures. Furthermore, we should at least try to make the problem of positioning for intimacy a part of sexual health education of AYA with SMA and comparable neuromuscular disorders.

A major topic in the interviews was the potential benefits of contracture management in their individual situation. It is indeed not clear whether conservative treatments can prevent or delay contracture progression. Systematic reviews showed that there is low level evidence to support the use of orthoses in Duchenne muscular dystrophy (DMD)[10–12] and two Cochrane Reviews showed that stretching in neurological disorders does not have a lasting impact on joint mobility when applied for less than 7

months[14–17]. In the absence of evidence, the prudent recommendations on contracture management[7], based on expert opinion and consensus and aimed at minimizing loss of function, should be balanced with affected individuals' priorities. Many participants mentioned that contracture management should have a clear goal for them. Some AYA are not convinced that contracture management can significantly influence the course of the contracture and are, therefore, not motivated to use orthoses. Many participants highlight the difficulty of future uncertainties in relation to their contractures and are, therefore, undecided about whether or not to opt for burdensome or time-consuming preventive management. It should be noted that DMT may change the attitude of an affected individual, since goals of management may differ if maintenance of standing or standing transfers were achievable. None of the participants at the time of the interview was receiving treatment with DMT. However, our study indicates that patient empowerment – in particular the feeling of making your own decision – may increase compliance with treatment regimens. In general, prevention of contractures, rather than trying to reduce an existing contracture, will probably improve compliance. This is in line with the consensus update on standards of care recommendation for SMA[7], which emphasizes the importance of introducing orthotics before contractures develop.

It is important to consider that with the introduction of DMT perspectives and goals regarding contracture management for AYA with SMA may have changed and may continue to change with advancement in assistive device technology. Livingstone et al. highlights the lack of publications regarding rehabilitation management in children with SMA. A recent scoping review and associated case report highlights the importance of a comprehensive and proactive support and the case report illustrate the possibilities of assistive devices for the participation of a child with SMA type 12 [4]. Participants in our study stated that postural management would have been more acceptable for them, if it had a clear goal, which may have resulted in improved level of functioning/ or participation, as described in this case report. With the increased use of technology in assistive devices for functional activities, like sit to stand power wheelchairs[25,26] or arm assists, it is even more important to prevent contractures. Townsend et al.[27] recommended use of (knee) ankle foot orthoses ((K)AFO) to ensure joints are aligned and to prevent valgus forces at the knees in supported standing. Fujak et al.[28] recommended earlier provision of AFO's to children with non-ambulatory SMA while foot position is correctible, which aligns with the specific goal of being able to wear regular shoes into adulthood identified by participants in this study. It should be acknowledged that recommendations for contracture prevention using standing frames or standing wheelchairs may well address other shared-goals. For example, the use of standers provides additional benefits like bladder and bowel function[29].

Given the availability of DMT, this study highlights the need for early intervention in relation to postural management to accommodate altered management goals. We stress the importance, in the light of the findings of our study, to monitor and revisit treatment goals, benefits and adverse effects on a regular basis as part of the shared goal-setting and decision-making.

This study is unique in presenting the patient perspective on the impact of contractures and contracture management in SMA. Future perspectives should focus on individualized contracture management, tailored to a person's functional level. A limitation of our study is that we noticed, after coding the interviews, that sexual activities was a topic mentioned by three participants in a different context. Unfortunately, we did not specifically ask about sexual activities in the first interviews. Our results may, therefore, underestimate the importance of this topic for AYA with SMA.

Secondly, we only included non-ambulant participants with SMA types 2 and 3. Ambulatory affected individuals with contractures may have different viewpoints. Additional interviews with this group would be of interest in the light of DMT and future increase of motor milestones. Although we used purposive sampling to try to include a heterogeneous group with SMA types 2 and 3, purposive sampling of level of functioning would have been of added value for the generalizability of the study.

This study emphasizes that shared goal-setting and decision-making regarding contracture treatment are of great importance. Of note, this study gives insight into the patient perspective regarding the impact of contractures and contracture management, performed in adolescents and young adults who started contracture management 10–20 years ago. The data from this study may be useful for making treatment decisions in a new generation of individuals with SMA. Specifically, DMT and the potential motor function improvement it affords highlights the need for early preventative contracture management using shared goal-setting in treated AYA with SMA.

Implications for rehabilitation

- The variability of the perceived impact of contractures in non-ambulant adolescents and young adults with spinal muscular atrophy (SMA) underscores the need for individualized assessment and contracture management based on discussions about challenges, benefits and burden.
- In the treatment plan for contracture management in SMA it is important to take into account: (1) that adolescents often experienced physiotherapy as additional comfort, with less feeling of stiffness, and (2) that most perceived

orthosis and standers as unnecessary and burdensome as contracture management.

- Clinicians should consider postural management in an early stage given the improved prognosis on motor development of children with SMA.
- Clinicians should monitor and revisit treatment goals, benefits and adverse effects on a regular basis as part of the shared goal-setting and decision-making in contracture management for children with SMA.

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APPENDIX 2.1. INTERVIEW GUIDE

1. Introductory questions

Question: what do you know about contractures in general?
Question: what joints are affected in your case?

2. Questions about possible symptoms

Question: do you have pain due to the contractures?
Question: do you experience stiffness in joints where you have contractures?

3. Questions about current and previous contracture treatment

Explanation about contracture management: one can think of splints, casting, use of a stander, physiotherapy or stretching moments.

Question: what kind of contracture management are you using and how satisfied are you with it?
Question: what treatment have you used in the past and how do feel about that?

4. Questions about level of functioning/participation

Question: in what way do the contractures affect your daily functioning?

Depending on the participant, questions will be asked about the following themes:

- *Mobility*: exercise/sports/activities using the hands: writing/typing/handling cutlery/drawing/painting
- *Social interaction, relationships and communication*: making contact with other AYA/adults: friendships/relationships
- *Personal care*: independence in daily personal care/household
- *Important areas of life*: school/part-time job/work
- *Social*: hobby/leisure/musical instrument etc.

5. Questions about worries/fear/self-image/self-confidence

Question: do you ever worry about the contractures? Do the contractures affect how you look at yourself or how you think about your appearance?

6. Impact on someone's family

Question: have you talked about contractures at home, how do your parents feel about contractures and contracture management?



3

Dutch rehabilitation physicians' perspectives on contracture management in children with spinal muscular atrophy: challenges in a changing landscape

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ABSTRACT

Background: Many children with hereditary proximal spinal muscular atrophy (SMA) develop joint contractures. With the introduction of disease-modifying treatments (DMTs) for SMA, the improved functional prognosis may change the focus of (preventive) contracture management.

Objective: This study aimed to describe current approaches to contracture management among Dutch pediatric rehabilitation physicians caring for children with SMA receiving DMT, and to explore the underlying considerations and clinical reasoning that inform their decisions on contracture management in the evolving therapeutic landscape.

Methods: All registered pediatric rehabilitation physicians (n=151) received a survey, addressing two main topics: (1) indication and purpose of contracture management, and (2) alignment of clinical decision-making with current guidelines. To this end, three standardized case scenarios were presented. Respondents were asked to indicate whether their current choices, were consistent with the guideline recommendations. To obtain a deeper understanding of the considerations and clinical reasoning regarding contracture management in the era of DMTs, we held an advisory group meeting. We audio-recorded the discussions and analyzed the content thematically.

Results: The response rate was 56%; 41 of these respondents were not involved in SMA care. 38 of the 44 surveys, completed by participants involved in SMA care, were suitable for analysis. All respondents (strongly) agreed about 'optimal sitting posture' being an important treatment goal, 95% agreed on 'pain prevention' and 87% on 'maintaining function'. Physicians recommended daily use of hand splints less frequently in children who started DMT before onset of symptoms (35%) than in children who started DMT at an advanced disease stage (54%). Thematic analysis revealed three themes shaping clinical reasoning: (1) functional prognosis as key element in decision-making; (2) clinical uncertainty regarding contracture intervention; and (3) incorporation of contextual factors.

Conclusion: Dutch pediatric rehabilitation physicians describe challenges in clinical decision-making regarding contracture management in a changing landscape for SMA. The use of key principles could facilitate the process, including: (1) assessing the child's functional prognosis; (2) engaging in open discussions with parents about uncertainties arising from limited clinical experience and the evolving understanding of disease trajectories in the early post-DMT era; and 3) applying the ICF framework to incorporate contextual factors into clinical decision-making regarding contracture management.

Keywords: spinal muscular atrophy, contractures, treatment, children, adolescents

INTRODUCTION

Hereditary proximal spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease, caused by the homozygous loss of function of the *survival motor neuron* (*SMN*) *1* gene[1]. Onset of SMA is before the age of 3 years in the large majority of patients[2].

Age at onset in childhood and achieved motor milestones are used to classify SMA into type 1 (onset in the first six months of life, non-sitters), type 2 (onset between 6–18 months, sitters) and type 3 (onset between 18–36 months (type 3a) or after 36 months but before 18 years (type 3b), walkers).

The introduction in the past few years of disease-modifying treatments (DMTs) has changed the prospects of children with SMA considerably. A large majority now experiences motor function improvement or stable disease[3] instead of the steady decline that defines its natural history. Improved outcome may imply new phenotypes and disease trajectories that require different approaches in supportive care, such as treatment of joint contractures[4,5]. The 2017 international standards of care[6] provide important pro-active guidance for contracture management in SMA, but recommendations are based on experiences in a population of individuals with SMA who were not treated with DMTs.

In the Netherlands, reimbursement for treatment with DMTs has become available incrementally since May 2017. Newborn screening was introduced in June 2022. Given the motor milestone improvement seen with the use of DMT[3], there was a need to reconsider contracture management in individuals with SMA. Prior to the introduction of DMTs, contracture management was an important part of rehabilitation therapy; however, a poor clinical prognosis did not appear to motivate individuals with SMA[7], their caregivers, or healthcare professionals in the Netherlands to adhere to a strict contracture prevention regimen. Considerations for contracture management vary significantly per individual as they depend on factors such as age, disease progression, joint range of motion, and functional level. In the Netherlands, many pediatric rehabilitation physicians report a lack of clarity in contracture management with the introduction of DMTs. The question raised among Dutch pediatric rehabilitation physicians is, therefore: '*how should one apply contracture management in a changing landscape in children with SMA?*'.

This study aimed to describe current approaches to contracture management among Dutch pediatric rehabilitation physicians caring for children with SMA receiving DMT,

and to explore the underlying considerations and clinical reasoning that inform their decisions on contracture management in the evolving therapeutic landscape of SMA.

MATERIALS AND METHODS

We performed a two-part sequential mixed-methods study, comprising 1) a cross-sectional survey among Dutch pediatric rehabilitation physicians involved in contracture management of children with SMA, and 2) an advisory group meeting with (pediatric) rehabilitation physicians, designed to reflect on their care practices and their considerations in preventive and therapeutic contracture management. This study was not subject to Dutch Medical Research Involving Human Subjects Act. All respondents gave informed consent in the (online) survey. Respondents could not proceed before completing the consent form.

Survey

We developed the survey questions through discussions among members of the study team and modified them in response to the feedback from multidisciplinary team members (researchers, rehabilitation physicians and physical therapists) of the Netherlands SMA Center at the University Medical Center Utrecht (UMCU). Two rehabilitation physicians piloted the survey, which consisted of 24 questions aimed at identifying pediatric rehabilitation physicians' views and practice regarding contracture management in SMA. The survey contained both open-ended questions (i.e. asking respondents to answer in their own words) and closed-ended questions (multiple-choice items, partly supplemented with an optional open-text field for additional comments) and took approximately 20 minutes to complete.

Context of treatment availability in the Netherlands during the study period

Nusinersen first became available in May 2017 for SMA type 1 and from January 2018 for young children (up to the age of 6 years) with SMA types 2 and 3 (compassionate use and early access programs, respectively) and was reimbursed for children up to the age of 9.5 years at the start of treatment as of August 2018. Reimbursement of gene therapy (Zolgensma®) was implemented in December 2021 for presymptomatic cases with 2 or 3 *SMN2* copies. At the time of the survey nusinersen (Spinraza®) in December 2021 for presymptomatic cases with 2 or 3 *SMN2* copies. At the time of this study nusinersen was the most administered DMT in the Netherlands. Newborn screening was introduced a few weeks before the advisory group meeting.

We identified three standardized case scenarios representing groups of children with varying disease severity:

1. Presymptomatically treated group: children who started with DMT prior to the onset of clinically manifest symptoms.
2. Symptomatically treated, group 1: symptomatic children who initiated DMT within two years after diagnosis.
3. Symptomatically treated, group 2: symptomatic children who started with DMT more than two years after diagnosis.

Questions for this survey are based on both the Dutch guideline SMA type 1 [8], as well as the International Standards of Care for SMA (Diagnosis and Management of SMA: Part 1 Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care)[6].

Because the registry of Dutch pediatric rehabilitation physicians does not include data on diagnosis groups (i.e. whether a physician works with children with SMA), we invited all pediatric rehabilitation physicians (n=151) to the survey. We first asked the physicians whether they worked with children with SMA. If the rehabilitation physician was not treating a child or children with SMA, the survey ended immediately. Data collection took place using Castor's Electronic Data Capture software (www.castoredc.com). We sent a reminder to the non-responders after two weeks.

The survey consisted of 4 parts (survey included as supplemental material – Supplementary file 3.1):

Part 1: General questions
In this section, questions are asked about work setting – (academic) hospital or rehabilitation center -and number of children with SMA in care.

Part 2: Questions on measuring joint range of motion
In this section, questions about measurements of joint range of motion are asked.

Part 3: contracture management, indication and purpose
In this section, the questions are based on international standards of care[6] (i.e. pain and decrease in function) and expert opinion. Respondents rated the extent to which they agreed with the recommendations of a certain treatment goal, by answering on a 5-point Likert scale: totally agree, agree, neutral, disagree or totally disagree. The full list of survey questions is provided in the supplemental material/information (Supplementary file 3.1).

Part 4: Questions about contracture management in relation to guidelines
This section of the questionnaire aimed to evaluate the extent to which the current clinical decision-making in the era of DMT aligns with the Dutch national guideline SMA[8] and the international Standards of Care[6]. To this end, respondents were presented with descriptions of the 3 treatment groups. Respondents rated the extent to which they agreed with each recommendation on a 4-point Likert scale: I strongly disagree with the statement, disagree, agree or strongly agree.

Then, the respondents ranked each recommendation for the three different treatment groups: presymptomatically treated group, symptomatically treated group 1 & 2. The full list of survey questions is provided in the supplemental material/information (Supplementary file 3.1).

Advisory group meeting
In the survey, respondents could consent to being approached for a later in-depth interview about the survey results. For the advisory group meeting, we invited pediatric rehabilitation physicians who participated in the survey and consented to being approached for the in-depth questions. Selective sampling optimized the representation of the Dutch pediatric rehabilitation physicians population. We invited a total of 14 physicians for the meeting, aiming for a broad variation, consisting of physicians working in different work settings (both hospital and rehabilitation center). Physicians in a University hospital typically carry out check-ups on a large group of children with SMA once or twice per year; physicians working in rehabilitation centers schedule appointments with children with SMA on a more regular basis. In addition to the pediatric rehabilitation physicians working with (young) children, a rehabilitation physician working with (young) adults was asked to join the advisory group meeting, in order to add a different point of view. We invited this physician to include experiences with adults regarding contractures and (previous) contracture management.

In the advisory group meeting, we discussed views on contracture management with the aim of obtaining insight into the underlying considerations and clinical reasoning that inform their decisions on contracture management in the evolving therapeutic landscape of SMA. We preferred the interaction of a group meeting over survey questions or (individual) interviews, in order to facilitate a dialogue among rehabilitation physicians and to create a consensual joint vision for future directions. The central theme of the advisory group meeting was to discuss dilemmas and considerations in the clinical decision-making process regarding (preventive) treatment of contractures in children with SMA. The topic guide was developed based on survey outcome of parts 3 and 4.

The moderator invited participants to share their considerations and experiences regarding contracture treatment through broad exploratory questions, followed by more specific questions that instigated discussion. The session ended with questions on how we should design future contracture treatment within the changing landscape for SMA, particularly after the introduction of DMTs and of newborn screening (topic guide is included as supplemental material – Supplementary file 3.2).

The 90-minute session was conducted online via Microsoft Teams (an online communications and collaboration platform). One of the authors (AB) with experience and expertise in focus group facilitation moderated the session. At the beginning, participants were briefed on the purpose and rules, including: introduction of all participants; explanation of the use of recordings; respecting participant privacy and opinions; confidentiality of participant identity. The moderator ensured all participants had an opportunity to express their thoughts. We recorded the session and analyzed the transcript to derive various themes. We then carried out a member check and asked participants to check the key messages and complete them with five personal recommendations regarding contracture treatment.

Data collection

We collected survey data in July 2021. The online survey started on July 1st, followed by a reminder on July 19th. The advisory group meeting was held one year later on July 8th 2022.

Data analysis

When ≥75% of the survey had been completed per respondent, data were analyzed with descriptive statistics using IBM SPSS Statistical data software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY).

Three of the authors (IOL, AB, JWG) further analyzed the transcript to identify important clinical themes.

RESULTS

Results from the survey

Parts 1 and 2: general questions

A total of 85 of 151 invited physicians responded to the survey (response rate 56%), 41 of whom indicated that they were not involved in the care of children with SMA. Six respondents did not complete the online survey (completion of survey <75%), leaving 38 surveys for analysis. Of these 38 respondents, 9 work in a university hospital (24%), 8 in a general hospital (21%), 26 in a rehabilitation center (68%) and one works in another unspecified setting. Six respondents work in two settings.

The annual patient load of 29 respondents (76%) was 1–5 children with SMA, of 5 (13%) it was 5–10 children, of three rehabilitation physicians (8%) it was 10-20 children and one (3%) looked after more than 20 children with SMA.

Part 3: Contracture management, indication and purpose

The importance of contracture management was given a median rating of 8 out of 10 [min–max 7–10]. Responses to open-ended question 3.2 indicated that the increased importance of contracture management following the introduction of disease-modifying therapies (DMTs) is primarily attributed to improved functional prognosis, increased life expectancy in SMA type 1 and the significant impact of contractures on limiting further motor development, even when muscle strength improves. In contrast, rehabilitation physicians who perceive no change in the importance of contracture management emphasize that contracture treatment was already a major focus prior to DMT. They describe similar indications for intervention, but note that the perceived effects of these interventions have changed and are now considered to differ.

The perceived importance of specific treatment goals, derived from the closed-ended questions, is presented in Table 3.1. Maintaining function, sitting posture, and preventing pain were rated as the most important objectives by respondents.

Concerning the timing of standing frame introduction (part 3.5), one participant initiated use between 0 and 1 year of age, 23 between 1 and 2 years, 13 between 2 and 5 years, and one after the age of 5 years. Reasons for discontinuation of contracture management reported in the open-ended responses (part 3.6) include:

- The intervention was considered disproportionately burdensome relative to the anticipated benefits for the child and family;

- The degree of contracture had progressed to a point where the use of a standing frame or orthoses no longer yielded clinically meaningful outcomes;
- Motivation on the part of the child and/or parents was insufficient to justify continuation of the intervention;
- The child experienced pain associated with the use of the standing frame or orthoses;
- Ongoing contracture management was deemed unlikely to result in additional functional gains;
- Discontinuation was initiated at the request of the child or family.

Table 3.1. Purpose of contracture management in children with SMA according to pediatric rehabilitation physicians (part 3)

Purpose	Strongly agree n (%)	Agree n (%)	Neutral n (%)	Disagree n (%)	Strongly disagree n (%)
To maintain function	**12 (31.6%)**	**21 (55.3%)**	4 (10.5%)	0 (0%)	1 (2.6%)
To prevent pain	**8 (21.1%)**	**28 (73.7%)**	0 (0%)	2 (5.3%)	0 (0%)
Optimal sitting posture	**15 (39.5%)**	**23 (60.5%)**	0 (0%)	0 (0%)	0 (0%)
Patient appearance	2 (5.3%)	**19 (50%)**	**13 (34.2)**	3 (7.9%)	1 (2.6%)
At parents request	0 (0%)	6 (15.8%)	**18 (47.4%)**	**9 (23.7%)**	5 (13.2%)
Avoiding the need for surgery	2 (5.3%)	**25 (65.8%)**	**7 (18.4%)**	3 (7.9%)	1 (2.6%)

* Highest and second highest percentages are presented in bold.

Part 4: Contracture management, prevention/treatment in relation to guidelines

Tables 3.2 and 3.3 list the topics for which Dutch pediatric rehabilitation physicians are less likely to follow the advice/recommendations of the guidelines [ratings, by Dutch pediactric rehabilitation physicians, of statements derived from guidelines (part 4)]. Regarding the recommendations of the Dutch guideline for SMA type 1 (Table 3.2), the main results are: 37–48% (strongly) disagreed with the statement that muscles should be stretched at least 3–5x per week. One-third of the respondents disagreed with using static and/or dynamic orthosis in the presymptomatically treated group. All but 1 respondent (strongly) agreed with using orthosis in the two symptomatically treated groups. Thirty to thirty-six percent, depending on the subgroup, (strongly) disagreed with the statement: use a brace if postural scoliosis is present.

Results on the level of agreement about statements by the international SoC for SMA (Table 3.3). For non-sitters, 46-63% of the respondents (strongly) disagreed with the statement '*I recommend daily use of hand splints for range of motion and functioning*' in all three subgroups. For subgroups 2 and 3, only 15% disagreed with the statement

Table 3.2. Ratings of various statements, derived from the Dutch guidelines on SMA type 1, by Dutch pediatric rehabilitation physicians (Dutch guideline SMA type 1: published online 2018. Startpagina - Spinale musculaire atrofie (SMA) type 1 - Richtlijn - Richtlijnendatabase)

Statement/advice		Presymptomatically treated group (subgroup 1)		Sympptomatically treated, group 1 (subgroup 2)		Symptomatically treated, group 2 (subgroup 3)	
Level of agreement with the statement, n (%)		(Strongly) agree	(Strongly) disagree	(Strongly) agree	(Strongly) disagree	(Strongly) agree	(Strongly) disagree
Stretch muscles and maintain their length, within the pain threshold, at least three to five times a week, sustaining the final position for at least thirty seconds.	I advise parents to stretch muscles in accordance with the previous statement.	14 (52%)	**13 (48%)**	17 (63%)	**10 (37%)**	17 (63%)	**10 (37%)**
Combat contractures by performing prolonged stretching. Static and dynamic orthoses can be used for this purpose.	I use static and/or dynamic orthosis in this patient group.	17 (63%)	**10 (37%)**	26 (96%)	**1 (4%)**	27 (100%)	**0 (0%)**
Consider using a brace for children with SMA type 1C or children receiving drug therapy if postural scoliosis is present.	I consider the use of a brace for children with SMA type 1C or children treated with DMTs, if postural scoliosis is present.	18 (64%)	**10 (36%)**	19 (70%)	**8 (30%)**	18 (66%)	**9 (34%)**

We asked participants to rank different pieces of advice, indicating the extent of their agreement with that recommendation. Ranking options were: I strongly agree, agree, disagree or strongly disagree with this advice. The participants ranked each statement for the following (sub)groups: (1) Presymptomatically treated group: children who started with DMT prior to the onset of clinically manifest symptoms. (2) Symptomatically treated, group 1: children who initiated DMT within 2 years after diagnosis. (3) Symptomatically treated, group 2: children who started with DMT more than 2 years after diagnosis. * Percentages (strongly) disagree per subgroup are presented in bold.

'*For children who cannot sit independently, I recommend the daily use of AFOs and/or KAFOs for range of motion*'. In sitters, 26–37% of the respondents (strongly) disagreed with the statement '*I recommend a minimum frequency of stretching of 5–7 times a week*' in all three subgroups.

In the ambulant group, 41% (strongly) disagreed with the statement 'I recommend active stretching 2–3x per week' in the presymptomatically treated group.

Dutch expert advice and recommendations

A total of six rehabilitation physicians, consisting of five pediatric and one adult rehabilitation physician, were able to join the advisory group meeting. Three of the pediatric rehabilitation physicians work in a rehabilitation center; the other two and the adult rehabilitation physician work in a university hospital. All rehabilitation physicians involved in this study have a dedicated focus on neuromuscular disorders in their clinic, have a minimum of five years of experience of treating children with SMA (three of them had over 10 years of experience) and they are all members of the national working group on neuromuscular disorders (additional information on advisory group experts is included as supplemental material – Supplementary file 3.3). We asked the participants of the advisory group to indicate their caseload (at the time of participation) of children with SMA, which varied from a minimum of one child to over 30 children.

Three main themes emerged from the analysis of the advisory group deliberations: (1) functional prognosis as key element in decision-making; (2) clinical uncertainty of contracture interventions, and (3) considerations in the light of ICF-based functioning: incorporating contextual factors.

Functional prognosis as key element in decision-making

All advisory group experts agreed about functional prognosis being a key element in decision-making by pediatric rehabilitation physicians regarding contracture treatment. Participants stressed the importance of the following factors to be taken into account for a functional prognosis: number of SMN copies, age, age at start of treatment with DMT, personal and environmental contextual factors, muscle strength and range of motion.

> *Participant: 'I notice that in a non-ambulatory patient, regarding contracture management of the legs, I am more likely to go along with parents when they indicate discontinuing contracture treatment. When hands are involved, I am more keen on continuing contracture treatment to see if we can come up with other tricks or ways to continue contracture treatment.'*

Table 3.3. Ratings of various statements, derived from the International Standards of Care for SMA, by Dutch pediatric rehabilitation physicians; Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care - ScienceDirect by Mercuri et al.[6]

Statement/advice		Presymptomatically treated group (subgroup 1)		Symptomatically treated, group 1 (subgroup 2)		Symptomatically treated, group 2 (subgroup 3)	
Level of agreement with the statement, n (%)		(Strongly) agree	(Strongly) disagree	(Strongly) agree	(Strongly) disagree	(Strongly) agree	(Strongly) disagree
Non-sitters	For children who cannot sit independently, I recommend a minimum stretching frequency of 3–5 times a week.	17 (63%)	**10 (37%)**	21 (78%)	**6 (22%)**	21 (78%)	**6 (22%)**
	For children who cannot sit independently, I recommend daily use of hand splints for range of motion and functioning.	9 (37%)	**17 (63%)**	13 (50%)	**13 (50%)**	14 (54%)	**12 (46%)**
	For children who cannot sit independently, I recommend the daily use of AFOs and/or KAFOs for range of motion.	17 (65%)	**11 (35%)**	23 (85%)	**4 (15%)**	23 (85%)	**4 (15%)**
	For children who cannot sit independently, I recommend daily use of TLSO for positioning.	16 (62%)	**10 (38%)**	18 (67%)	**9 (33%)**	18 (67%)	**9 (33%)**

Sitters	For children who can sit independently, I recommend a minimum frequency of stretching of 5–7 times a week.	17 (63%)	**10 (37%)**	20 (74%)	**7 (26%)**	20 (74%)	**7 (26%)**
	For children who can sit independently, I recommend using a standing table for a maximum of 60 minutes, with a minimum frequency of 3–5x per week and an optimal frequency of 5–7x per week.	21 (78%)	**6 (22%)**	23 (93%)	**2 (7%)**	23 (93%)	**2 (7%)**
Ambulant	For ambulatory children, I recommend active stretching 2–3x per week (with an optimal frequency of 3–5x per week).	16 (59%)	**11 (41%)**	22 (81%)	**5 (19%)**	23 (85%)	**4 (15%)**

We asked participants to rank different pieces of advice, indicating the extent of their agreement with that recommendation. Ranking options were: I strongly agree, agree, disagree or strongly disagree with this advice. The participants ranked each statement for the following (sub)groups: (1) Presymptomatically treated group: children who started with DMT prior to the onset of clinically manifest symptoms. (2) Symptomatically treated, group 1: children who initiated DMT within 2 years after diagnosis. (3) Symptomatically treated, group 2: children who started with DMT more than 2 years after diagnosis. * Percentages (strongly) disagree per subgroup are presented in bold.

Participants stressed the importance of regular and specific physical examinations (i.e. range of motion, muscle strength) and monitoring side-effects of contracture management and combining this information with the expected functional prognosis of the child to evaluate the effects of contracture treatment.

> *Participant: 'A brother and sister, both SMA type 3, have a completely different foot position. So functional prognosis is not only based on SMN copy number.'*

With frequent monitoring of physical function and treatment effects, a pediatric rehabilitation physician has the opportunity to initiate or switch contracture intervention in consultation with child and/or parent.

Clinical uncertainty of contracture interventions

The advisory group experts agreed on the difficulty of predicting the outcome of contracture treatment for an individual child. The uncertainty of the benefit for the individual child in the immediate and more distant/longer-term future was mentioned as being a problem; therefore, the group agreed that it was important to communicate this uncertainty to parents.

The group discussed the lack of evidence on the use of orthoses, specifically on the use of Knee-Ankle-Foot-Orthoses. There was no consensus on the effectiveness of KAFOs. There are unanswered questions about KAFOs, namely (1) what type of orthosis should be advised (static, dynamic, type of hinge that should be used)? (2) should KAFOs be used in young children, taking into consideration the tolerability and potential negative side-effects (for example, pressure ulcers or sleep deprivation due to wearing splints at night)?

Considerations in the light of ICF-based Functioning: incorporating contextual factors

The advisory group reached consensus about the use of the International Classification of Functioning, Disability and Health (ICF) framework[9] as a helpful tool in clinical decision-making and in creating a person-centered care plan. This ICF framework[9] is a tool, commonly used in Dutch rehabilitation care, to describe an individual's level of functioning, that includes 'body function/structure', 'activities/participation' and contextual factors (personal and environmental factors)[9]. The ICF describes an individual's level of functioning in terms of 'body function/structure', 'activities/participation' and contextual factors (personal and environmental factors) and facilitates goal-setting and evaluation of effects of contracture management. The group indicated the importance

of routine evaluation of the following factors over time: sleep, the social-emotional and cognitive development of a child, living situation of a child and family circumstances.

Examples/quotes by participants

'Sometimes a living situation doesn't allow a child to stand in a stander at home.'

'The parenting skills could influence the decision-making.'

Also, participants of the advisory group meeting described a feeling amongst parents of being willing to try anything for their child, and feelings of guilt, doubt and uncertainty in relation to doing everything for the wellbeing of their child, as part of being a 'good parent'. Examples of why parents experience these feelings:

1. Feelings of guilt/doubt when they stop a certain type of contracture treatment;
2. Feelings of guilt/doubt when they want to continue the treatment, but the orthosis/family factors/child/situation makes it impossible for them to continue with it;
3. Feelings of guilt/doubt when parents continue the treatment, despite the contracture worsening, and even though they do their utmost, the contractures worsen over time.

After the member check and the final input of participants' most important recommendations, we collated the recommendations of all participants.

1. Functional prognosis

- Address physical activity and prevention of secondary impairments and health conditions in the care plan.
- Promote active range of motion to maintain muscle length (if necessary with the help of devices like arm support).
- Determine the main focus in non-ambulant children with SMA; functional prognosis of the arms and hands could be of great importance and are usually the main focus in non-ambulant children.

2. Clinical uncertainty of contracture intervention

- Address the uncertainty, not only because of lack of scientific evidence but also practical and personal uncertainties[10] (what works for this individual child) and be honest about it.
- Even though there is a lack of evidence, in individual cases, the advice is to try different interventions to prevent and/or delay contractures.

3. Incorporating contextual factors

- Take individual factors into account: for example, is it feasible for the child, how does the child sleep and how does the child feel emotionally?
- Take environmental factors into account: is it feasible for the family/parents and the siblings?
- Support children and families in the choices they make and address social-emotional goals in the care plan.
- Also, the advisory group experts explicitly recommend to ask adolescents whether they think the contractures affect their appearance and how this impacts them. This could be a potential goal of contracture treatment.
- Communicate with parents and/or a child: what experience do you want to give a child with regard to standing/walking during his childhood?

DISCUSSION

Dutch pediatric rehabilitation physicians experience challenges in clinical decision-making regarding contracture management in the absence of clear clinical guidance in a rapidly evolving therapeutic landscape for SMA. They urge the importance of 'optimizing sitting posture', 'prevention of pain' and of 'maintaining function' as treatment goals in contracture management of children with SMA. Furthermore, advisory group experts highlighted that careful consideration of the broader ICF perspective on functioning is essential when jointly developing a contracture management plan with the child with SMA and their parents. They emphasized that, beyond body functions and structures, such a plan should also take into account personal and environmental factors that influence the child's activity and participation.

Finally, advisory group experts reported difficulties in giving clear recommendations on the necessity of orthoses and/or passive stretch management, as evidence to support these interventions is lacking.

Historically, treatment-naïve children with SMA developed progressive weakness with secondary contractures[4,5,11]. Due to lack of evidence-based interventions[12–15] contracture management in SMA has been highly challenging and has complicated rehabilitation recommendations more broadly. Therefore, the international standards of care (SoC) were carefully developed based on expert opinions from numerous international specialists. However, these recommendations were derived from experiences in patient populations who had not been treated with DMTs[6]. With the introduction of DMTs, the clinical phenotype of SMA has changed considerably. Over the past

years, rehabilitation physicians have had to redefine their perspectives on contracture management, not only in response to the improved prognosis and evolving functional abilities of these children, but also owing to the limited empirical evidence available to guide clinical decision-making. Although rehabilitation physicians are familiar with the SoC, difficulties were experienced in implementing recommendations of the SoC in the personalized care of children treated with DMTs, in this highly heterogenous group.

Respondents described the importance of 'prevention of pain' and 'avoiding the need for surgery' as targets for contracture management. However, the risk of pain and future surgery in SMA is unclear. Lager and Kroksmark[16] showed that pain is a frequent problem amongst adolescents (12–18 years old) with SMA in Sweden, however no specific information was provided on pain due to contractures. Incidence of pain in adults with NMD varies amongst studies from 40 to 75%[17–19]. It is unlikely that soft tissue contractures are, in themselves, a source of pain at rest[19]. Pain seems to become apparent when joints are pushed to the end of their range. It would be of benefit to have a better understanding of the impact of contractures amongst adults, i.e. pain, past surgery, problems with sitting posture due to contractures, problems with fitting shoes. Approximately half of the respondents (47.4%) rated the goal "at the request of parents" as neutral, highlighting the need to clarify its meaning. Understanding why parents request contracture treatment and supporting them through in-depth discussions is essential. Clinicians should collaboratively set, monitor, and revisit treatment goals with parents and children, regularly weighing potential benefits and adverse effects as part of shared decision-making in contracture management for children with SMA, and engage in open discussions with parents regarding uncertainties arising from limited clinical experience and the evolving understanding of disease trajectories in the early post-DMT era. This can help inform other on how to communicate when new treatment options become available for other neuromuscular diseases.

We observed noteworthy results on the contracture management in the group of presymptomatic treated children. Across all categories (non-sitters, sitters, and ambulant), higher proportions of respondents expressed (strong) disagreement with the statements of the SoC compared to the symptomatically treated groups. The survey did not provide data explaining why respondents were less likely to recommend different contracture management strategies for this group. For the ambulant group, one possible explanation is that respondents assumed these children would not develop contractures, or would do so to a lesser extent, compared to those in the symptomatically treated groups. These unexpected findings may also reflect the clinical challenges faced by pediatric rehabilitation physicians in this emerging field, as they were asked

to consider children with whom they had no prior clinical experience. Mortenson et al.[20] recently highlighted that empirical evidence is needed to understand the best rehabilitation approaches for SMA post DMTs, in response to the uncertainties Canadian therapists experienced in the care for children with SMA receiving DMT.

The advisory group experts stressed the importance of a careful individual evaluation of which intervention would be of help while taking into account personal and environmental factors. Therefore, we emphasize the importance of using the International Classification of Functioning, Disability, and Health (ICF), as it provides a comprehensive and multidimensional framework allowing to update rehabilitation models and individualized care plans encompassing body functions and structures, activities and participation, as well as personal and environmental factors[9]. The ICF framework helps contextualize contracture management by linking impairments in body function and structure to broader functional goals, enabling personalized, holistic rehabilitation planning. The ICF also accounts for contextual factors such as home setup, caregiver support, and motivation. These can significantly influence the success of contracture interventions and should be considered when designing rehabilitation plans.

An illustrative example from this study highlights the use of the ICF framework: two children with similar disease progression may follow different contracture plans due to personal and environmental factors. For instance, a child with communication difficulties may derive greater long-term benefit from investing his/her (limited) energy in speech and language therapy rather than in interventions targeting hip and knee contractures. This underscores the importance of tailoring individualized contracture treatment goals to each child's unique context, priorities, and potential functional gains in the ICF framework. Another illustrative example, in relation to the use of the ICF framework and focusing on personal and environmental factors, concerns the feelings of guilt and doubt described by parents in relation to doing everything for the wellbeing of their child, Gibson et al.[21] referred to similar experiences of parents with rehabilitation treatment. In a qualitative study amongst parents and children with cerebral palsy (CP), they described beliefs about the value of walking held by children with CP and their parents, and how these beliefs inform rehabilitation choices and perceptions of 'success'. They described that tapering of walking interventions contributed to feelings of guilt and doubt. Also there might be feelings of disappointment for a health care professional. They might have a desired outcome, which doesn't fit with progression of contractures. This desired outcome might have important implications for the individual choices of a health care professional. Whereas one individual might see a straight leg as a desired outcome and is prepared to try everything to achieve

the goal, another might see the preferred goal as secondary and be much less likely to try multiple options[22].

The strengths of this study include the number of rehabilitation physicians that responded to the survey, which lends robustness and representativeness to the survey. This study was conducted within the first few years after the introduction of DMTs in the Netherlands, a period during which the functional prognosis of individual children receiving DMTs was still uncertain. Although some information was available from clinical trials, this study represents the first real-world clinical experience gained by Dutch rehabilitation physicians themselves. In the absence of empirical evidence, it is essential to share clinical experiences internationally to bridge knowledge gaps.

A potential limitation is that the survey data did not assess reasons for non-adherence across the entire sample; this aspect was explored only in the in-depth qualitative part of the study. This study is limited with regard to the reflection of presymptomatic children. When designing the survey, we aimed to explore whether physicians would develop different treatment plans for children in the presymptomatic group who started DMT before the onset of symptoms, compared to children with SMA who started their treatment later in life, often with pre-existing contractures. At that time we had little knowledge of what DMTs would do for newborns (both symptomatic and presymptomatic). Upon discussing the survey results, we noted that pediatric rehabilitation physicians found these questions challenging to answer, due to the limited clinical experience available with the presymptomatically treated group at the time of the survey. Some questions were too hypothetical. In the new generation of children with SMA, it is important to regularly assess joint mobility and monitor the development of contractures over time, and to systematically record these data in a registry, enabling longitudinal analyses to better understand the prognosis of contractures and the factors that influence it. In the Netherlands, there is frequent monitoring of joint range of motion, both by the pediatric rehabilitation physician and the involved physiotherapist(s). This is important in the light of the difficulties experienced in the timing of initiation of contracture treatment. Pediatric rehabilitation physicians may be uncertain when to start the treatment in asymptomatic children with SMA. It is a very promising group in terms of their functional prognosis, which should, therefore, motivate clinicians to start early in order to prevent contractures. There is, however, a trade-off, as children might only develop minor contractures later on in life and are potentially being treated unnecessarily during childhood. A recent qualitative study[7] amongst adolescents and young adults with SMA showed that there is little motivation for standers/orthosis in general, but when there is a clear treatment goal, motivation increases. Also, recent

initiatives in rehabilitation care within the evolving therapeutic landscape[20], including specific attention to contracture management[23], represent promising developments for this new generation of children.

Finaly, despite the small sample of pediatric rehabilitation physicians involved in the care for children with SMA, we are convinced that our study included a representative sample from diverse work settings, encompassing a sufficient range of experience with SMA. Our results may not, however, be generalizable internationally.

CONCLUSION

In line with Trabacca et al.[24] we stress the importance of using the ICF framework when updating practice guidelines/the standards of care regarding contracture management, for people with SMA in this era of disease-modifying therapies. The Dutch approach focuses on multidisciplinary care, collaboration between healthcare professionals and a patient-centered approach, with a focus on activities and participation, rather than solely on body functions and structures, taking into account personal and external factors. The use of the ICF framework is essential for developing better rehabilitation practice guidelines, specifically for individual contracture guidance. With an optimized individual contracture plan, defining child-specific treatment goals which work towards optimizing the level of participation, the quality of life can be improved for children with SMA.

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SUPPLEMENTARY FILE 3.1

Survey for pediatric rehabilitation physicians involved in the care of children with SMA: contracture treatment

The e-mail below, addressed to pediatric rehabilitation physicians, concerns the care of children with a neuromuscular disorder.

Dear colleague,

The care for children with SMA has changed considerably in recent years due to the introduction of new drugs for SMA, nusinersen (Spinraza®) currently being the most important. Due to the effects of these treatments on the motor development of a large number of these children, contracture management can now be seen in a different light. In this project, we want to learn together how we can best shape contracture treatment in children with SMA. It is important to first describe the initial situation and to identify current bottlenecks in the (preventive) treatment of contractures. Our ultimate goal is to optimize the care for children with SMA.

We would ask you to complete the online questionnaire regarding the current contracture policy. The questions/statements are based, among other things, on the international "Standards of care" for SMA and the Dutch guideline for SMA type 1. The results of these surveys have been included in a broader study into the impact of contractures on daily functioning. Completing the questionnaire will take you about 20–30 minutes. Even if you are not involved in the care of children with SMA, would you please open the digital questionnaire and answer the first 2 questions. If you indicate in question 2 that you are not treating children with SMA, the questionnaire will automatically stop.

Part 1: General questions

1. You work as a rehabilitation doctor in a (multiple options possible):
   university hospital, (community) hospital, rehabilitation center, other...

2. How many children with SMA do you see, or are receiving treatment by you, per year, on average?
   0, 1–5, 5–10, 10–20, >20 (If you answer 0, the questionnaire will stop)

Part 2: Measurement of contractures

1. How many times a year do you see a child with SMA for a check-up (every contact moment, incl. technical/shoe consultation)?
   Occasionally, 1x per year, 2x per year, 3–5x per year, >5x per year

2. How do you monitor joint mobility (range of motion) in children with SMA? (multiple options possible)
   Measurement by rehabilitation physician, measured by team member (physical/ occupational therapist), measured by (physiotherapist/occupational) therapist in the community, this is not measured.

3. Which joints are measured?
   Shoulder/elbow/wrist/fingers/hip/knee/ankle/other, namely...

4. How often do measurements take place in children <5 years of age with SMA type 1 or 2?
   Very frequently (quarterly or more often), regularly (about every six months), occasionally (approximately annually)

5. *Open text field for explanation* How does documentation of joint mobility take place in your center (multiple answers possible)?
   a. *As text in electronic patient dossier (EPD) / e-chart*
   b. *In a numeric field in EPD*
   c. *Graphics EPD*
   d. *Separate database outside the EPD*
   e. *Other, i.e.*

Part 3: Contracture management, indication and purpose

Thoughts on the importance of contracture treatment

1. Please rank the importance of contracture prevention (rating from 0 (lowest) to 10 (highest)).
   Open text field for additional comments (optional)

'An important number of the children with SMA in the Netherlands is currently being treated with DMT, nusinersen (Spinraza®) being the most important. Due to the effects of these treatments on the motor development of a large proportion of these children, the contracture management policy has also been placed in a different light.'

2. Do you think the need for contracture prevention has changed since the implementation of DMT (in this case nusinersen (Spinraza®))?
   Yes/no
   (Mandatory open-text field at yes): The need for contracture prevention has changed, because...
   (Mandatory open-text field at no): The need for contracture prevention has not changed, because...

3. Please indicate the extent to which you agree with the following statements. 0=n/a, 1=strongly agree, 2=agree, 3=neutral, 4=disagree, 5=strongly disagree
   - Contracture prevention is important for maintaining function
   - Contracture prevention is important for the prevention of pain/stiffness
   - Contracture prevention is important for a good sitting posture and activities of daily living (ADL)
   - Contracture prevention is important for a patient's appearance
   - Contracture prevention is carried out at the request of child/parent
   - Contracture prevention is important to avoid surgical intervention

Thoughts on starting/stopping and type of contracture treatment

4. I initiate therapy as part of the management of contractures: (multiple answers possible)
   Before a contracture can develop, as soon as a contracture arises, as soon as a contracture worsens, as soon as a contracture gives rise to complaints, that depends on the joint, that depends on the treatment of other joints which has already started, otherwise:

5. If I recommend starting to use a standing table, then preferably at the age:
   0–1 years, 1–2 years, 2–5 years, >5 years
   Open text field: which conditions (of the child or external) do you consider necessary for starting to use a standing table?

6. Can you indicate for what reasons you would stop the treatment of contractures?
   Note (required field):

Part 4: Contracture management, prevention/treatment in relation to guidelines

Dutch guideline SMA type 1

The following statements are based on the advice regarding contracture prevention from the guideline on Spinal muscular atrophy (SMA) type 1 (Startpagina - SMA type 1 - Richtlijn - Richtlijnendatabase).

For the following patient groups, regardless of whether or not you treat a child in this specific target group, could you indicate the extent to which you agree with the statement? *1=strongly agree, 2=agree, 3=disagree, 4=strongly disagree*

Please give answers for three different patient severity levels:

1. **Presymptomatically treated group**: children who started with DMT prior to the onset of clinically manifest symptoms.
2. **Symptomatically treated, group 1**: children who initiated DMT within two years after diagnosis.
3. **Symptomatically treated, group 2**: children who started with DMT more than two years after diagnosis.

Stretch the muscles and maintain length, within the pain threshold, at least three to five times a week, sustaining the final position for at least thirty seconds.

Proposition 1: *I advise parents to stretch muscles fully and maintain them in accordance with the above statement*.

Proposition 2: *Combat contractures by performing prolonged stretching. Static and dynamic orthoses can be used for this, if indicated.*
Basically, I apply static and/or dynamic orthoses in this target group.

Proposition 3: *Consider using a corset for children with SMA type 1C or children who are receiving medication if postural ketosis is present.*
I am considering using a corset for children with SMA type 1C or children who are being treated with medication if postural glucose is present.

International Standards of Care
The following statements are based on the recommendations on contracture prevention for children with SMA types 1, 2 and 3 from the Standards of Care for SMA: *Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care by Mercuri et al. 2018* (Diagnosis and

management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care - ScienceDirect).

For the following patient groups, regardless of whether or not you treat a child in this specific target group, could you indicate to what extent you agree with the statement? *1=strongly agree, 2=agree, 3=disagree, 4=strongly disagree*

Please give answers for three different patient severity levels:

1. **Presymptomatically treated group**: children who started with DMT prior to the onset of clinically manifest symptoms.
2. **Symptomatically treated, group 1**: children who initiated DMT within two years after diagnosis.
3. **Symptomatically treated, group 2**: children who started with DMT more than two years after diagnosis.

Non-sitters

Stretching: Daily use of upper lower limb orthoses for stretching and to promote function and range of motion. Static orthoses, knee immobilizers and hand splints are recommended for positioning and stretching. AFOs and KAFOs can be used for stretching and positioning. TLSOs (thoraco-lumbo-sacral orthosis) are used for positioning. Supported standing.

The minimal frequency for stretching and range of motion is 3–5 times per week. The minimal frequency for bracing to be effective is 5 times per week.

Proposition 1: In children who cannot sit independently, I recommend a minimum frequency for stretching of 3–5 times a week.

Proposition 2: For children who cannot sit independently, I recommend daily use of hand splints for range of motion and functioning.

Proposition 3: For children who cannot sit independently, I recommend daily use of AFOs and/or KAFOs for range of motion.

Proposition 4: For children who cannot sit independently, I recommend daily use of TLSO for the purpose of positioning.

Sitters

Stretching: Orthoses are used for the upper and lower limbs to promote function and ROM. Regular stretching for segments known to be at risk of contractures: hip, knee and ankle, wrist and hand. Knee immobilizers, KAFOs, and AFOs are recommended for positioning and standing. RGOs (Reciprocating Gait Orthosis) and KAFOs can be used for supported ambulation. TLSOs and hand splints are used for positioning.

Minimal frequency for stretching and ROM: 5–7 times/week. When stretching or performing joint mobilization, ensure joint segments are aligned throughout the treatment. Supported standing should be up to 60 minutes and minimal frequency is 3–5 times/week, optimal 5–7 times/week.

Proposition 3: In children who can sit independently, I recommend a minimum frequency of stretching to maintain ROM of 5–7 times/week.

Proposition 4: In children who can sit independently, I recommend using a standing table for a maximum of 60 minutes, with a minimum frequency of 3–5 times/week and an optimal frequency of 5–7 times/week.

Ambulant

Stretching: minimal frequency: 2–3 times/week, optimal: 3–5. Maintain flexibility through active assisted stretching and include the use of orthoses according to specific needs.

Proposition 5: In ambulatory children I recommend actively stretching 2–3 times/week (with an optimal frequency of 3–5 times/week).

Are there any aspects related to contracture treatment that have not been highlighted in the above survey that you think are important to share with us? {Open text field:}

If you are willing to be approached at a later date for in-depth questions about this survey, would you please enter your name and e-mail address and/or telephone number here?

SUPPLEMENTARY FILE 3.2

Topic guide for discussion at the advisory group meeting
Thoughts on (preventive) contracture management in children with SMA

Important:

- All questions are posed in the context of SMA (types 1–3, age range 0–18 years old).
- We want to understand why Dutch rehabilitation physicians make specific choices and why these vary between them.
- There is no right or wrong, all information is useful.
- We made an audio recording.

Goal-setting:

1. Questioning the general principles
2. Prompting

General principles:

- What comes to mind about contracture treatment in the context of a child with SMA?
- In your opinion: which is the most problematic contracture and why?
- Which factors do you take into account, and what do you consider, when making a treatment plan for contractures?
- Do you sometimes argue with a physical therapist/occupational therapist/ psychologist or other health care professional about contracture management of a child? Which factors in the discussion are the most important?
- What is your opinion about the impact of contracture management? Do you feel your experience plays a role in decision-making?
- In your opinion, what would be the most important improvement in care with regard to contracture management? Or, what do you think is missing from the contracture management protocol in the Netherlands?
- Are there views on other conditions that you take into account in your decision-making?

Prompting:

- What is the most commonly referred to 'contracture of hinderance' in adulthood? What are the most important questions about contractures in (young) adults?
- What is your opinion about contracture management in the 'new group' of children with newborn screening, presymptomatic- or early symptomatic-treated children?

- What is your opinion about preventive contracture management in relation to symptomatic contracture management?

SUPPLEMENTARY FILE 3.3

Additional information advisory group experts

	Years of experience in treating children with SMA	Dedicated focus on NMD in clinic?	Member of national working group on NMD?	Work setting?	Caseload of children with SMA at the time of participation?
Expert 1	>10 years	Yes	Yes	Rehabilitation center	1–5
Expert 2	5–10 years	Yes	Yes	Rehabilitation center	5–10
Expert 3	>10 years	Yes	Yes	Rehabilitation center	5–10
Expert 4	5–10 years	Yes	Yes	University hospital	10–20
Expert 5	5–10 years	Yes	Yes	University hospital	>30
Expert 6	>10 years	Yes	Yes	University hospital	>30




INTERMEZZO



4

‘This battle, between your gut feeling and your mind. Try to find the right balance’: parental experiences of children with spinal muscular atrophy during COVID-19 pandemic

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ABSTRACT

Aim(s): Parents of children with spinal muscular atrophy (SMA) often struggle with the all-consuming nature of the demands of caring for a child with substantial physical needs. Our aim was to explore experiences, challenges and needs of parents of a child with SMA in a COVID-19 pandemic situation.

Method: Nineteen parents of 21 children (15 months to 13 years of age) with SMA-types 1–3, participated in semi-structured interviews in June to July 2020. The interviews were analysed using inductive thematic analysis.

Results: Parents mentioned the protection of the health and well-being of the child as the central perspective and driving force during the COVID-19 pandemic. Three subthemes were identified: (1) responsibility, (2) balancing vulnerability & resilience and (3) (in)security. Some parents focused on the positive aspects during the lockdown, such as continuation of nusinersen treatment and family life. Some parents described helpful and positive cognitions to cope with the situation. In general, parents described a need for information with regard to COVID-19 and their child with SMA and a need for discussing their dilemmas and insecurities with a health care professional.

Interpretation: Parents put the health and well-being of their children first during the pandemic. From this study we learned that parents of children with SMA need information and value direct contact with a healthcare professional to share their dilemmas and insecurities. The dialogue can help to empower parents in the conflicts and decisions they have to make during a pandemic.

Keywords: COVID-19 pandemic, decision-making, family, parenting, spinal muscular atrophy, well-being

INTRODUCTION

Hereditary proximal spinal muscular atrophy (SMA) is a severe neuromuscular disease that causes progressive muscle weakness and impairment. Due to the weakness, children are in need of supportive (para)medical care and there is a high caregiving demand from the parents. Recently, 3 genetic therapies have been introduced (i.e. nusinersen, risdiplam, onasemnogene abeparvovec) that improve motor function in a substantial percentage of patients.

Before the introduction of genetic therapies, parents already struggled with the all-consuming demands of caring for a child with substantial physical needs and the ways in which this affects the emotional and social lives of the entire family[1–5]. A qualitative study of parents' experiences of taking care of their children with SMA in the context of new treatments[6] showed that autonomy and a feeling of being in control are important factors for parents to be able to carry out their task of caregiver, especially when they are confronted with additional factors.

On February 27, 2020, the first case of COVID-19 was confirmed in the Netherlands[7]. The COVID-19 pandemic resulted in a general 'lockdown' in the Netherlands in the spring and summer of 2020 with movement restrictions and social distancing of people other than your own household members. These restrictions especially affected patients with a chronic disease and their family members[8]. People had to work from home and school and day care centers were closed. Regular outpatient hospital visits were postponed, but urgent and necessary care was continued if possible.

In the beginning of the COVID-19 pandemic nothing was clear about the transmissibility of COVD-19 and the risk for children with neuromuscular diseases. SMA is characterized by respiratory muscle weakness and increased vulnerability to viral infections[9]. From the start of the COVID-19 pandemic, parents with a child with SMA were confronted with new levels of challenges and uncertainty, including whether intrathecal nusinersen treatment could be continued, extra demands in caregiving, increasing stress and need for additional decision making about going to school and therapies.

Parents had to make many difficult decisions, often lacking sufficient and specific information[8,10]. Since the outbreak of the COVID-19 pandemic, several articles have been published about the difficulties parents of children with chronic disabilities experienced due to the COVID-19 pandemic[8, 10–16]. Families with children with disabilities or chronic diseases experienced difficulties due to social distancing, reduction in

services (like rehabilitation), the mental load (anxiety and depression) in combination with the lack of help/support and other restrictions to prevent the spreading of the virus.

All of the above mentioned studies were online surveys[8, 10, 11, 13–16], providing quantitative data. Only in one study[11] added open text box questions qualitative data, providing some insight in the experiences of parents of children with cancer, in relation to the virus, lockdown and isolation in children with cancer. The results globally demonstrated views and experiences of this population, and the authors emphasize the importance of future studies in order to understand the ongoing experiences of families. In general, we feel it is important to get insight into the perspectives and experiences of parents, including the reasoning behind the choices parents made. The aim of this study was to explore experiences, challenges and needs of parents of a child with SMA in a COVID-19 pandemic situation.

METHOD(S)

We conducted an exploratory qualitative interview study with parents of children with SMA. This study is reported in accordance with the guidelines of the Standards for Reporting Qualitative Research (SRQR) checklist[17].

Participants

We invited parents of a child with SMA type 1, 2 and 3, aged <16 years to participate in this study. Treatment of SMA with genetic therapies in the Netherlands is centralized, in the UMC Utrecht (UMCU). Not being able to communicate in Dutch or English was reason for exclusion from the study.

We recruited parents through an invitation in the widely read newsletter of the SMA Center at the UMCU that is being sent to all families of children with SMA. Parents of children with SMA type 1 who were in regular contact with the social worker of our team were reminded of the invitation at the end of the conversation. Parents who were willing to participate received an information letter. Two weeks after this first announcement, all parents of children with SMA type 1, 2 or 3, <16 yrs who had not responded to the invitation also received an information letter.

Parents were contacted to schedule the interview after their consent. We ensured anonymity of participants by changing names in the transcripts before the start of the coding process. We assigned a research number to all participants and the key to the

corresponding personal data could only be accessed by researchers planning and conducting the interviews (ES, MM) and by the study coordinator (CvS).

The Medical Ethics Committee of the University Medical Center exempted this study from Medical Research Involving Human Subjects Act (17-904); all participants gave informed consent.

Data collection

We collected data by means of semi-structured interviews using a topic list with relevant issues of the COVID-19 pandemic, including the impact of the COVID-19 pandemic on well-being of the family, resilience, and expectations parents have from the hospital and clinicians (see topic list in Appendix 4.1). The content of the topic list was based on expert clinician input and parent's questions and input in the first months of the pandemic. Two trained psychological assistants (ES, MM) performed these semi-structured interviews via telephone calls between June 3rd and July 30th, 2020. In this time frame in the Netherlands we faced the original COVID strain. The interviews were audio-recorded and transcribed verbatim.

Data analysis

We collected and analyzed data simultaneously in an iterative process. A thematic analysis was conducted as described by Braun and Clarke[18].

First, researchers (ES, DP, MM, CvS and MK) prepared and familiarized themselves with the data by listening to interviews and reading transcripts. Notes of the initial ideas were collected and discussed within the research team. Second, two transcripts were open-coded by two authors (ES and DP) independently. They compared and discussed findings and codes until they reached consensus. Next, four researchers (CS, ES, MM and DP) coded six interviews in different pairs, and through discussions in regular team meetings constructed a preliminary code tree. ES coded the remaining transcripts.

Based on the list of codes, four authors (ES, CvS, DP, MM) discussed potential themes and interrelated elements, led by MK. We discussed and formed (sub)themes, checked if the themes worked in relation to the coded extracts (Level 1) and the entire data set (Level 2) and generated a thematic 'map' of the analysis. ES refined each theme in consultation with CvS, DP, MM, IOL, and MK. The proposed definitions of the themes were checked by ES with the original transcripts and codes. Finally, three authors (ES, IOL, MK) worked out the overall story line. The preliminary results were discussed with the entire team. QRS Nvivo 12 software was used to support data analysis.

RESULTS

Participants

We sent the invitation for participation to 120 families. Parents from 24 families gave permission to be contacted (20%), with a withdrawal of five parents after initial permission. We included parents of 19 families with 21 children with SMA (Table 4.1). After 16 interviews we approached code saturation and after three additional interviews we confirmed code saturation. Duration of the interviews varied from 40 to 90 minutes, with an average of 55 minutes. In two interviews, both parents were present. We interviewed 16 mothers without the father present and one father without the mother. Parents' and children's characteristics are summarized in Table 4.1.

Table 4.1. Characteristics of parents participating in the interview (n=19)

Characteristics	n
Gender of the parent	
Mother	16
Father	1
Couples	2
SMA type	
SMA type 1	6
SMA type 2	10
SMA type 3	5
Age child (years)	
Min–max	1–13
Median	7
Interquartile range (IQR)	5
Sex child	
Male	10
Female	11
Siblings	
Yes	12
No	7
Families with two children with SMA	2
Treatment for SMA	
None	1
Nusinersen (Spinraza®)	17
Risdiplam (Evrysdi®)	3

Qualitative analysis of the interviews showed that the essence of the experiences of the respondents fell under four main themes, with one overarching theme and three subthemes. Protecting the health and well-being of the child was found as the central

perspective and driving force mentioned by parents. With three subthemes: 1) responsibility, 2) balancing vulnerability & resilience and 3) (in)security.

These (sub)themes cannot be interpreted separately, as they are intertwined (Figure 4.1). The overarching feelings regarding the health and well-being of their child affect parents' considerations regarding responsibility, (in)security, and the balance of vulnerability and resilience, which in turn in the interviews often were interrelated.

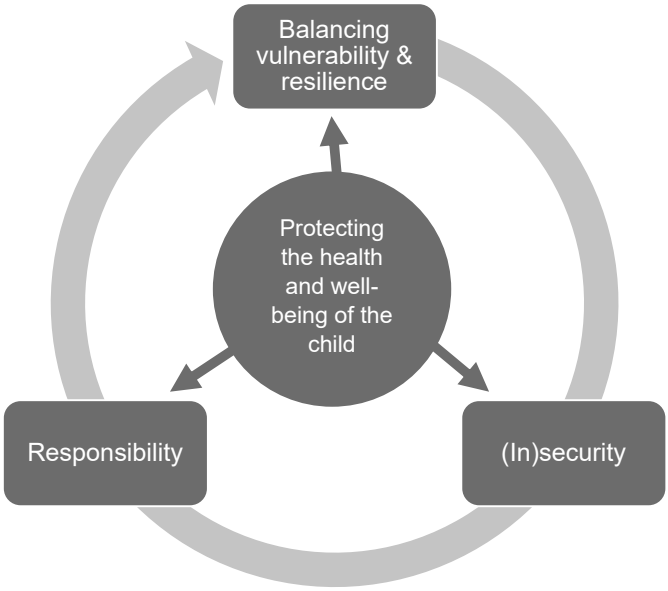


Figure 4.1. Overarching theme and three subthemes.

Protecting the health and well-being of the child

'This battle, between your gut feeling and your mind. Try to find the right balance.'

This quote summarizes the predominant feeling of parents with a child with SMA during the COVID-19 pandemic. The priority of all participating parents was to protect the health and well-being of their child. In an attempt to prevent any family member getting infected with the virus, there was no other choice than to withdraw from public life during the lockdown at the peak of the pandemic for most of the families.

'I was so worried, that I decided that nobody could enter or leave the house, no caregivers. Our bubble reduces my worries.'

'We completely isolated ourselves, at least the first eight weeks... we didn't do anything, no therapy, no caregivers at our place, nothing: just the five of us.'

Parents experienced various difficulties in decision-making after some of the restrictions in the Netherlands were lifted (because of reduction of COVID-19 infections in the country).

'... you have many things to consider, you have to overthink a lot and make a lot of decisions...'

Parents struggled with the necessity to keep their children inside in order to reduce the risk of a COVID-19 infection. For some children it was difficult not to have social contacts, and parents described the struggle of their children because they missed their family members, caregivers, school and friends.

'Yesterday, she went back to school again for the first time, which she found amazing. She had missed her friends at school a lot, she is really keen on social contacts, wants to play with other kids and is really nice to other children. Yes... she missed that a lot.'

Parents struggled how to make the best decision for the well-being of their child, balancing between the risk of an infection and the social-emotional well-being of their child by letting them go to school and play with friends.

'My daughter also sees other children going outside. There was the limitation of COVID-19 restrictions, with children below 12 years old going outside. I felt like having two choices. I could anxiously keep my child home, to protect her from the risk of getting infected... thereby creating a child that is sad, miserable and grumpy. Or I could choose to increase the risk of getting infected, but I see my child being happy, participating in society and enjoying her life.'

Responsibility

'Yes, yes, we will manage to find the discipline to deal with the situation, because it is for the best of your child. We will do anything for our child.'

Parents felt great responsibility to protect the health and well-being of their child with SMA. Most parents wanted to continue intrathecal treatment with nusinersen for their child, to ensure continued effectiveness. Most parents considered treatment for SMA more important than doing everything to prevent infection with COVID-19.

Sometimes parents described the feeling that they did not even think about having a choice; delaying treatment was not an option. Also, some parents said they were lucky to have had an appointment for nusinersen injection prior to the lockdown, so there was no need to visit the hospital again soon.

'... well you want your child to get the nusinersen treatment and therefore you need to go to the hospital, that's how it is.'

Almost all supportive treatments, such as physical therapy, hydrotherapy and occupational therapy were cancelled because of the lockdown. Parents were afraid that not having therapy for a long time would negatively affect their child's well-being and felt responsible to take over these therapies as much as they could, mostly using video consultation with a therapist. Sometimes parents allowed therapists to come over, but with restrictions and personal protective equipment. Staying at home was still favoured in comparison to going to a physical therapist or rehabilitation centre. When therapies restarted in the Netherlands (due to limiting of COVID-19 restrictions), parents often decided to slowly resume therapies, sometimes starting in their home environment. Parents felt a challenging balance in taking responsibility to make the right decision for their child with SMA: physical therapy is medically necessary but with additional risk of getting infected with the COVID-19 virus.

'So in this case the mind beats the gut feeling, because it is important to take care of the child's teeth and eyes, so the doctors' appointments had to continue.'

'... we really tried to keep our child active and putting him in the stander every day.'

'We did go to really important appointments, because there are also different welfare interests than the prevention of a COVID-19 infection.'

Also, some parents described their child with SMA being more sad than usual because they missed their peers. Parents felt responsible for the mental well-being of the child with SMA and the (mental) well-being of their siblings.

'I want for her to be able to participate in society, despite the fact that we from our point of view are afraid that she will be infected.'

Parents and siblings also missed their social contacts. Parents expressed the dilemma to balance between the best practice for their child and relaxing/social time for themselves or siblings.

Balancing vulnerability and resilience

At the start of the pandemic, parents felt anxious and vulnerable due to the increasing number of infections while information on risks for children were lagging behind. For example, in the first weeks of the lockdown parents reported to be more scared, compared to the time of interview a few months after the start of the pandemic. Parents expressed that their anxiety decreased when it became known that children were less susceptible to (severe disease caused by) the virus and did not play an important role in virus spreading. This influenced their decision making.

Parents expressed having a hard time, but quickly followed with statements of always being capable of coping with the situation. One parent, for example, mentioned that she was glad her husband had to work from home and that she wouldn't have known how to deal with everything if he would be working at the office. Another parent said: '*the restrictions were tough and if I wasn't able to go out for a walk to have some time for myself, I would not have been able to deal with the situation*'.

Coping strategies for parents that stood out were: 1) to compare with others: '*fortunately, we only have one child with SMA*' or '*we are lucky, because our child is not in need of a lot of medical care in comparison to my sisters' child*'; 2) to adapt to the situation: '*from the day our child was born we constantly need to adapt to new situations, now again we need to adapt to the COVID-19 situation, but we are used to adapting now*'; 3) focussing on the positive aspects: '*it is a very challenging time, but thankfully we have a garden*'.

Finally, one parent stated: '*a lot of people felt it was intense to stay at home and that it was difficult to cope with restrictions, but that's what we have to deal with all the time*'.

Sometimes it helped parents to set their own hesitations aside in favour of their child. However, other parents still expressed their fear of infection as being extremely high at the time of the interview, thus maintaining their previously instated restrictions. Although parents felt vulnerable, with sometimes feelings of anxiety and depression, parents also showed resilience.

> *'... well, I have experienced it as pretty tough, you know why? I have a very high workload and was also taking care of the children, combined with all the homeschooling and having to make telephone calls for work. Well, I managed, but every now and then it was though and I wasn't happy at all. Absolutely not...'*

'It was tough and really heavy. Because next to taking over the therapy, I also had to home school my child and taking over all the caring. My day literally only consisted of three things: taking care, home-schooling and taking over therapy.'

'Your mood goes in all directions, from very confident and calm to just overtired and hysterical and then back again.'

Parents felt there was less time for themselves to relax and go out with friends and siblings were missing their friends. They described that being a 2-parent family, taking time for themselves, the thought that giving up was no option and a positive mindset had helped. Despite of these supporting factors, parents often experienced insecurities.

'You know, we're not going to give up. We are fighters and we go for it. We have to deal with it, do what we have to do without realizing how hard it is.'

(In)security

The interviews showed that some situations created a feeling of insecurity in parents while other situations did not.

'You have to make a lot more decisions, you have to think about a lot of things and make new choices, like could my child be in contact with other children?'

'Exactly, people ask whether she is going to school again or when we want her to go back to school. I don't know!'

Almost all parents experienced a lack of information. During the COVID-19 pandemic, the frequency of the contacts between all parents and health care professionals was decreased. And when they did speak to each other, the health care professional often did not have the answers parents were yearning for. Many parents were disappointed with the scarcity and ambiguity of information they received. Parents often did not feel sufficiently in control to be able to fulfil the caregiving demands. Many parents described a feeling of insecurity to go to the hospital for an appointment. Sometimes this feeling disappeared after the hospital visit. One parent described to have been reassured after the hospital visit.

'That first fear of going to the hospital. Is it safe to go to the hospital, do professionals maintain the 1.5 meter social distance, is everyone protected? But everyone was really relaxed in the hospital, after seeing that, I was more relaxed myself.'

Parents felt more secure when it seemed that children were not severely affected, that children with neuromuscular disorders did not seem to have a higher infection rate nor being severely affected and that general infection rates decreased. Several parents decided to wait a couple of weeks (or during the summer holiday) and finally they felt safe to let their child go back to school.

'... when it was clearly stated in the news that COVID-19 is not really dangerous for children, I became less anxious.'

'We looked at the infection numbers, and technically it was going better. You should take the step, because you can't keep them at home until December.'

Going to school was a physical risk, but parents were tired from all weeks at home, working, teaching and caring for their children. Children were yearning to go back to school and see their friends. For most parents, these feelings supported the decision to overcome the insecurity of letting them go to school.

'But I dared it anyway, although I still have doubts because I still find it scary, but yes I did it. It is important for her well-being and her 'mood', so to speak. Because sitting at home is quite difficult for them too.'

One parent explained the difficulty to overcome the feeling of insecurity and letting their child go back to school again. This parent replaced the feeling of insecurity by creating a little security to go to school himself to help their child with going to the restroom. Thereby reducing the risk of a COVID-19 transmission through an attendant helping their child. This in fact is also again an example of the parents balancing between vulnerability and resilience.

DISCUSSION

This qualitative study highlights the main focus of parents in the COVID-19 pandemic situation: protecting the health and well-being of their child with SMA. Parents experienced a constant challenge to balance between the well-being of their child and the risk of introducing COVID-19 in their home, with three important themes underlying this central theme: responsibility, balancing vulnerability & resilience and (in)security. These three themes, underlying the central theme, are interrelated (Figure 4.1). With the physical and mental well-being of their child as central in their perspectives, the responsibility parents feel, in combination with (in)securities in situations that are constantly changing, they balance vulnerability and resilience. Because the themes

are interrelated, they cannot be separated from each other. From the interviews it became clear the COVID-19 pandemic in the early stages, when we performed the interviews, increased insecurity, and with the responsibility parents feel for the health and well-being of their child, affected the constant attempts of parents to balance resilience and vulnerability. During the COVID-19 pandemic parents experienced new and additional challenges to balance the physical health of their child and the social-emotional well-being of the family.

While protecting the health and well-being of their child with SMA was a general theme of this study, we also found variation between individual experiences. This variation, between parents and within parents over time, was most clear in the subthemes: balancing between vulnerability and resilience, balancing between feelings of security and insecurity, and the feeling of being responsible for your child while risking to sacrifice their own needs.

For some parents it was a tough time, and for others it felt like they finally found some time to slow down, normalize and experience some relaxation. During the analysis the research group identified self-sacrifice to be an important theme. However, this was not mentioned by the parents themselves, nor did they reflect on their experiences in this way. This is an interesting interpretation of the research group, which underscribes the importance of listening to parents to understand their individual perspectives and needs, and, preventing assumptions from a professional's perspective.

The needs of a parent can change over time, but typically are observed and compared between periods before and after a major change. The rapidly evolving pandemic forced parents to adjust to new information almost every day. As different parents have different needs at different times, it is important for health care professionals to tune in on parents' specific questions and (information) needs, and to understand why they are important to them at that time. Obviously, parents described a need for information in regard to COVID-19 and their child with SMA. Clinicians can do well by having individual conversations with parents to reflect on their insecurities and challenges. Even if no clear answers could be given, parents often felt supported when they had the opportunity to discuss their uncertainties with a health care professional. It may be helpful for parents to know that they are not the only ones who are struggling, and to normalize the challenges they face and the impact on their lives.

This study obviously has limitations. We cannot exclude selection bias, since parents experiencing huge challenges and stress may have declined participation in this study.

Although we found three fathers willing to participate (of which 2 couples were included), most of the participants were mothers. It may well be that the lived experiences of mothers differs from those of the fathers.

Nonetheless, the results of this study underscribe the importance of autonomy and feelings of control when taking care of a child with SMA. Our study also shows the important role that clinicians have to empower parents of children with special (care) needs especially when they are confronted with additional challenges, such as the COVID-19 pandemic. Even though the current study specifically focused on families of children with SMA, and did not examine other populations of children, it is likely that some of the themes identified could be comparable in children without disabilities and their families (e.g., [19]). Moreover, the themes identified have also been found in subgroups of children with other special (care) needs (e.g., [20]).

Key messages

- Protecting the health and well-being of the child with SMA is the central perspective and driving force mentioned by parents, during the COVID-19 pandemic.
- During the COVID-19 pandemic parents focused on keeping balance between the risk of getting affected by COVID-19 and the mental & physical well-being of their child with SMA, siblings and family.
- Parents appreciate information and conversation with health care professionals to reflect on the insecurities/decision-making process of parents.

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APPENDIX 4.1

Topic list

General questions

- How many children do you have?
- If several children, how many of your children are diagnosed with SMA and what type?
- How old are your children?
- How old is your child with SMA?
- What type of property do you live in?

Fear of COVID-19 infection

- Are you worried about a COVID-19 infection in your child with SMA?
- On a scale of 0–10, how much are you worried about a COVID-19 infection for your child?
- Which COVID-19 restrictions do you use?
- For your child with SMA? (completely at home/still outdoors for …)
- For yourself? (completely at home/still outdoors for …)
- For the other children in the family (completely at home/still outdoors for …)
- Who do you allow to come to your place?
- Is your child with SMA going back to school?
- Are the other children in your family going back to school?

Impact of the COVID-19 restrictions on the care of the child with

The questions I am going to ask you are always first about what it was like BEFORE the COVID-19 pandemic and then about how that has changed since the pandemic.

Medical care:

- What treatment does your child receive for SMA?
- How often did you normally come to the hospital?
- How is that now? If different: why is that? Own decision or from others?
- What do you think about that?

Education:

- What type of education does your child admit or what kind of day care does your child attend?

- How many days a week?
- Is it changed during the pandemic, how is it now? If different: why is that?
- How do you feel about the current situation?

Care at home (paramedical, care etc.):
- What types of therapy and/or care does your child receive? (physical therapy, occupational therapy, speech therapy, home care, etc., and where?)
- Is it changed during the pandemic, how is it now? If different: why is that?
- How do you feel about that?
- Do the restrictions have an impact on your child's health? If so, which ones?

Effect of the COVID-19 pandemic on parental well-being

The following questions are about the consequences of the COVID-19 restrictions on your well-being

- To what extent do you manage to combine your work with caring for your children?
- Are there financial consequences for your family?
- How do you assess your mood in general over the past 2 weeks?
- Is your mood different than before the COVID-19 pandemic?
- How do you assess your night's sleep?
- What was this like before the COVID-19 pandemic?
- What do you miss the most?
- What is the reason that it is not possible now: COVID-19 restrictions, extra care for the children, financially, otherwise ...

Effect of the COVID-19 pandemic on your child's well-being

The following questions are about the consequences of the COVID-19 pandemic on the well-being of your child

- How do you assess your child's mood in general over the past 2 weeks?
- What was this like before the COVID-19 pandemic?
- How do you assess your child's night's sleep
- What was this like before the COVID-19 pandemic?
- Do you notice a difference in how your child with SMA experiences the COVID-19 pandemic and how his/her brothers and/or sisters experience this? (difference in fear of infection, difference in dealing with the restrictions to prevent infection)

Characteristics resilience in parents

Some parents feel that, no matter how difficult it is, they can handle the situation. Other parents have the feeling that they are completely overwhelmed.

- How's that like for you? To what extent do you feel you can handle the situation? What determines this?
- What are you doing to keep up?
- How good do you think you can keep it up?
- Does the COVID-19 pandemic give you something positive?
- What is important to you in life for yourself?
- What is important to you in life for your child?

Expectations of the hospital/healthcare providers

- Are you satisfied with the information you receive from your healthcare providers in the hospital?
- Are you satisfied with the care you receive from your healthcare providers in the hospital?
- Do you think things could be better?
- Would you appreciate an additional conversation with one of my colleagues to discuss your concerns? (social worker or psychologist)



PART 2

Development of joint range of motion in the era of DMTs



5

Course of joint range of motion in children with spinal muscular atrophy receiving disease-modifying treatment

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ABSTRACT

Background: Progressive decreases in joint range of motion (ROM) is a well-recognized complication in the natural history of spinal muscular atrophy (SMA). How joint ROM evolves in children with SMA receiving disease-modifying treatment (DMT) needs to be documented.

Purpose: To examine the longitudinal course of joint range of motion in young children with SMA receiving disease-modifying therapy.

Methods: We included children with SMA (with 2 or 3 *SMN2* copies) who started treatment within the first 18 months of life in a prospective national tertiary cohort study. Our examination consisted of joint range of motion of the knee, elbow and wrist; the longitudinal course was studied using linear mixed-effects models.

Results: We analysed 165 visits of 39 children (median age 22 months (interquartile range [6–45]) with treated SMA over a 3-year follow-up period. The median age at start of treatment was 2 months [0–8]. We found an average yearly decline in knee extension mobility of 3°. The overall course of range of motion for elbow and wrist remained stable.

Conclusion: The course of joint mobility in children with SMA, who started treatment with DMT in the first 18 months of life, is characterised by a decline in knee extension and a stable range of motion of wrist and elbow joints. We stress the importance of monitoring knee extension range of motion at least every 6 months and adopting a proactive approach to maintain full knee extension for optimal lifelong mobility.

Keywords: Spinal muscular atrophy, contractures, joint range of motion, children, disease-modifying treatment, prevention

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease, caused by the homozygous loss of function of the survival motor neuron (*SMN*) *1* gene[1]. It demonstrates a large variation in severity[2], ranging from infantile and childhood to adult onset. This can be explained primarily by the variation in the copy number of the near-homologous second human *SMN* gene (*SMN2*) that produces sufficient amounts of SMN protein for embryonal development, but not for maintenance of motor neuron function. SMA severity correlates inversely with *SMN2* copy number.

For clinical purposes, the SMA classification system recognizes several SMA types in treatment-naïve patients. Type 1 is characterized by infantile onset, stalled gross motor development that impedes the child from learning to sit independently and a median life expectancy of approximately 8 months[3]. Children with SMA type 2 experience onset of symptoms before 18 months of age and achieve the ability to sit. In contrast, children with SMA type 3 experience onset of symptoms after the age of 18 months and achieve the ability to sit and walk independently. In SMA with adult onset, i.e. type 4, limitations may occur in specific higher level functional activities. The natural history of all SMA types is characterized by progression of muscle weakness, resulting in functional loss[4,5].

Pharmacologically increasing intracellular SMN protein concentrations is the aim of the three disease-modifying therapies (DMT) of which the first, nusinersen (Spinraza®), has been approved in the US in December 2016 and in Europe in June 2017. Nusinersen and risdiplam (Evrysdi®) increase SMN protein through a splicing modification of the *SMN2* gene, while onasemnogene abeparvovec (Zolgensma®) is an adeno-associated serotype 9 (AAV9)-based gene therapy that restores *SMN1* in motor neurons. All therapies have been shown to improve survival in SMA type 1 and motor function in SMA type 1–3 [6–9], and presymptomatic treatment yields the best results.

Impaired motor function is not only caused by weakness and fatigability, but also by progressive scoliosis and contractures[10]. Prevalence of contractures in treatment-naive SMA patients varies with age, SMA type and ambulatory status, with a reported prevalence range of 22% to 100%[2,11–17]. In their 2011 study, Fujak et al.[18] reported that in the upper extremity the most pronounced restriction was observed in the elbow joint, characterized by severe flexion contractures. A characteristic of SMA type II is the early development of restricted radial deviation of the wrist, leading to ulnar deviation contractures in some patients[18]. In the lower extremity, Fujak et al.[12], also reported contractures typically began at the knee, followed by involvement of the hip and ankle.

Prevention of contractures has become an even more important goal of rehabilitative management, as a sufficient joint range of motion is a prerequisite in order to benefit from muscle strength gains as a result of disease-modifying treatment (DMT). However, the course of joint range of motion in treated patients with SMA remains to be documented. We undertook this study to prospectively describe the mean joint range of motion over a 3-year follow-up period, in young children with SMA who started treatment with DMT in the first 18 months of life.

METHOD(S)

Study design

We performed an observational prospective study between April 2021 and August 2024 to evaluate range of motion of three joints (knee, elbow and wrist) in young children with SMA, treated with DMT (who started DMT within the first 18 months of life). We performed assessments during the normal clinic/outpatient visits to minimize the burden for child and parents. Intervals between these visits to the Netherlands SMA Center varied between 4 to 12 months. We shortened the initial 8-monthly interval for assessment of joint range of motion to 4-months to avoid large follow-up gaps due to missed appointments.

Reporting this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement[19].

Setting

We performed this study at the Netherlands SMA Center, at the University Medical Center Utrecht (UMCU), the only hospital in the Netherlands (population 18 million) that provides treatment with DMT for individuals with SMA. Nusinersen first became available in May 2017 [20] for SMA type 1 and from January 2018 for young children (up to the age of 6 years) with SMA types 2 and 3 (compassionate use and early access programs, respectively) and was reimbursed for children up to the age of 9.5 years at the start of treatment as of August 2018.

During the study several changes in the treatment regimen of SMA occurred in the Netherlands:

- Reimbursement of gene therapy (Zolgensma®) in December 2021 for presymptomatic cases with 2 or 3 *SMN2* copies.
- The introduction of newborn screening in the Netherlands in June 2022.

- Risdiplam (Evrysdi®) was the third DMT with reimbursement (July 2023) for 2 groups of children: (1) patients with SMA from 2 months to 25 years of age with SMA types 1, 2 or 3, and (2) presymptomatic cases with 1, 2, 3 or 4 *SMN2* copies.

Participants

All children with a genetically confirmed diagnosis of SMA (a homozygous deletion of the *SMN1* gene) and 2 or 3 *SMN2* copies, who started DMT (Spinraza®, Zolgensma® or risdiplam) within the first 18 months of life were eligible. At the start of the study 30 children with SMA (and 2 or 3 *SMN2* copies) fulfilled the criteria. During the study period children with a new genetically confirmed diagnosis that fulfilled the criteria could potentially be included. We documented age at diagnosis and age at start of DMT.

The Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands classified this study as exempt from the Medical Research Involving Human Subjects Act (20-791); all children and/or parents gave signed informed consent. All participants in this cohort are included in an ongoing prospective population-based cohort study in the Netherlands, approved by the local Medical Ethical Committee (registered at the Dutch registry for clinical studies and trials, NL29692.041.09).

Assessments of joint range of motion and motor function

Joint range of motion was assessed by four experienced pediatric physiotherapists (DvdW, TR, KS and DvD), who used a universal plastic 18 cm goniometer. Prior to the study, all physiotherapists completed a comprehensive training in standardised goniometry assessment and documentation of range of motion scores according to a standard operating procedure (SOP). The SOP included a detailed description of testing positions and goniometer placement based on standard goniometric measurements (Additional file 5.1)[21]. To ensure quality and consistency of goniometry assessments throughout the study period, training sessions were repeated every 6 months.

Based on a combination of available historical data[11,12,14–16,18], joint functionality[13,15], clinical experience, and practical feasibility, we chose to measure the knee, elbow, and wrist joints in this study. For the knee and elbow, we were particularly interested in extension deficits[5,22–24], as these pose a greater functional problem in SMA, for example in standing and reaching, respectively. Given the emergence of a new phenotype and the uncertainty regarding how different muscle groups might respond to DMT[25], we additionally included other joint motions (elbow flexion, knee flexion in supine/prone, and popliteal angle) to provide a context to contracture development. We collected, the following, quantitative passive ROM (left/right) data: wrist (ulnar/

radial deviation), elbow (flexion/extension) and knee (flexion/extension). Goniometry values were recorded to the nearest 5˚.

Contracture management questionnaire

All participants received rehabilitation care that included an individual plan for contracture management. We documented the type of contracture management using a specifically designed questionnaire (Additional file 5.2) that covered the use of stretching exercises, orthoses and standing frame in the week before the study visit.

Statistical analysis

We used descriptive statistics for baseline characteristics; continuous variables (age and duration of DMT) are presented as median (interquartile range (IQR)) given the skewed distribution, and categorical variables (type of DMT) as frequency (percentage). We used linear mixed-effects models (LMMs) to analyse changes in joint range of motion over time where age at assessment was included as the time variable. LMMs account for differences in timing between assessments. The fixed part of the model contained a term for age and age squared to visualize a potential non-linear trajectory; due to small between-subject variability in rates of change over age, only a random intercept per individual was added as a random effect. The average trajectory over age was summarized by a model that only contained a fixed effect for age. The results of the non-linear models are graphically presented with regression lines and its 95% confidence intervals (CI). The results of the linear models are presented in Table 5.2; p-values were based on a likelihood ratio test with one degree of freedom. We described contracture management by reporting the number of participants for each type of management per age category.

We used R (v4.3.1; R Core Team 2023) for all statistical analyses[26]. LMMs were fitted using *nlme* (v3.1-166)[27] and *ggplot2* (v3.5.1)[28] was used for data visualization.

RESULTS

Participants

Forty-nine children with SMA in our national population-based SMA registry were eligible. Seven children and their parents declined to participate. We recruited a total of 42 children (21 male; 21 female) between April 2021 and August 2024. We could not assess three children (‘no measurements, n=3’) at baseline as they were restless at the time of assessment; their data were not used in this study. The remaining 39

children were aged between 0–6 years at baseline (median: 22 months). The median duration of being treated with DMT at baseline was 14 months (IQR 5–33). All children remained on DMT throughout the study. The demographic and clinical characteristics are summarized in Table 5.1.

Table 5.1. Demographics and clinical characteristics

Parameters	All participants (n=39)	2 *SMN2* copies (n=18)	3 *SMN2* copies (n=21)
M:F	20:19	9:9	11:10
Type of DMT, n (% of total)			
Spinraza®	17 (44)	10 (55)	7 (33)
Zolgensma®	21 (54)	7 (39)	14 (67)
Risdiplam	1 (2)	1 (6)	0 (0)
Age at diagnosis, months*	2 (0–6)	2 (0–3)	2 (0–11)
Age at start of DMT, months	2 (0–8)	2 (0–3)	6 (1–11)
Age at study entry, months	22 (6–45)	31 (9–48)	19 (6–32)
Duration of DMT at study entry, months	14 (5–33)	24 (6–45)	9 (5–25)

DMT: disease-modifying treatment; n: number of participants. All data are described as median (range Q1–Q3), unless otherwise specified. A subset of participants (n=8) altered their type of DMT during the study period. For Table 5.1, we report the DMT that was most recently administered at the time of study entry. * n=2 unknown participants' age of diagnosis.

Longitudinal course of joint range of motion in relation to age

We obtained joint range of motion data from a total of 165 visits of 39 children. The average number of visits per child was 4 (min–max 1–7). Thirty-nine children completed their first visit; 38 completed two visits; 33 three visits; 23 four visits; 19 five visits; 9 six visits and 4 seven visits. Median follow-up was 16 months (IQR 8–24). For the LMM analysis we used the average of the measurements of the left and right side, with the assumption that SMA has a nearly symmetrical loss of range of motion[12,18]. In Figure 5.1 we present range of motion data, combined with the non-linear regression lines and its 95% CI. The 95% CIs for the model-estimated baseline and slope parameters are shown in Table 5.2. Range of motion data for subgroups with either 2 or 3 *SMN2* copies are presented in Additional file 5.3.

Knee flexion and extension

We obtained a total of 165 assessments for knee extension, 141 for the popliteal angle, 158 for knee flexion in supine position and 107 for knee flexion in prone position. Our non-linear analysis is shown in Figure 5.1.

For knee extension, we found a significant decrease in range of motion over time, a yearly loss of 3° (Table 5.2).



Figure 5.1. Joint range of motion.

Table 5.2. Model parameters joint range of motion. Intercept and average monthly change in degrees (=slope)

Joint range of motion (ROM)	N (p)	N (ass)	Intercept (SE)	Monthly change ROM (SE)	95% CI of monthly ROM change	p-value
EE	39	164	1.507 (1.89)	0.092 (0.034)	0.03; 0.16	.008
EF	39	155	149.42 (1.05)	-0.022 (0.021)	-0.06; 0.02	.297
KE	39	165	1.576 (2.24)	-0.246 (0.041)	-0.33; -0.17	<.001
POP	39	141	22.727 (2.51)	0.103 (0.049)	0.01; 0.20	.038
KF-s	39	158	140.78 (1.96)	0.008 (0.035)	-0.06; 0.08	.824
KF-p	35	107	136.73 (2.29)	-0.026 (0.050)	-0.12; 0.07	.605
RD	39	156	22.21 (1.35)	-0.030 (0.028)	-0.08; 0.02	.279
UD	39	156	40.89 (1.56)	0.103 (0.032)	0.04; 0.17	.002

Model parameter estimates, standard errors, and confidence intervals for the linear mixed-effects models are shown. ROM = joint range of motion; EE = Elbow Extension; EF = Elbow Flexion; KE = Knee Extension; POP = popliteal angle; KF-s = Knee Flexion - supine; KF-p = Knee Flexion - prone; RD = Radial Deviation; UD = Ulnar Deviation; N (p) = number of participants; N (ass) = number of assessments (left = right); SE = standard error; CI = confidence interval.

Additionally, our linear data showed an average increase in range of motion of 1.24°/year (95% CI: 0.12; 2.40) for the popliteal angle and 0.10°/year (95% CI: -0.72; 0.96) for the knee flexion-supine and -0.31°/year (95% CI: -1.44; 0.84) for the knee flexion in prone position.

In more detail, visual inspection of plotted data showed 8 children, aged between 0–2 years, who started with a limited knee extension mobility (<0°) to improve range of motion in the subsequent 2 years.

Elbow flexion and extension

We obtained a total of 164 assessments for elbow extension and 155 assessments for elbow flexion. The non-linear model showed a relatively stable range of motion (Figure 5.1). We found a yearly change for the elbow extension of 1.10° (95% CI: 0.36; 1.92) and -0.26° per year (95% CI: -0.72; 0.24) for the elbow flexion.

Wrist ulnar and radial deviation

We obtained 156 assessments for longitudinal analysis of both ulnar and radial deviation. Our non-linear model is shown in Figure 5.1. Our linear analysis showed a decrease in range of motion of -0.36°/year (95% CI: -0.96; 0.24) for radial deviation and an increased range of motion of 0.12°/year (95% CI: 0.48; 2.04) for ulnar deviation.

Received contracture management

We obtained a total of 140 questionnaires from 33 children regarding the contracture management regime they received during the period of study participation. The median number of completed questionnaires per child was 4 (IQR 1–7). Figure 5.2 illustrates the reported use of different interventions for contracture prevention and/or treatment. Subsequently, we show the number of children that use bracing (hand splints/knee immobilizers/AFOs), perform stretch exercises or supported standing. For this population the use of knee immobilizers and hand splints is rare. AFOs are used in a larger group of children, starting from the age of 12–18 months. Most of the children performed stretching exercises from the age of 24–30 months. The standing frame was used throughout the study by 12 children, 4 children started during the study and 17 did not use a standing frame during the study (n=6 children data not available). At 24–30 months 5/9 children used a standing frame; at 78–84 months 7/7 reported the use of a standing frame.

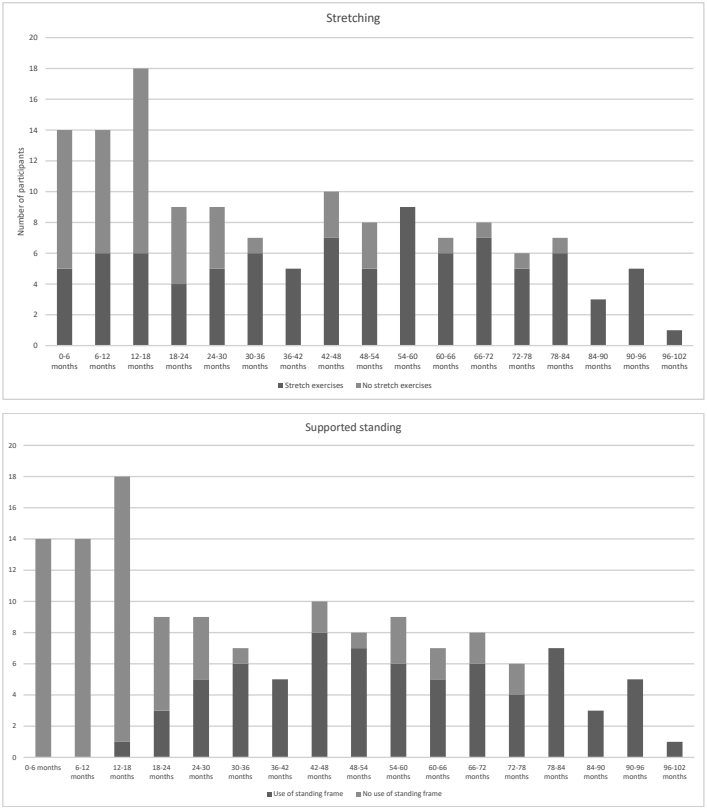


Figure 5.2. Information on patient reported contracture management, divided in age groups. Reporting on the use of orthoses (knee immobilizers, ankle foot orthoses and hand splints), stretch exercises and supported standing. *Figure 5.2 continues on next page.*

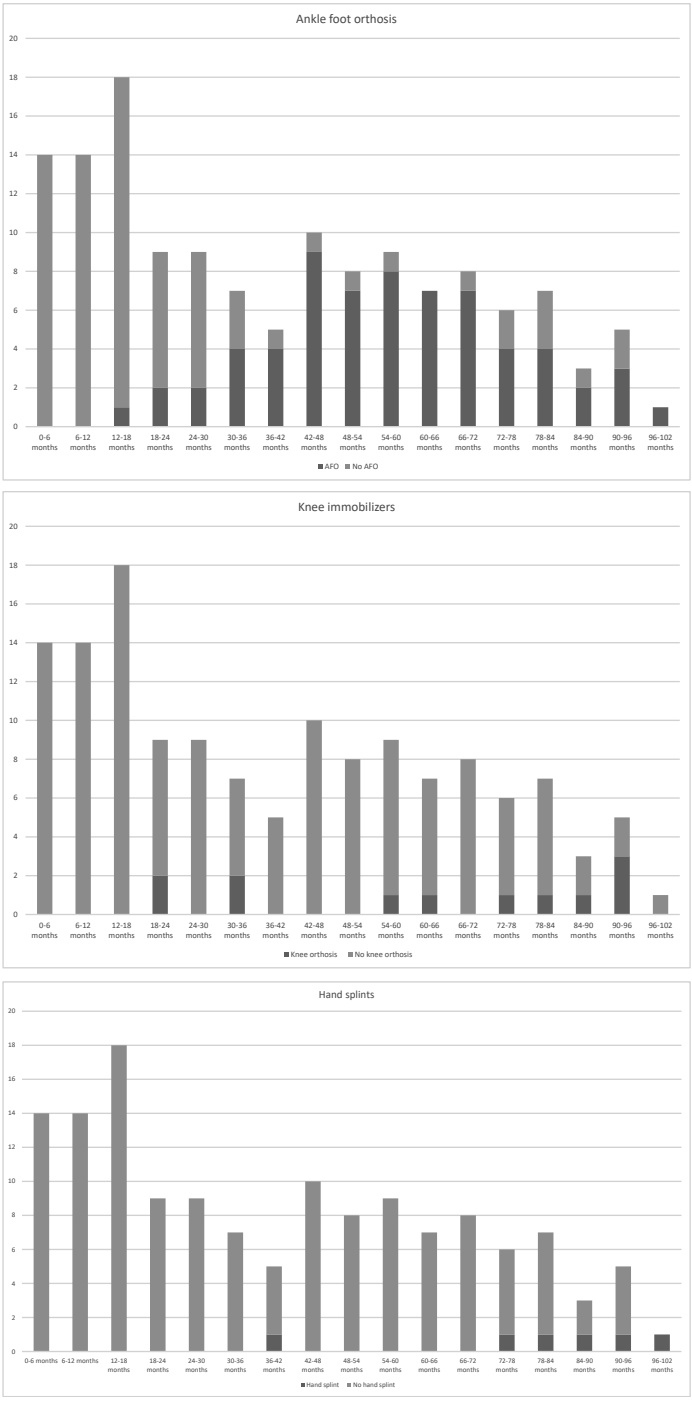


Figure 5.2. ***Continued*.**

DISCUSSION

In this prospective study, we evaluated the course of joint range of motion in young children (0–8 years of age) with SMA who received treatment with DMT (Spinraza®, risdiplam or Zolgensma®). The overall range of motion of wrist and elbow remained stable over the age range, but knee extension mobility decreased with an estimated yearly decline of three degrees.

The development of significant joint contractures in treatment-naive children with SMA is common[12,14,18]. Despite the fact that others have pointed out the significance of studies on joint range of motion in treated SMA patients[29], the current literature is limited to a case-report[30] and a pilot study[31] with a limited follow-up duration and number of joints studied.

Within the investigated age range, our findings are in line with previous observations regarding joint range of motion patterns of elbow flexion, popliteal angle, or knee flexion (both supine and prone positions) and in particular that the ROM remained stable. Limitations in elbow/knee extension and wrist deviation are well-known complications in untreated children with SMA and we therefore hypothesized that DMT[32–34] would postpone or even prevent contracture development in elbow/knee extension and wrist deviation. Although there are limitations when directly comparing our findings to data from a retrospective cohort study[12] due to clear differences between our longitudinal analysis and the analysis used in the previous studies (i.e. a cross-sectional description per age group), our data may indicate that the pattern of contracture development and progression under DMT may differ from that previously reported. For example, Fujak et al.[18] reported significant contractures of the elbow, i.e. a 16.7% loss of ROM present in children aged 0–2 years old and 36.1% loss of ROM present in children aged 3–5 years old, while we did not observe limitations in elbow extension. Although we cannot completely exclude the possibility that the observed differences between studies are due to the cross-sectional nature of previous efforts[18]. The observation regarding wrist deviation contractures is similar/identical[18].

How do our data compare to what is known from normal development? The values in our group correspond reasonably well with the reference data for elbow extension from children aged 3 to 9 years, showing a mean ROM of 7 degrees[35]. The knee extension observed in children with SMA treated with DMT shows considerably lower joint range of motion compared to the reference norm of 4 degrees reported for both boys and girls, suggesting that in this age range children with SMA deviate from their typically developing peers. To the best of our knowledge, there are no published reference values for wrist deviation in young, normally developing children.

Knee flexion contractures are the most common contractures in treatment-naïve children with SMA type 2 [12]. This probably reflects the relative weakness of knee extensors in comparison with hamstrings in children with SMA[5,22–24]. Although DMT treatment may postpone contracture development, our data indicate a similar vulnerability pattern as in studies performed before DMT were introduced[12,14] suggesting that continued and protocolized surveillance is needed to identify children at risk. The fact that muscle weakness is more pronounced in legs than in arms in children with SMA might explain why elbow extension (despite the relatively severe weakness of triceps in comparison with biceps muscles[5]) and wrist range of motion in our cohort remained stable over time.

While the overall results show a decrease in knee extension range of motion of, on average, three degrees per year, the range of individual changes was large. This implies that some children may be more vulnerable than others and underlines the importance of surveillance of children with a routine check-up by a trained assessor every 6 months. Additional file 5.1 contains an example of a standardized protocol to this end. In our cohort, a decline in knee extension range of motion was observed after the age of 2 years. Dutch rehabilitation teams often started using standing frames after the age of 2 years, indicating a mismatch of current preventive interventions and clinical need. Despite limited evidence for interventions targeting joint mobility in neuromuscular disorders[36,37], international Standards of Care[38] advocate early implementation of supported active and prolonged passive stretching[39]. Given that knee extension was the earliest and most affected joint motion, early preventive strategies – such as stretching, orthotic support, and/or standing frames – should be initiated probably in the first year of life and at least prior to detectable decrease in range of motion.

Strengths and limitations

The strengths of the present study are the longitudinal observations across the age range of 0 to 8 years in a population-based sample. Range of motion measurements included knee and elbow extension and wrist deviation. Knee and elbow extension are of particular interest because of the characteristically severe weakness of the quadriceps and triceps muscles as compared to arm and leg flexors[5,22–24]. Contractures of knee, elbow and wrist can greatly impact the level of functioning and participation. A child's ability to stand and make transfers, to handle objects and to successfully and independently perform daily activities such as eating, combing hair and writing depend on a sufficient ROM of knee, elbow and wrist.

We acknowledge that our study also has limitations. Even though joint range of motion assessment by trained clinicians is a reliable method to determine the quantitative range of motion in neuromuscular disorders[40–42], performing goniometry in young children is challenging. We used parental assistance, timing of measurements shortly after feeding, and other commonly used approaches in clinical practice with young children to facilitate measurements. Our study started in the COVID-19 period, during which rescheduling of outpatient appointments could not be avoided. This largely explains missing data.

Differences in prevalence of contractures could also be influenced by differences in contracture management strategies in children with SMA. Even though we collected data on the use of equipment and therapies for contracture management during the study, we did not collect such information in the period before children were enrolled. Moreover, we do not know the details of received contracture management, such as the duration and intensity while children were in follow-up in this longitudinal study. In addition, patient-reported outcomes on contracture management are susceptible to socially desirable responses. Nevertheless, for this study the patient-reported outcomes provided the most feasible means of capturing information on contracture management.

We did not include measurements of ankle range of motion (dorsiflexion/plantarflexion) or elbow pronation/supination, even though these ranges of motion are relevant for limb functionality. Consistent with Fujak et al.[12], contractures typically develop first at the knee, followed by the ankle and hip, which led us to prioritize the collection of knee data as a starting point in our study design. The reliability and validity of goniometric elbow measurements in adults show high intra- and interrater reliability for pro- and supination[43] Our clinical experience in young children, however, is that these measurements are highly challenging. Therefore, we prioritized wrist deviation measurements.

Future studies

Many questions about contracture development remain unanswered and require further research. The origin of contractures is still under debate and appears to be multifactorial[39]. Contributing factors hypothesized are muscle weakness, leading to a decreased ability to actively move a limb through its full range of motion; static positioning for prolonged periods of time; and imbalance of agonist and antagonist muscles[14,44]. Primary or secondary muscle changes such as fatty infiltration that may affect muscle length and flexibility[45,46], that are unevenly distributed between agonists and antagonists could also contribute to contracture development[45]. Studies that aim at

further dissecting the underlying mechanism of contracture development are needed, to explore why some joints are affected differently in treated SMA.

Our study provides a start for further research in children with SMA treated with DMT. Specific clinical characteristics that may determine the course of joint range of motion may include baseline motor function, type of DMT and age at start of DMT. Unfortunately, the sample size of our study was not sufficient to examine the independent contribution of these factors. We recommend that future studies examine the trajectory of joint range of motion in age groups beyond those investigated in the present study and include at a minimum knee/elbow extension and wrist deviation.

CONCLUSION

This is the first longitudinal, population-based cohort study on contracture development in children with SMA, aged 0–8 years old, who receive DMT. Our study shows a high risk of loss of range of motion for the knee extension and a low risk of range of motion decline in elbow and wrist. This study demonstrates the importance of systematically assessing joint range of motion using a standardized protocol.

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ADDITIONAL FILE 5.1: Procedures manual

Assessment of passive range of motion of bilateral joint mobility of wrist, elbow and knee. Measurements will be taken with a universal plastic 18 cm goniometer.

Reference 'Handleiding: Standaard Lichamelijk Onderzoek' (excluding wrist)[23]

Assessment to include passive joint range of motion of:

1. **Wrist**: ulnar/radial deviation
2. **Elbow**: flexion/extension
3. **Knee**: flexion/extension and popliteal angle

Regarding the force applied by the examiner, we aim for the following:

1. The extreme angle of joint mobility will be determined by three gentle bouncing motions to the end range, followed by measurement of the maximum range of motion.

Passive range of motion of the wrist

Ulnar/radial deviation

Patient position:

- Sitting with the upper arm hanging down alongside the body, elbow in 90-degree flexion, and forearm in 90-degree pronation.
- If the patient cannot sit independently:
  - Sitting in a wheelchair with the upper arm hanging down as far as possible alongside the body or supported on an armrest, elbow in 90-degree flexion, and forearm in pronation.
- If measured with patient lying down in supine position:
  - Lying on the back, upper arm on the examination table, elbow in 90-degree flexion, and forearm in pronation.

Examiner position:

- Standing in front of the patient.
- Forearm is supported on a table/bench/armrest/wheelchair tray with the elbow in 90-degree flexion.

- Executing hand at the level of the patient's hand.

Execution:

- Movement is performed separately for the left and right hand:
  - Move the hand into maximum radial deviation while keeping the elbow in the same position.
  - Move the hand into maximum ulnar deviation while keeping the elbow in the same position.
- Ensure the forearm does not change position.

Joint axis location:

- Parallel to the forearm.

Goniometer arms:

- **Proximal**: Over the forearm (positioned centrally between the radius and ulna proximally).
- **Distal**: Over the hand at digit 3 (follows metacarpal 3).
- **Goniometer pivot**: Distally between the radius and ulna (proximal to the base of MC-3).

Joint position 0°:

- Neutral wrist position (no palmar or dorsal flexion).

PROM score (degrees):

- Measured angle = angle between digit 3 and forearm.
- Documented angle = angle between neutral position and ulnar/radial deviation.

Passive range of motion of the elbow

Flexion

Patient position:

- Sitting with the shoulder in 90-degree anteflexion, elbow in maximum extension, forearm as far as possible in 90-degree supination.

- If the patient cannot sit independently:
  - Sitting in a wheelchair, shoulder as far as possible in anteflexion, elbow/ upper arm supported on a table/wheelchair tray/examination table.
- If measured lying down:
  - Lying on the back on the examination table, upper arm resting on the table, elbow in maximum extension, forearm in supination as far as possible.

Examiner position:

- Standing beside or behind the patient.
- Supporting the upper arm on a table/wheelchair tray/examination table.
- Executing hand at the distal forearm of the patient.

Execution:

- Movement is performed separately for the left and right arm:
  - Bring the ipsilateral elbow into maximum flexion while keeping the executing hand at the distal forearm.
  - The supporting hand stabilizes the upper arm.

Joint axis location:

- Lateral epicondyle of the humerus.

Goniometer arms:

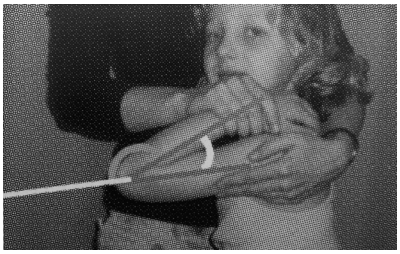
- **Proximal**: Alongside the upper arm towards the humeral head.
- **Distal**: Alongside the forearm towards the radial head.

Joint position 0°:

- Full elbow extension.

PROM score (degrees):

- Measured angle = angle between upper arm and forearm.
- Documented angle = 180° - [angle between upper arm and forearm].



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 25°; the documented (blue) angle is 180° - 25° = 155°.

Passive range of motion of the elbow

Extension

Patient position:

- Sitting with the shoulder in 90-degree anteflexion, elbow in maximum flexion, forearm in supination as far as possible.
- If measured lying down:
  - Lying on the back on the examination table, upper arm resting on the table, elbow in maximum flexion, forearm in supination as far as possible.
  - Note: If supination is incomplete, measure the angle in the sagittal plane.

Examiner position:

- Standing beside or behind the patient.
- Supporting hand under the patient's upper arm or via examination table support.
- Executing hand at the distal forearm of the patient.

Execution:

- Movement is performed separately for the left and right arm:
  - Bring the ipsilateral elbow into maximum extension while keeping the executing hand at the distal forearm.
  - The supporting hand stabilizes the upper arm.

Joint axis location:

- Lateral epicondyle of the humerus.

Goniometer arms:

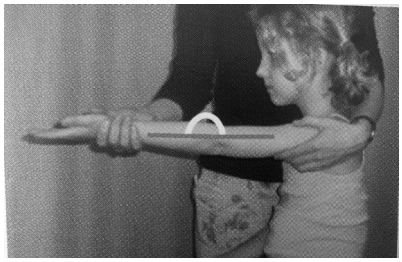
- **Proximal**: Alongside the upper arm towards the humeral head.
- **Distal**: Alongside the forearm towards the radial head.

Joint position 0°:

- Full elbow extension.

PROM score (degrees):

- Measured angle = angle between upper arm and forearm.
- Documented angle = [angle between upper arm and forearm] – 180°.



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 180°; the documented angle is 180°-180° = 0°.

Passive range of motion of the knee

Flexion (supine position)

Patient position:

- Lying on the back with extended hips and knees.

Examiner position:

- Standing beside the examination table at the patient's pelvis level.
- Supporting hand on the patient's knee.
- Executing hand at the patient's ankle.

Execution:

- Movement is performed separately for the left and right leg:
  - Flex the ipsilateral knee maximally with the executing hand while the contralateral leg rests on the examination table. It does not matter if the contralateral leg also flexes.

Joint axis location:

- Lateral joint space at the lateral collateral ligament.

Goniometer arms:

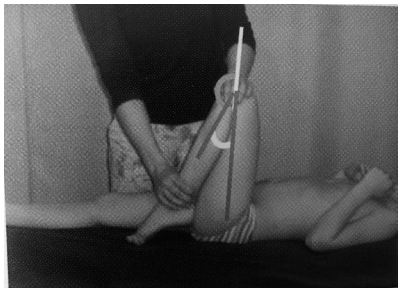
- **Proximal**: Along the lateral side of the thigh towards the greater trochanter.
- **Distal**: Along the lateral side of the lower leg, between the fibular head and the most lateral part of the malleolus.

Joint position 0°:

- Full knee extension.

PROM score (degrees):

- Measured angle = angle between upper and lower leg.
- Documented angle = 180° - [angle between upper and lower leg].



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 30°; the documented (blue) angle is 180° - 30° = 150°.

Passive range of motion of the knee

Flexion (prone position)

Patient position:

- Lying prone with extended hips and knees.
- *Regarding contractures*: If the child's navel touches the examination table, mobility is sufficient for inclusion, and knee flexion can be measured in the prone position.

Examiner position:

- Standing next to the examination table at the patient's pelvis level.
- Supporting hand placed on the patient's pelvis.
- Executing hand positioned at the patient's ankle.

Execution:

- Movement is performed separately for the left and right leg:
  - Flex the ipsilateral knee using the executing hand while the supporting hand stabilizes the pelvis. This hand monitors whether the pelvis lifts or rotates sideways.

Joint axis location:

- Lateral joint space at the lateral collateral ligament.

Goniometer arms:

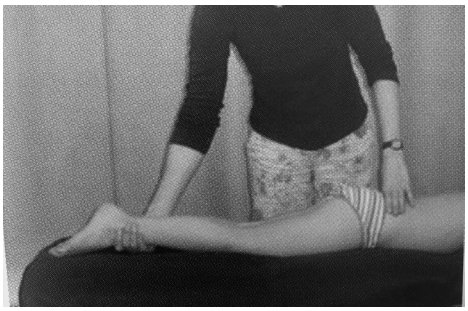
- **Proximal**: Along the lateral side of the thigh towards the greater trochanter.
- **Distal**: Along the lateral side of the lower leg, between the fibular head and the most lateral part of the malleolus.

Joint position 0°:

- Full knee extension.

PROM score (degrees):

- Measured angle = angle between upper and lower leg.
- Documented angle = 180° - [angle between upper and lower leg].




**Ref: 'Standaard Lichamelijk onderzoek'[23]*

Example: The measured (white) angle is 40°; the documented (blue) angle is 180° - 40° = 140°.

Note: If the procedure is difficult due to a highly mobile child (e.g., young children who are difficult to instruct), parents may be asked to stabilize the child at the pelvic crest. The examiner performs the first measurement to ensure that the pelvic crest does not easily lift, confirming the accuracy of measurements when parents assist in stabilizing. This allows the examiner to use both hands freely for measurement.

Passive range of motion of the knee

Extension

Patient position:

- Lying on the back with extended hips and knees, heel resting on the table (contrary to the illustration where it is shown elevated).

Examiner position:

- Standing beside the examination table at knee level.
- Supporting hand on the patient's knee.

Execution:

- Movement is performed separately for the left and right leg:
- Extend the ipsilateral knee using the executing hand while the contralateral leg remains resting on the examination table.
- Force may be applied if necessary.

Joint axis location:

- Lateral joint space at the lateral collateral ligament.

Goniometer arms:

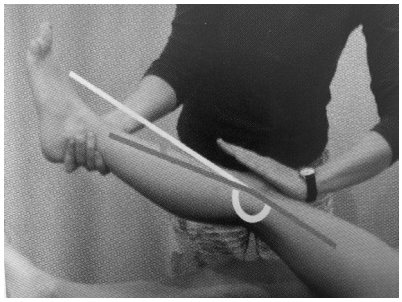
- **Proximal**: Along the lateral side of the thigh towards the greater trochanter.
- **Distal**: Along the lateral side of the lower leg, between the fibular head and the most lateral part of the malleolus.

Joint position 0°:

- Full knee extension.

PROM score (degrees):

- Measured angle = angle between upper and lower leg.
- Documented angle = [angle between upper and lower leg] - 180°.



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The blue angle indicates a limitation in left knee extension. The measured (white) angle is 170, the documented (blue) angle is 170° - 180° = -10°.

Passive range of motion of the knee

Extension in hip flexion (popliteal angle)

Patient position:

- Lying on the back with 90-degree hip flexion and maximally flexed knee on the ipsilateral leg, while the contralateral leg rests on the examination table.
- *Note*: If knee flexion contracture is present in the contralateral leg, position the patient at the edge or diagonally on the examination table, allowing the lower leg to hang over the edge (keeping the hip in extension). *Not feasible for some children with SMA, due to anxiety and reduced muscle strength.*

Examiner position:

- Standing beside the examination table at pelvis level.
- Supporting hand on the patient's knee.
- Executing hand at the patient's ankle.

Execution:

- Movement is performed separately for the left and right leg, using a gentle bouncing motion with minimal force:
  - Extend the ipsilateral knee using the executing hand.
  - Stop when the contralateral leg starts to move.
  - Apply minimal force.

Joint axis location:

- Lateral joint space at the lateral collateral ligament.

Goniometer arms:

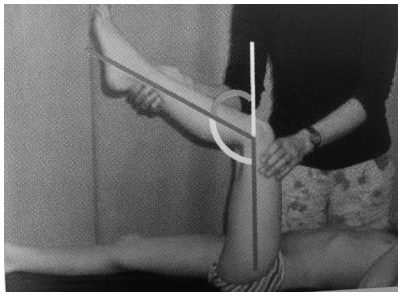
- **Proximal**: Along the lateral side of the thigh towards the greater trochanter.
- **Distal**: Along the lateral side of the lower leg, between the fibular head and the most lateral part of the malleolus.

Joint position 0°:

- Full knee extension.

PROM score (degrees):

- Measured angle = angle between upper and lower leg.
- Documented angle = 180° - [angle between upper and lower leg].



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 115°; the documented (blue) angle is 180° - 115° = 65°.

ADDITIONAL FILE 5.2: Contracture management questionnaire

The following questions concern the preventive treatment of joint deformities (contractures) in your child. When completing the questionnaire, we ask you to think of an average week in the recent period.

Stretching:

- Does your child receive physiotherapy? Yes/No
- **If 'Does your child receive physiotherapy?' is equal to 'yes' answer this question:**
  Are stretching exercises for the joints performed during this therapy? Yes/No
- Do you perform stretching exercises with your child yourself? Yes/No
- Are there other healthcare providers who mobilize your child's joints? Yes/No

Orthosis/splints

- Does your child use orthosis? Yes/No
- **If 'Does your child use orthosis' is equal to 'Yes' answer this question:**
  For which body parts does your child use orthosis? (multiple choice, multiple answers possible)
  Feet? Knees? Wrists? Other orthosis?

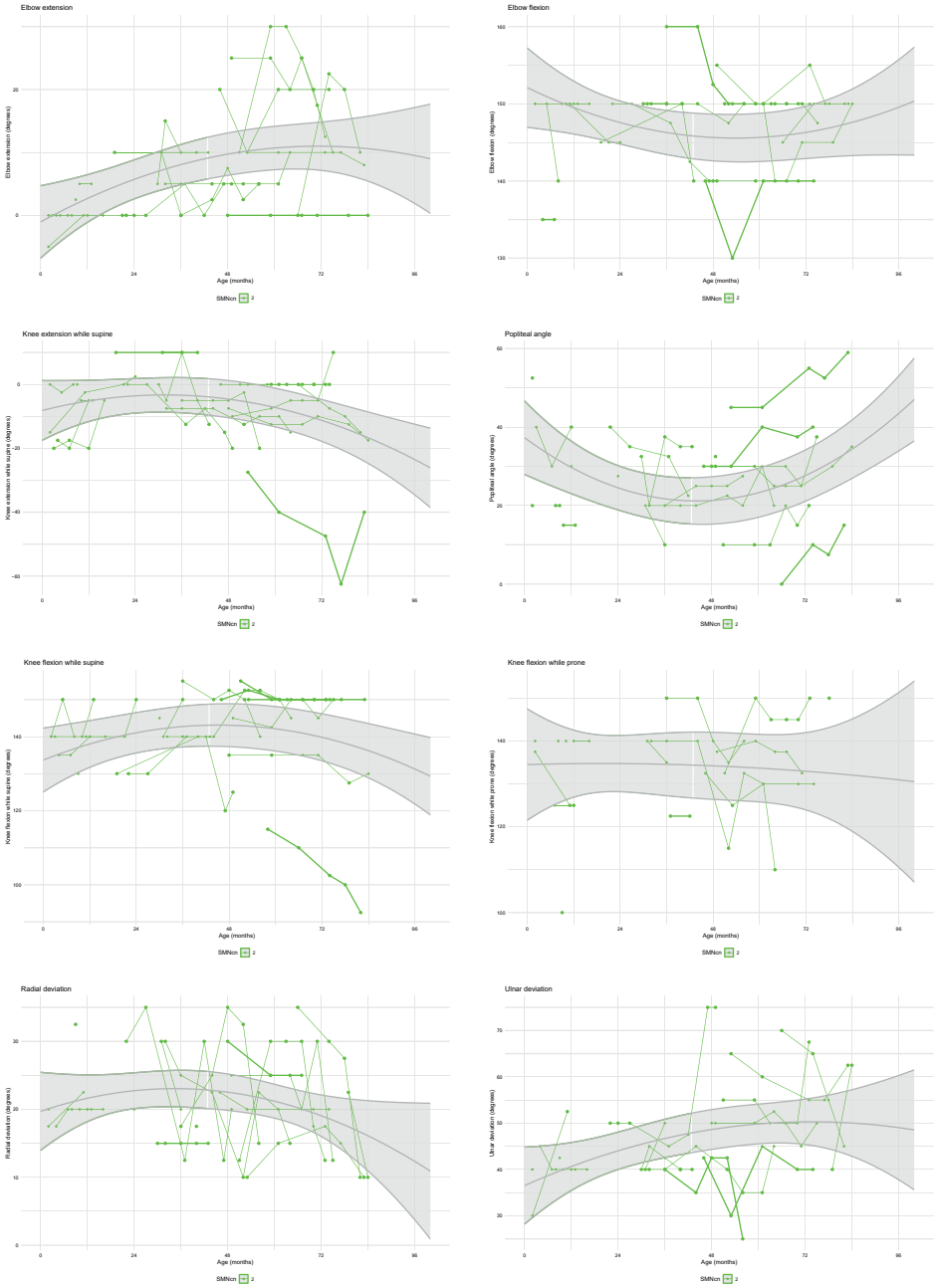
Standing frame

- Does your child use a standing frame? Yes/No

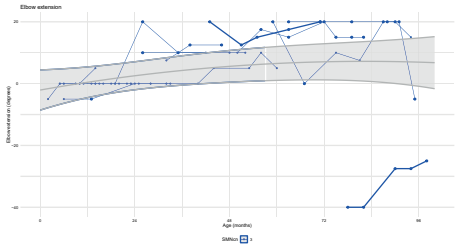
Thank you very much for completing this questionnaire. We look forward to seeing you at the hospital for the joint measurements.

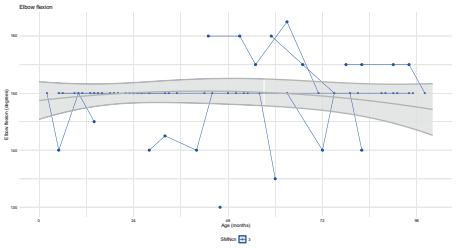
ADDITIONAL FILE 5.3: Range of motion data for subgroups with either 2 or 3 *SMN2* copies

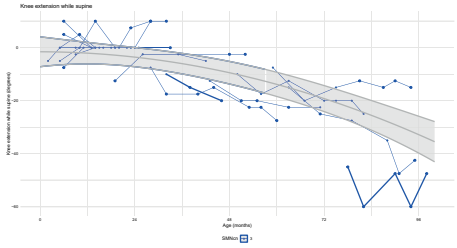
Joint range of motion – 2 *SMN2* copies

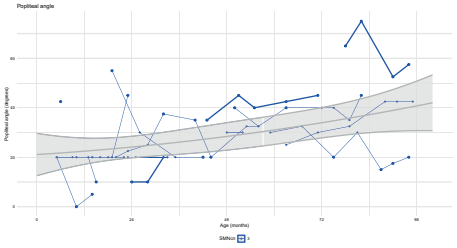


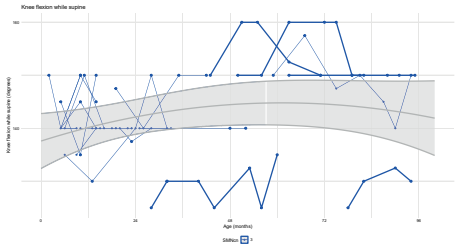
Joint range of motion – 3 *SMN2* copies

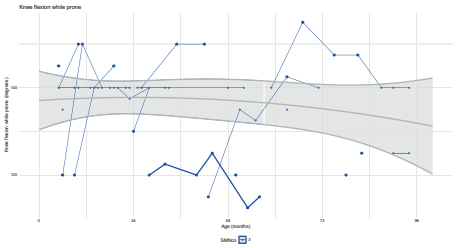


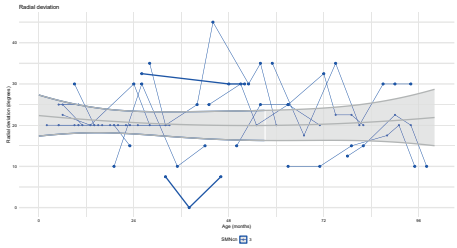


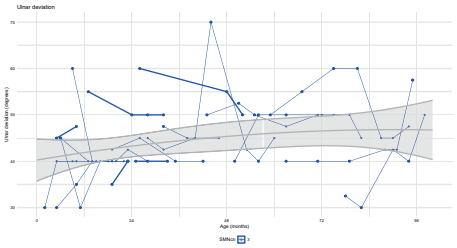














6

Longitudinal changes in joint range of motion in relation to muscle strength imbalances in children with spinal muscular atrophy

Irene L.B. Oude Lansink, Roosmarijn Brenninkmeijer, Danny R. van der Woude, Thijs Ruyten, Fay-Lynn Asselman, Daphne N. Weemering, Jan Willem Gorter, W. Ludo van der Pol, Ruben P.A. van Eijk, Anita Beelen, Bart Bartels

Muscle & Nerve, under review

ABSTRACT

Background: Contractures remain common in children with spinal muscular atrophy (SMA), despite treatment with disease-modifying therapies (DMTs). Their underlying causes are not fully understood, but may involve an imbalance between agonist and antagonist muscle strength.

Aims: To prospectively describe joint range of motion (ROM), muscle strength and agonist-antagonist ratio (AAR) of the elbow and knee in children with SMA and explore associations between these parameters.

Methods: We included children with genetically confirmed SMA (2, 3, or 4 *SMN2* copies) receiving DMT in a national cohort. Knee and elbow muscle strength and ROM were repeatedly assessed over three years. Longitudinal courses were analysed using linear mixed-effects models.

Results: Analysis included 190 visits from 42 children (median age 9.6 years [5–17]) during a 3.5 year study period. Median baseline treatment duration was 3.1 years (IQR 2.3–3.4). Elbow extension ROM remained stable over time. Strength of elbow flexor (1.44 Nm/year [95% CI: 1.04; 1.85]) and elbow extensors increased. Elbow AAR increased (0.317/year [95% CI: 0.16; 0.48], p<0.001). There was no significant association between muscle strength/AAR and elbow ROM. Knee extension ROM declined by 2° annually (95% CI: -3.85; -0.18). Strength of the knee extensors (0.92 Nm/year [95% CI: 0.32; 1.52]) and knee flexors improved, but AAR was higher but stable (-0.072/year [95% CI: -0.56; 0.42], p=0.78). Associations could not be determined due to few assessments.

Discussion: Large longitudinal studies are needed to determine whether the observed higher knee AAR leads to progressive contractures.

Keywords: Spinal muscular atrophy, contractures, isometric muscle strength, children, disease-modifying therapies

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease, caused by degeneration of anterior horn cells of the spinal cord[1]. SMA is caused by deficiency of survival motor neuron (SMN) protein due to loss of the *SMN1* gene function. Due to the progressive muscle weakness, treatment-naïve children decline in function[2,3]. Treatment-naïve SMA exhibits remarkable variability in disease severity, ranging from an early infantile-onset form with profound motor impairment (type 1), through childhood-onset forms (types 2 and 3) characterized by delayed gross motor development and progressive loss of motor function, to an adult-onset form (type 4) that generally presents with limited disability[4]. Over the past years, there is a shift in phenotypes of SMA due to the introduction of three disease-modifying therapies (DMT), all aimed at increasing intracellular SMN protein concentrations. Nusinersen (Spinraza®) and risdiplam (Evrysdi®) increase SMN protein through a splicing modification of the *SMN2* gene, while onasemnogene abeparvovec (Zolgensma®) is an adeno-associated serotype 9 (AAV9)-based gene therapy that restores *SMN1* in motor neurons. All DMTs have been shown to improve survival in SMA type 1 and stabilize or even improve motor function in SMA type 1–3 [5–9]. Without DMT, nearly all individuals with SMA develop joint contractures at some stage in life[10,11].

Contractures are a common feature in many neuromuscular disorders, however there is still limited understanding of how changes in motor function, muscle strength and contracture formation relate. Their onset, progression, and joint involvement differ within and between conditions. This variation suggests that contributing factors, such as muscle strength and imbalance, may exert disorder-specific effects. In SMA, several studies have linked joint contractures to different factors, including muscle weakness, muscle imbalance around a joint and prolonged periods of static positioning[11–13]. This lack of clarity poses challenges for providers seeking optimal treatments for impairments such as contractures. Muscle strength imbalance is considered a key determinant of contracture formation, and contractures are frequently observed in the presence of major muscle imbalance[14].

While the prognosis for children with SMA has improved due to the advent of DMT, contractures remain a clinical concern, and individual changes in range of motion are reported, ranging from hyperextension to severe contractures[15]. To better understand the relationship between joint range of motion and muscle strength imbalances over time, longitudinal data is required. Therefore, this study aims to describe the longitudinal course of elbow and knee joint range of motion and muscle strength, and strength

ratios, and to explore the association between these factors, in children with SMA treated with DMT (with varying ages at treatment initiation).

METHOD(S)

Study design

We performed an observational study between April 2021 and January 2025 to examine the longitudinal course of knee and elbow joint range of motion, muscle strength, and agonist-antagonist ratio in children with SMA treated with DMT. We performed 8-monthly assessments during regular care visits. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement[16].

Setting

We performed this study at the Netherlands SMA Center, at the University Medical Center Utrecht (UMCU), the national referral center for DMT of individuals with SMA.

Participants

All children with a genetically confirmed diagnosis of SMA (a homozygous deletion of the *SMN1* gene) and 2, 3 or 4 *SMN2* copies, aged 4–18 years old and receiving DMT (Spinraza®, Zolgensma® or risdiplam) were screened for inclusion. We invited all children with a medical research council (MRC) grade of ≥3 for knee flexors and/or extensors and/or elbow flexors and/or extensors, to participate. Eligibility required that children were able to 1) sit safely in a stable position on the Biodex isokinetic dynamometer; 2) comprehend and follow instructions; and 3) demonstrate sufficient cooperation to complete the strength assessments reliably.

The Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands classified this study as exempt from the Medical Research Involving Human Subjects Act (20-791). Written informed consent was obtained from parents, and from children where applicable. Additionally, all participants in this cohort are included in an ongoing prospective population-based cohort study in the Netherlands, approved by the local Medical Ethical Committee (registered at the Dutch registry for clinical studies and trials, NL29692.041.09).

Contracture management

We collected data on individual contracture management (stretching exercises, orthoses, and standing frames) during an average week using a specifically designed self-report questionnaire (Additional file 6.1).

Assessments of joint range of motion

We selected knee extension and elbow extension for assessment, since the quadriceps and triceps muscle are severely affected in SMA[18–21]. Joint range of motion was assessed with a universal plastic 18 cm goniometer by trained professionals (BB, DvdW, RB, TR and IOE). Prior to the study start, goniometry assessment and documentation of range of motion scores were standardized between assessors. The standard operating procedures included a detailed description of testing positions and goniometer placement based on standard goniometric measurements (Additional file 6.2)[22]. We collected quantitative passive ROM data of the right side in all participants. In any case the right side was unable to be measured, the ROM of the left side was documented. Goniometry values were recorded to the nearest 5˚.

Assessments of muscle strength

Peak muscle torques for extensors and/or flexors of the elbow and/or knee joint were measured using the Biodex dynamometer (Biodex System 4 Pro: Biodex Medical Systems, Shirley, NY, USA) under isometric conditions and with gravity correction. Experienced assessors performed all tests (DW, BB, RB, TR and IOE) according standardized procedures[24]. If assessment of the right side was not possible, the left side was measured.

Isometric measurements started with a practice test of at least five consecutive extension and flexion attempts at a 90-degree fixed position, so that the patient could become acquainted with the measurement technique. After a 30 seconds break, the actual test consisted of three maximal voluntary isometric contractions in extension followed by three maximal voluntary isometric contractions in flexion in a 90-degree fixed position, with a duration of five seconds per contraction and a five-second interval between directions. We first performed isometric measurements of the knee followed by those of the elbow. We used standardized verbal encouragement to maximize effort. If the coefficient of variation (COV) between contractions was >15% for knee measurements or >20% for elbow measurements, the test was repeated once. If the COV did not improve, the results were visually inspected to determine a reliable test and whether peak torque could be included in the analysis. The highest peak torque of each assessment was used for analysis.

Statistical analysis

We used descriptive statistics for baseline characteristics; continuous variables (age, *SMN2* copy number, age at diagnosis, type and duration of DMT and number of visits) are presented as median (interquartile range [IQR]), and categorical variables (type of DMT) as frequency (percentage). Muscle imbalance was assessed by calculating the agonist–antagonist ratio (AAR), defined as the peak torque of flexor muscles divided by the peak torque of extensor muscles. In some cases, participants were able to generate measurable torque in only one direction (flexion or extension), but not the other. For these missing measurements, a standard value of 1.5 Nm was imputed to calculate the AAR, 0.1 Nm below the lowest torque observed in this study (1.6 Nm).

Linear mixed-effects models (LMMs) were used to describe the longitudinal changes in joint range of motion, muscle peak torque, and AAR. Months since baseline was included as a fixed time effect. To account for inter-individual variability, a random intercept per participant was included. We also tested whether the change over time was different between participants by including a random slope. Likelihood ratio tests with two degrees of freedom were used to determine significance. For the elbow, inclusion of a random slope did not significantly improve model fit for ROM; however, for the other variables (AAR, PT-EF, PT-EE) it resulted in a better fit. Therefore a random-intercepts model was used for ROM, and random slopes were added for the other outcomes. For the knee, there were insufficient repeated measurements per participant to reliably estimate individual slopes; therefore, the final model also comprised a fixed effect for time and a random intercept per participant. The overall significance of the time trajectory was assessed using likelihood ratio tests with one degree of freedom.

The population average trajectories of the linear mixed effects models were visualized together with their 95% confidence intervals. We described contracture management by reporting the number of participants for each type of management per age category. We used R (v4.3.1; R Core Team 2023) for all statistical analyses[26]. LMMs were fitted using *lme4* package (v1.1.37)[27] and *ggplot2* (v3.5.1)[28] was used for data visualization.

As an exploratory analysis, we calculated for each individual their monthly change in muscle strength, AAR and ROM by calculating the difference between the first and last measurement and dividing it by the number of months between measurements. Patients with only one measurement received a score of zero. Subsequently, we calculated Spearman correlations between changes in the different outcomes.

RESULTS

Participants

We screened 106 children with SMA, aged 4 to 18 years, for eligibility. From these: 41 did not meet the eligibility criteria; 16 children/or parents did not want to participate; and 6 for other reasons, such as medical condition. We could not collect data for one participant because the parents withdrew consent before the first study visit. We included a total of 42 children between April 2021 and January 2025; 18 were male and 24 were female; the median age at baseline was 9 years old (IQR 8–12). Children were treated with either Spinraza® or risdiplam. The median treatment duration at study baseline was 3.1 years (IQR 2.3–3.4). All children remained on DMT throughout the study. The median follow-up duration was 30 months (IQR 19–40). The demographic and clinical characteristics are summarized in Table 6.1.

Table 6.1. Demographics and clinical characteristics

Parameters	All participants (n=42)	2 *SMN2* copies (n=2)	3 *SMN2* copies (n=27)	4 *SMN2* copies (n=13)
Sex, n (%)				
Female	24 (57%)	0 (0%)	15 (56%)	9 (69%)
Male	18 (43%)	2 (100%)	12 (44%)	4 (31%)
Type of DMT, n (%)				
Spinraza®	37 (88%)	1 (50%)	23 (85%)	13 (100%)
Zolgensma®	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Evrysdi®	5 (12%)	1 (50%)	4 (15%)	0 (0%)
Age at diagnosis, months	24 (19–38)	27 (23–28)	23 (17–27)	48 (32–114)
Age at start of DMT, months	74 (55–124)	55 (55–56)	71 (53–111)	92 (66–139)
Age at study entry, months	116 (100–154)	94 (88–104)	112 (99–149)	122 (100–168)
Duration of DMT at study entry, months	37 (28–41)	39 (34–48)	37 (29–42)	28 (17–40)
Follow-up duration, months	30 (19–40)	37 (34–41)	32 (22–40)	24 (16–36)
Number of visits	5 (3–6)	6 (6–6)	5 (4–6)	4 (3–6)

DMT = disease-modifying treatment; n = number of participants; SMN = survival motor neuron. All data are described as median (range Q1–Q3), unless otherwise specified. A subset of participants (n=10/42) altered their type of DMT during the study period. For this table, the DMT which was most recently administered at the time of study entry is reported.

Contracture management

We obtained a total of 192 questionnaires on contracture management from 42 children. The median number of completed questionnaires per child was 5 (IQR 4–6). All participants received rehabilitation care that included an individualized plan for

contracture management. For each intervention, we recorded whether it was applied throughout the entire study period, applied only partially, or not applied at all. Figure 6.1 provides a summary of contracture management throughout the study period. Stretching was the most used intervention, with 81% of children performing stretching exercises at least partially during the follow-up period. Ankle orthoses were used (at least partly) by 72% of children, standers by 39%, knee orthoses by 23%, and only one child used an elbow orthosis.

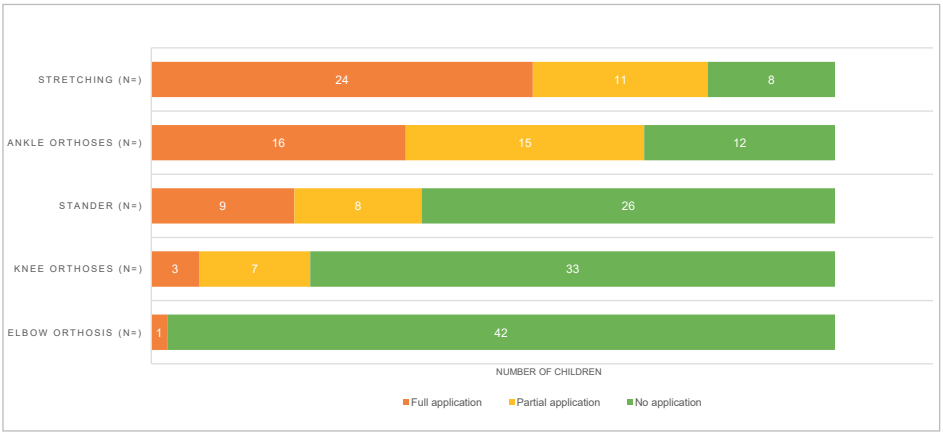


Figure 6.1. Contracture management. Full application indicates that the intervention was reported in all questionnaires during the study; partial application indicates that it was reported in some questionnaires; and no application indicates that it was not reported in any questionnaire. N = number of children.

Longitudinal course of joint range of motion

We obtained a total of 190 elbow and 64 knee ROM assessments from respectively 42 and 18 children (patient characteristics: Table 6.1 and Additional file 6.3 respectively), with a median follow-up of 30 months (IQR 19–40). The median number of assessments per child was 5 (IQR 3–6) for the elbow and 4 (IQR 1–4) for the knee. Figure 6.2 presents ROM data with non-linear regression lines and 95% confidence intervals (95% CI). Model-estimated baseline and slope parameters are shown in Table 6.2. Elbow extension ROM remained stable (0.25°/year [95% CI: -0.47; 0.97]; p=0.49), with substantial variation (30° extension limitation to 25° hyperextension). The first limitation in elbow extension (<0°) was observed at age 8.5 years. Knee extension ROM showed a significant decline over time, with an estimated annual loss of 2° ([95% CI: -3,85; -0.18]; p=0.032) (Table 6.2).

Table 6.2. Model parameters

	N (p)	N (ass)	Change per month	95% CI	p-value
Elbow extension ROM	42	190	0.021	-0.039; 0.081	.49
Elbow flexion strength (PT)	40	167 (171)	0.120	0.087; 0.154	<.001
Elbow extension strength (PT)	40	107 (171)	0.046	0.011; 0.082	.013
Agonist-antagonist ratio elbow	40	103 (171)	0.026	0.013; 0.040	<.001
Knee extension ROM	18	64	-0.170	-0.321; -0.015	.032
Knee flexion strength (PT)	17	62 (64)	0.129	0.049; 0.211	.002
Knee extension strength (PT)	17	54 (64)	0.077	0.027; 0.127	.003
Agonist-antagonist ratio knee	17	52 (64)	-0.006	-0.047; 0.035	.78

Model parameter estimates and confidence intervals for the linear mixed-effects models. CI = confidence interval; N (ass) = number of assessments (number of assessments including imputed 1.5 Nm for missing values); N (p) = number of patients; PT = peak torque (Nm); ROM = range of motion.

Longitudinal course of isometric muscle strength peak torque (PT)

Isometric peak torque was measured in 42 children. For the elbow, 167 flexion and 107 extension measurements were obtained (median per child: 4 [IQR 3–5] flexion, 3 [IQR 0–4] extension). Figure 6.2 shows muscle strength data with regression lines and 95% confidence intervals. Elbow flexion torque increased by 1.44 Nm/year ([95% CI: 1.04; 1.85]; p<0.001), and extension by 0.55 Nm/year ([95% CI: 0.13; 0.98]; p=0.013). For the knee, 62 flexion and 54 extension measurements were collected, with flexion torque increasing by 1.55 Nm/year ([95% CI: 0.59; 2.53]; p=0.002) and extension torque by 0.92 Nm/year ([95% CI: 0.32; 1.52]; p=0.003).

Longitudinal course of agonist–antagonist ratio (AAR)

We obtained a total of 171 elbow and 64 knee ratios (Table 6.2). Elbow AAR increased by 0.31 per year ([95% CI: 0.16; 0.48]; p<0.001), while knee AAR remained stable (-0.072/year [95% CI: -0.56; 0.42]; p=0.78). Figure 6.2 displays longitudinal AAR data by *SMN2* copy number, with regression lines and 95% confidence intervals. The AAR of the knee is overall higher than for the elbow, the elbow AAR intercept is 1.56 and the knee intercept is 2.65.

Association between changes in joint ROM, muscle strength and AAR

There was no association between changes in elbow ROM and changes in muscle strength and AAR. Elbow extension ROM remained stable while muscle strength and AAR showed an increase. It was not possible to analyze associated factors for the knee joint with LMMs, due to the limited number of repeated observations per

participant(s). Spearman correlation analyses revealed no significant associations. The association between changes in joint ROM and changes in AAR is illustrated in scatterplots (Additional file 6.4).

Elbow joint

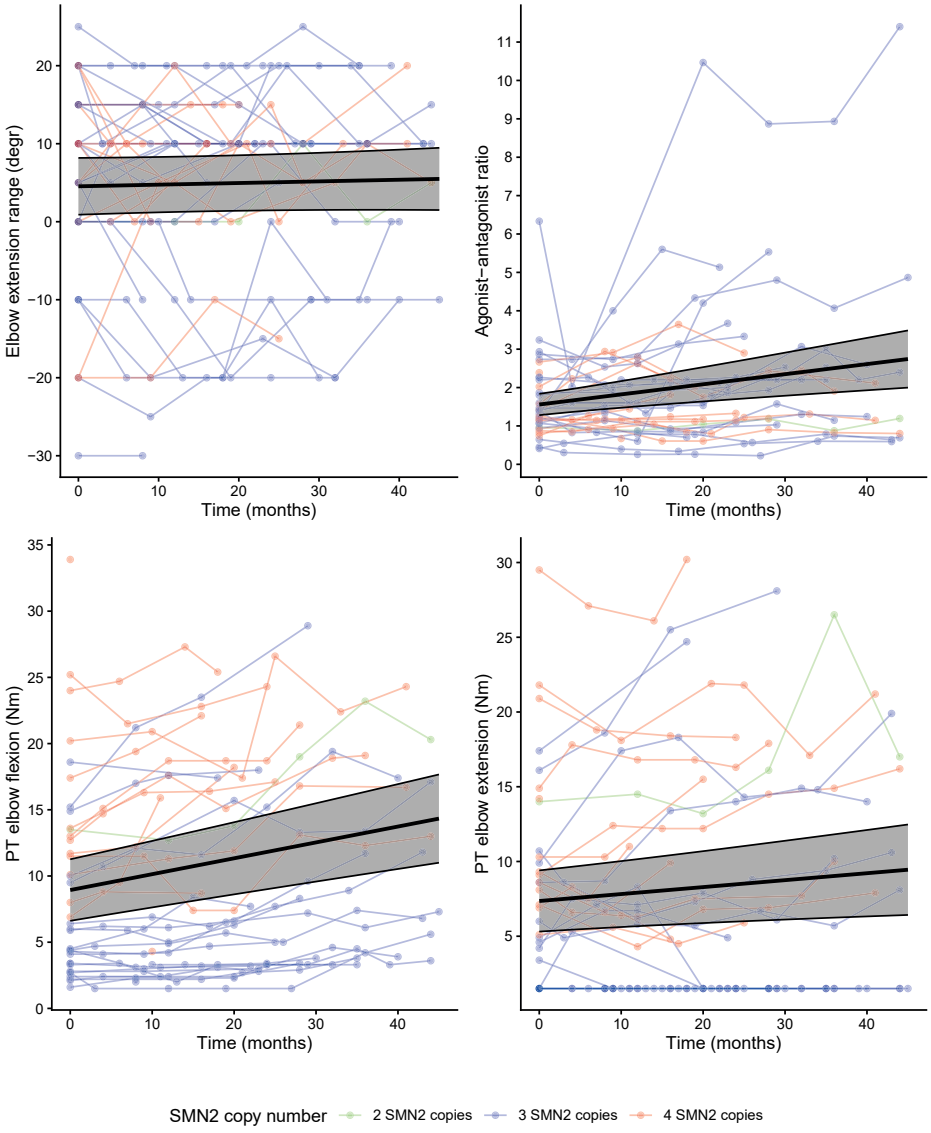


Figure 6.2. Linear mixed-effects models of elbow and knee joint. *Figure 6.2 continues on next page.*

Knee joint

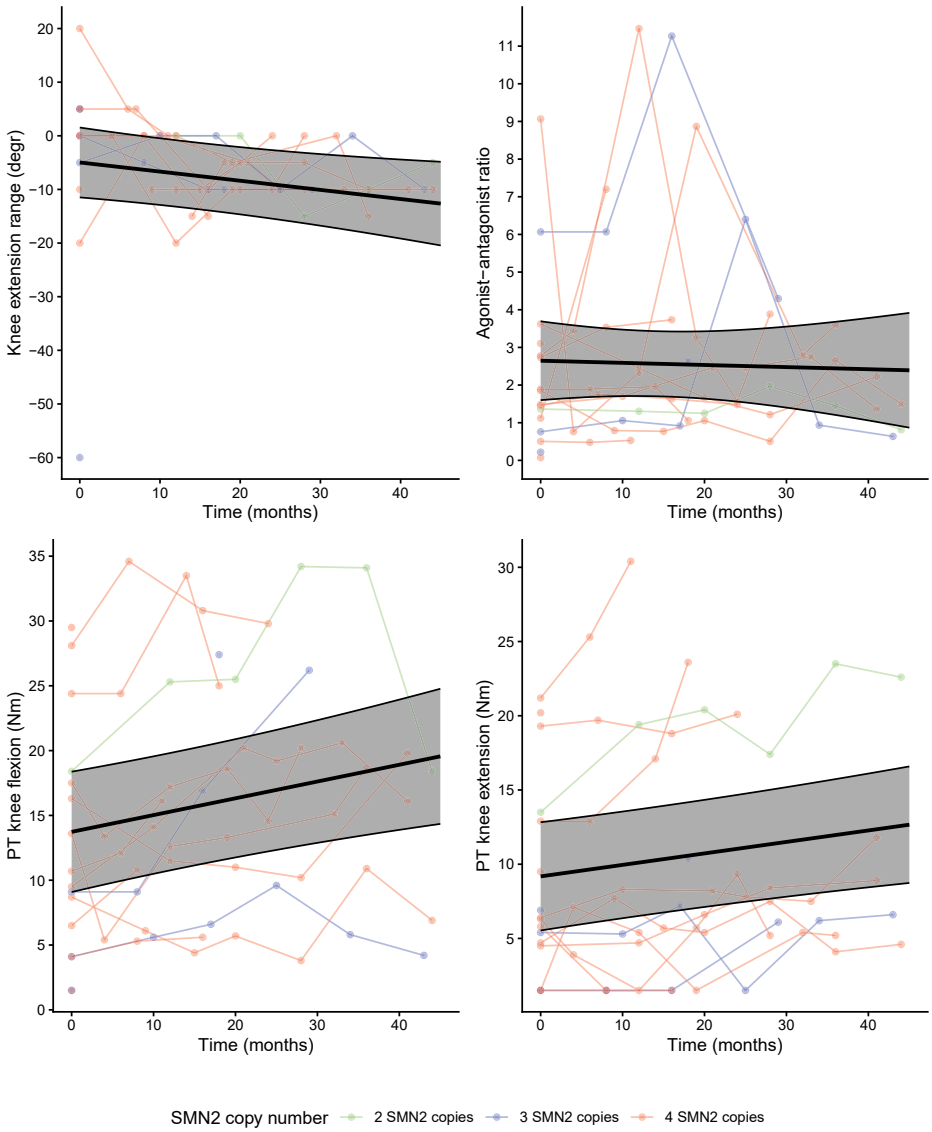


Figure 6.2. ***Continued.***

DISCUSSION

This study showed that, in children with SMA who received DMTs elbow extension range of motion remained stable over time while elbow muscle strength and the imbalance between flexors and extensors increased. Knee extension range of motion however declined while knee strength improved without increase in imbalance between

flexors and extensors. Unfortunately, the limited number of assessments per participant precluded a comprehensive analysis of the relationship between AAR and knee extension ROM within this study.

Because this is the first prevalent cohort of children receiving DMT in the Netherlands, our study population is heterogeneous in several respects, including age, age at DMT initiation, and disease progression prior to treatment. Despite this heterogeneity, the mean loss of both knee and elbow extension in our study was clearly lower than that previously reported in treatment-naïve children[10,11], and for the elbow in particular, range of motion remained stable. A recent study by Oude Lansink et al.[15] found that younger children treated with DMTs maintained their elbow ROM, which aligns with these findings. This is of particular interest in light of recent work by Baranello et al., who reported that treatment-naïve children aged 6–15 years are especially vulnerable to the development of progressive joint contractures, which negatively affect functional outcomes and may influence therapeutic response[29].

Assessing muscle strength in treatment-naïve populations with SMA presents significant challenges. Traditional methods such as manual muscle testing are commonly used, but their ordinal nature limits the possibilities for statistical analysis. As a result, quantitative muscle testing techniques like handheld dynamometry have been adopted to improve measurement precision. However, as highlighted by Iannaccone et al., these devices can demonstrate variable reliability and sensitivity, making accurate muscle strength evaluation in treatment-naïve patients difficult[30]. This variability results in the absence of directly comparable historical data for our cohort.

Notably, our study observed an increase in muscle strength among both flexor and extensor muscles at the elbow and knee joints, a finding that contrasts with natural history studies describing progressive muscle weakness as a hallmark across all SMA types[20]. Incorporating isometric dynamometry alongside established motor function scales (such as the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), the Hammersmith Infant Neurological Examination (HINE), and the Hammersmith Functional Motor Scale Expanded (HFMSE)) may enhance the accuracy of muscle strength measurement. Objective assessments facilitate the calculation of the AAR and offer valuable insights into a child's relative strengths and weaknesses with respect to specific AARs, supporting more nuanced strength evaluations in children with SMA.

An interesting phenomenon found in this cohort is the AAR of our cohort that exceeds that reported in reference populations[31]. Within the reference group, elbow and knee

ratios remained consistent throughout adolescence, measured at 1.3 and 0.8, respectively. In the reference population, quadriceps strength is greater than hamstring strength at the knee joint; however, our cohort showed the opposite pattern and demonstrates constant elevated ratios during adolescence. This is in accordance with typical SMA phenotype in which, flexor muscles are relatively spared compared to extensors, a pattern consistently demonstrated in MRI, ultrasound, and clinical studies[32]. Extensors are often disproportionately affected, which explains the relatively better function of flexors within the same patient[33]. This was also observed in our study with this higher AAR, as well as with significantly more missing values for extension strength of knee and elbow, compared to flexion strength. These findings suggest that flexor muscle strength surpasses extensor strength, which may contribute to a heightened tendency for maintaining increased flexion posture both during daytime and nighttime hours. For the knee, we already found an elevated AAR at baseline, which may explain why knee extension ROM continued to decline despite increases in muscle strength, which were insufficient to restore full ROM.

Strengths and limitations

Key strengths of this study include its longitudinal design, the use of quantitative isolated muscle strength measurements, and the use of a population-based cohort of children with SMA aged 5–18 years. By systematically screening all children receiving DMTs in the Netherlands and including 42 participants who completed Biodex assessments, the findings are broadly applicable and generalizable to comparable clinical populations.

We acknowledge several limitations in this study. Only children with relatively preserved muscle strength (MRC grade ≥3) could be included to perform Biodex assessments, restricting the sample and resulting in a small number of knee measurements. Quantitative muscle strength analysis was possible only for those able to perform Biodex assessments; inclusion of weaker children would have required manual muscle testing, precluding the current quantitative approach. This selection bias may have led to an underrepresentation of children exhibiting the most significant weakness, severe contractures, and highest susceptibility to contractures. This limits the ability to understand the relationships between joint range of motion and muscle strength. Additionally, some children could not complete assessments due to insufficient strength or difficulty with the required movements.

We sought to compare our strength measurements to normative values[34]; however, available reference data were insufficient for standardization. Future studies establishing normative Biodex values would greatly enhance interpretability.

Future directions

Current joint ROM data suggest a slower progression of contractures in comparison to natural history in moderately affected children. A similar change in contracture progression needs to be confirmed in a weaker population of children.

To further study the hypothesis that increased knee AAR contributes to the observed reduction in knee ROM over time, a larger number of participants and assessments is required. For the current heterogenous cohort, additional strength measurements in the weaker subgroup may provide important complementary information. The development of an assisted testing protocol could enable children with reduced muscle strength to undergo Biodex assessments as well. Tiffreau et al. already examined continuous passive motion mode protocols in a reliability study in adults with neuromuscular diseases, which demonstrated high reliability in weaker patients with MRC grades 2 and 3 [35,36].

Early treatment with DMTs in upcoming newborn screening cohorts is likely to improve outcomes. Future, more uniform groups may show better DMT effects on joint ROM. Attention should be given to monitoring AAR to check if initial values match reference standards. Systematic monitoring of changes in joint ROM, muscle strength and AAR is crucial for this group that may develop symptoms.

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ADDITIONAL FILE 6.1: Contracture management questionnaire

The following questions concern the preventive treatment of joint deformities (contractures) (in your child). When completing the questionnaire, we ask you to think of an average week in the recent period.

Stretching:

- Do you/Does your child receive physiotherapy? Yes/No
- **If 'Do you/Does your child receive physiotherapy?' is equal to 'yes' answer this question:**
  Are stretching exercises for the joints performed during this therapy? Yes/No
- Do you perform stretching exercises (with your child) yourself (with your parents)? Yes/No
- Are there other healthcare providers who mobilize your (child's) joints? Yes/No

Orthoses/splints

- Does your child use orthosis? Yes/No
- **If 'Does your child use orthosis' is equal to 'Yes' answer this question:**
  For which body parts does your child use orthosis? (multiple choice, multiple answers possible)
  Ankles? Knees?

Standing frame

- Does your child use a standing frame? Yes/No

Thank you very much for completing this questionnaire. We look forward to seeing you at the hospital for the measurements.

ADDITIONAL FILE 6.2: Goniometry procedures manual

Assessment of passive range of motion of elbow and knee. Measurements will be taken with a universal plastic 18 cm goniometer.

Reference 'Handleiding: Standaard Lichamelijk Onderzoek' (excluding wrist)[23]

Assessment to include passive joint range of motion of:

1. **Elbow**: flexion/extension
2. **Knee**: flexion/extension

Regarding the force applied by the examiner, we aim for the following:

1. The extreme angle of joint mobility will be determined by three gentle bouncing motions to the end range, followed by measurement of the maximum range of motion.

Passive range of motion of the elbow

Flexion

Patient position:

- Sitting with the shoulder in 90-degree anteflexion, elbow in maximum extension, forearm as far as possible in 90-degree supination.
- If the patient cannot sit independently:
  - Sitting in a wheelchair, shoulder as far as possible in anteflexion, elbow/upper arm supported on a table/wheelchair tray/examination table.
- If measured lying down:
  - Lying on the back on the examination table, upper arm resting on the table, elbow in maximum extension, forearm in supination as far as possible.

Examiner position:

- Standing beside or behind the patient.
- Supporting the upper arm on a table/wheelchair tray/examination table.
- Executing hand at the distal forearm of the patient.

Execution:

- Movement is performed separately for the left and right arm:
  - Bring the ipsilateral elbow into maximum flexion while keeping the executing hand at the distal forearm.
  - The supporting hand stabilizes the upper arm.

Joint axis location:

- Lateral epicondyle of the humerus.

Goniometer arms:

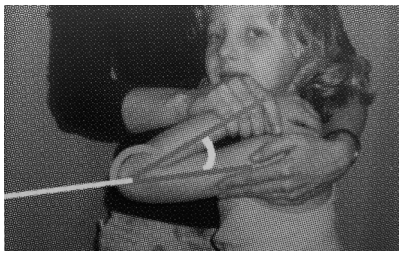
- **Proximal**: Alongside the upper arm towards the humeral head.
- **Distal**: Alongside the forearm towards the radial head.

Joint position 0°:

- Full elbow extension.

PROM score (degrees):

- Measured angle = angle between upper arm and forearm.
- Documented angle = 180° - [angle between upper arm and forearm].



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 25°; the documented (blue) angle is 180° - 25° = 155°.

Passive range of motion of the elbow

Extension

Patient position:

- Sitting with the shoulder in 90-degree anteflexion, elbow in maximum flexion, forearm in supination as far as possible.
- If measured lying down:
  - Lying on the back on the examination table, upper arm resting on the table, elbow in maximum flexion, forearm in supination as far as possible.
  - Note: If supination is incomplete, measure the angle in the sagittal plane.

Examiner position:

- Standing beside or behind the patient.
- Supporting hand under the patient's upper arm or via examination table support.
- Executing hand at the distal forearm of the patient.

Execution:

- Movement is performed separately for the left and right arm:
  - Bring the ipsilateral elbow into maximum extension while keeping the executing hand at the distal forearm.
  - The supporting hand stabilizes the upper arm.

Joint axis location:

- Lateral epicondyle of the humerus.

Goniometer arms:

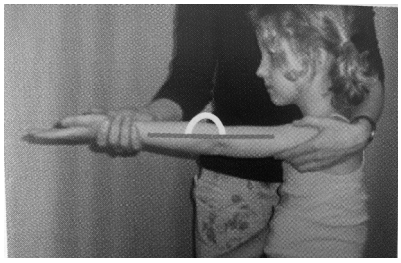
- **Proximal**: Alongside the upper arm towards the humeral head.
- **Distal**: Alongside the forearm towards the radial head.

Joint position 0°:

- Full elbow extension.

PROM score (degrees):

- Measured angle = angle between upper arm and forearm.
- Documented angle = [angle between upper arm and forearm] – 180°.



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 180°; the documented angle is 180°-180° = 0°.

Passive range of motion of the knee

Flexion

Patient position:

- Lying on the back with extended hips and knees.

Examiner position:

- Standing beside the examination table at the patient's pelvis level.
- Supporting hand on the patient's knee.
- Executing hand at the patient's ankle.

Execution:

- Movement is performed separately for the left and right leg:
  - Flex the ipsilateral knee maximally with the executing hand while the contralateral leg rests on the examination table. It does not matter if the contralateral leg also flexes.

Joint axis location:

- Lateral joint space at the lateral collateral ligament.

Goniometer arms:

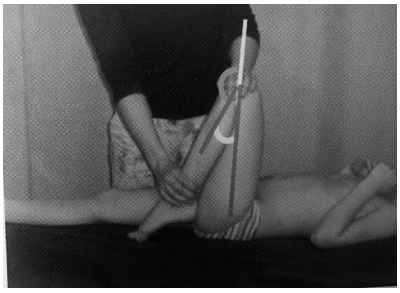
- **Proximal**: Along the lateral side of the thigh towards the greater trochanter.
- **Distal**: Along the lateral side of the lower leg, between the fibular head and the most lateral part of the malleolus.

Joint position 0°:

- Full knee extension.

PROM score (degrees):

- Measured angle = angle between upper and lower leg.
- Documented angle = 180° - [angle between upper and lower leg].



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The measured (white) angle is 30°; the documented (blue) angle is 180° - 30° = 150°.

Passive range of motion of the knee

Extension

Patient position:

- Lying on the back with extended hips and knees, heel resting on the table (contrary to the illustration where it is shown elevated).

Examiner position:

- Standing beside the examination table at knee level.
- Supporting hand on the patient's knee.

Execution:

- Movement is performed separately for the left and right leg:
  - Extend the ipsilateral knee using the executing hand while the contralateral leg remains resting on the examination table.
  - Force may be applied if necessary.

Joint axis location:

- Lateral joint space at the lateral collateral ligament.

Goniometer arms:

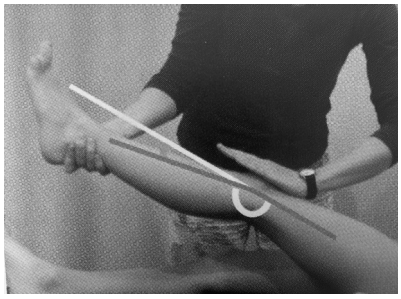
- **Proximal**: Along the lateral side of the thigh towards the greater trochanter.
- **Distal**: Along the lateral side of the lower leg, between the fibular head and the most lateral part of the malleolus.

Joint position 0°:

- Full knee extension.

PROM score (degrees):

- Measured angle = angle between upper and lower leg.
- Documented angle = [angle between upper and lower leg] - 180°.



**Ref: 'Standaard Lichamelijk onderzoek'*[23]

Example: The blue angle indicates a limitation in left knee extension. The measured (white) angle is 170, the documented (blue) angle is 170° - 180° = -10°.

ADDITIONAL FILE 6.3

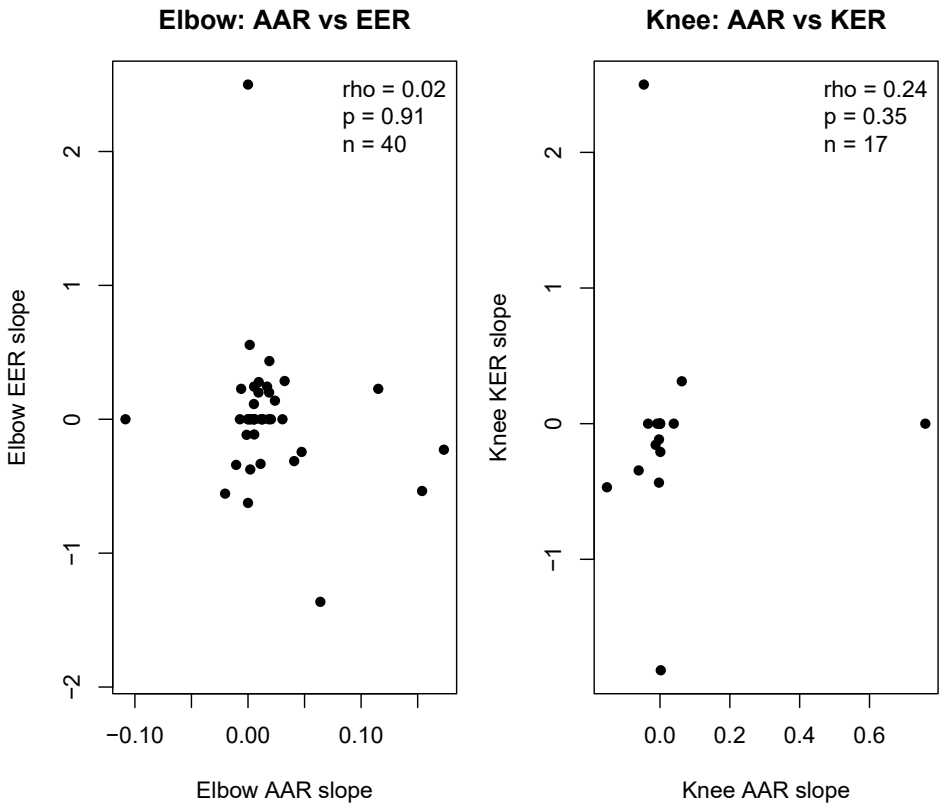
Demographics and clinical characteristics for knee assessments

Parameters	All participants (n=18)	2 *SMN2* copies (n=1)	3 *SMN2* copies (n=5)	4 *SMN2* copies (n=12)
Sex, n (%)				
Female	9 (50%)	0 (0%)	2 (40%)	8 (67%)
Male	9 (50%)	1 (100%)	3 (60%)	4 (33%)
Type of DMT, n (%)				
Spinraza®	18 (100%)	1 (100%)	5 (100%)	12 (100%)
Zolgensma®	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Evrysdi®	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age at diagnosis, months	44 (31–83)	36	39 (30–48)	56 (32–116)
Age at start of DMT, months	77 (58–123)	54	65 (62–85)	86 (64–130)
Age at study entry, months	116 (99–138)	83	111 (104–116)	122 (100–149)
Duration of DMT at study entry, months	29 (23–40)	29	39 (31–40)	29 (19–40)
Follow-up duration, months	18 (12–32)	36	16 (11–18)	19 (14–29)
Number of visits	3 (2–5)	5	2 (2–3)	4 (3–4)

DMT = disease-modifying treatment; n = number of participants; SMN = survival motor neuron.
All data are described as median (range Q1–Q3), unless otherwise specified.

ADDITIONAL FILE 6.4

Scatterplots illustrating Spearman correlation analyses



Scatterplots illustrating Spearman correlation analyses between monthly changes agonist-antagonist ratio (AAR) and joint range of motion (ROM) for elbow and knee. No statistically significant associations were observed (p>0.05). EER = elbow extension ROM; KER = knee extension ROM.



7

General discussion

The aim of this thesis is to advance our understanding of how limitations in joint range of motion, referred to as contractures, develop in children with spinal muscular atrophy (SMA) who are receiving disease-modifying treatments (DMTs). The available literature on the natural history of contractures in SMA is limited, as is our understanding of the efficacy of interventions such as stretching and orthoses. After the introduction of nusinersen, the first available DMT (first introduced in the Netherlands in 2017–2018), the importance of preventing contractures was increasingly recognized as essential to fully realizing the potential of DMTs. This was reflected in the increased emphasis in the revised standards of care for SMA published in 2018 [1]. However, an understanding of the development of contractures in children with SMA using DMT was still lacking when I started to work on the projects compiled in this thesis. Such understanding is necessary to ultimately come to individualized (preventive) contracture treatment strategies for children with SMA receiving DMTs.

In this final chapter, I place the findings presented in the previous chapters in a broader context and aim to translate the new knowledge generated in this thesis into practical recommendations for clinical practice. I will also attempt to outline the remaining research questions that warrant further investigation.

Contractures: assumptions regarding their pathogenesis

Contractures, defined as a limitation in joint range of motion (ROM) where the full passive range cannot be achieved, are a characteristic of many neuromuscular diseases (NMDs)[2]. While many healthcare professionals may take their presence for granted, the pathophysiology, distribution, and progression of contractures vary depending on the underlying disease mechanisms. Contractures are common in severe NMDs such as muscular dystrophies and SMA or occur in joints that are served by the most weakened muscle groups in less severe disorders, such as hereditary polyneuropathies. However, contractures in collagen 6-related disorders and Emery-Dreifuss muscular dystrophy (EDMD) suggest that their development not only depends on strength-imbalance of agonists and antagonists. Patients with collagen 6-related disorders like Bethlem myopathy and Ullrich congenital muscular dystrophy have contractures mainly in distal joints (elbows, knees, ankles)[3,4], but also at unusual sites. For example, involvement of the neck muscles may result in torticollis. Moreover, contractures may be among the first clinical signs in Bethlem myopathy, even before muscle weakness is evident[5]. EDMD is another muscular dystrophy with early and extreme contracture formation disproportional to the degree of muscle weakness and immobility[6–8]. EDMD contractures involve the elbows, ankles, and neck muscles,

resulting in a characteristic posture with limited cervical flexion. The early presence of contractures of the elbow flexors is contrasted by focal wasting of the biceps muscles. Unlike collagen 6-related disorders, EDMD contractures are more proximal and rigid. Different etiologies contribute to the development of these contractures. In collagen 6-related disorders, contractures predominantly result from defects in the extracellular matrix, leading to reduced muscle elasticity and increased fibrosis[3,4]. In contrast, in EDMD, contractures often arise as an initial symptom, preceding muscle weakness. EDMD is often caused by mutations in genes that contribute to the integrity of the nuclear envelope, and it is unknown how this leads to early contracture formation[6–8]. Finally, the occurrence of contractures in dermatomyositis indicates that other mechanisms than weakness, such as inflammation, may play a role in their pathogenesis.

Contractures in SMA commonly occur in hips, knees, ankles, shoulders, elbows and wrists, especially in non-ambulatory patients[9–11] and are believed to be mostly secondary to weakness, muscle strength imbalance and immobility rather than intrinsic connective tissue defects[9,12–15]. Contractures in treatment-naïve SMA typically begin early, progress slowly, and are closely linked to age and immobility. The high prevalence of contractures in SMA has been described in detail by Fujak et al. In this study of 143 patients with treatment-naïve SMA type 2, the authors documented significant contractures. Among those aged 16–20 years, up to 62.5% experienced loss of elbow extension ROM and 100% had reduced knee extension ROM, with average losses of 42.7° and 56°, respectively[13]. Prevalences increased with age; for example, reduced knee extension ROM was observed in 50% of assessments for ages 0–2 and 87% for ages 3–5 (mean loss 17°) and reduced elbow extension ROM was seen in 17% of assessments in children aged 0–2 and up to 81% in adolescents aged 16–20, underlining the progressive nature of contractures[12]. Other studies, e.g. Wang et al.[9], reported similar figures in cohorts of SMA type 2, i.e. 89% of teenagers had limited knee extension ROM (mean loss 48°) and 30% had reduced elbow extension ROM (mean loss 30°).

Notably, in addition to contractures, SMA is also characterized by prominent hyperlaxity of the metacarpophalangeal and other joints, reminiscent of the paradoxical combination of hyperlaxity[16,17] and contractures found in Ullrich congenital muscular dystrophy. The fact that, in SMA, the development of contractures in clinical practice, does not always correlate directly with the degree of muscle weakness, illustrates that the underlying mechanisms and muscle pathology in SMA may very well be more complex than assumed. This highlights the considerable prevalence of contractures as well as the poorly understood pathogenesis, which together pose significant chal-

lenges for rehabilitation professionals seeking to identify optimal treatment strategies for contractures[9,12–15].

Disease-modifying treatments

The improvement of motor function in children with SMA since the introduction of DMTs has led to altered phenotypes of SMA. The initial assumption[18] that DMT would lift patients to higher motor levels has been corroborated by clinical experience[19], although the percentages of children who acquire new motor milestones and thereby cross boundaries of SMA types during treatment, for example by learning to walk, are low[19]. The most prominent new phenotypes are observed among presymptomatic children with 2 *SMN2* copies or (pauci)symptomatic children with SMA type 1, who may, for example, develop sufficient strength to show anti-gravity movements in the extremities while axial, bulbar and respiratory muscles remain profoundly weakened.

Even with improved motor function, children with SMA continue to be at risk for developing contractures. If and how DMTs influence the development of contractures is not known. An understanding of their development in children with SMA treated with DMT is increasingly important, both to use the possible window of opportunity for interventions, but also to minimize treatment burden for children.

Before the introduction of DMTs, management of contractures of patients with SMA was generally less proactive in the Netherlands, as decisions regarding initiation and continuation were made within the context of a progressive disease. The introduction of DMTs has led to a changed approach to contracture management as outlined in the 2018 update of the international standards of care[1]. However, these recommendations were primarily based on data from treatment-naïve patients with SMA. They are also classified as ‘non-sitters’, ‘sitters’, and ‘ambulant’, which can be challenging when the prognosis for children is uncertain in this new treatment era. Following the introduction of DMTs, standards of care for contracture management have been implemented with more stringency in the Netherlands despite its uncertain impact. The first section of this thesis, therefore, examined perspectives regarding the impact and management of contractures of both patient and health professionals.

Part 1: Impact of contractures and contracture management

Part one of this thesis explored how adolescents and young adults (AYA) view the impact of contractures and their treatment (**Chapter 2**). Not surprisingly, AYA with SMA reported that contractures had relatively less impact on their daily lives than

muscle weakness, but they mentioned their relevance for acute care settings (for instance, when cast immobilization for fractures necessitates joint extension beyond the range permitted by the contracture, it can result in considerable discomfort) and more intimate considerations such as appearance and intimacy. Additionally, they advocated for personalized goal setting in areas like confection shoes. Physical therapy was viewed more favourably compared to other contracture management methods, such as standers and orthoses.

Dutch pediatric rehabilitation physicians identify optimizing sitting posture, preventing pain, and maintaining function as the primary goals of contracture management. Clinical decision-making, outlined in **Chapter 3**, is largely driven by an individual child's functional prognosis, including factors such as age, timing of treatment initiation, muscle strength, and range of motion. At the same time, physicians experience significant uncertainty regarding the efficacy of commonly used interventions, especially orthoses, due to a lack of robust evidence. Contextual factors, including family circumstances, feasibility, and the child's emotional and social well-being, are seen as essential elements in treatment planning. Physicians recommend a personalised treatment plan, guided by the International Classification of Functioning, Disability and Health (ICF-framework) for children with SMA, emphasising shared decision-making and frequent goal reviews. Flexibility and transparent communication about uncertainties remain essential amid ongoing therapeutic changes.

Intermezzo

When writing this final chapter of my thesis, the COVID pandemic was a distant memory. The realization of how easily care for children with chronic diseases can be disrupted was quite shocking for healthcare professionals, but it was nothing compared to what parents went through. During the COVID-19 pandemic, parents of children with SMA needed to constantly balance protecting their child (from exposure) with maintaining the well-being of the entire family. We explored how families experienced this period, in particular how they safeguarded their children's health and well-being, dealt with their yet again increased level of responsibilities and managed their insecurity caused by limited information on COVID-19. We learned that families thought that contact and dialogue with healthcare professionals remained essential for decision-making processes and in managing uncertainties, even if healthcare professionals could not provide all the answers.

Part 2: Development of joint range of motion in the era of DMTs

Part two of this thesis consists of data from longitudinal studies on joint ROM in children with SMA treated with DMTs. We found that in children aged 0–8 years, wrist and elbow joint ROM remained stable over a 3-year follow-up period. Knee extension ROM decreased with approximately 3° per year. In older children aged 6–18 years, elbow ROM remained stable and knee extension ROM decreased with approximately 2° per year. Muscle strength for both flexor & extensor of the knee and elbow increased over time. Muscle strength imbalance, defined as the agonist-antagonist ratio (AAR) increased for the elbow, whereas the knee ratio was higher but remained stable throughout the study period. In children with SMA treated with DMTs at different ages, changes in muscle strength imbalance around the elbow over time did not consistently correspond with changes in elbow extension ROM; since elbow extension ROM remained preserved. For the knee, an important observation was the decline in knee extension ROM over time and the higher knee AAR compared to reference values. However, the small number of participants and assessments limited the ability to examine a potential relation between AAR and knee extension ROM in this study. The agonist–antagonist imbalance may force the joint to remain in a flexed position and over time, this restriction of ROM likely causes length-related changes in the muscle-tendon complex. These changes may consist of loss of sarcomeres in series (i.e. muscle shortening), which produces the loss of full joint ROM, i.e. contracture. Although this may appear obvious, none of the available previous studies in the literature included strength assessments to confirm or reject this hypothesis.

DISCUSSION OF THE MAIN FINDINGS

Part 1: Impact of contractures and contracture management

AYA noted that in acute care scenarios, contractures can be a primary source of pain when they are stretched for prolonged periods. As a result, contractures may complicate acute care or increase the burden it places on patients. Jaw contractures, for example, due to fatty degeneration of the lateral pterygoid muscle[20] are frequent in non-ambulant AYA and often complicates intubation[21]. These contractures develop insidiously at a relatively young age, are progressive in years and cause severe reduction of the ability to open the mouth[20] and their presence may complicate emergency intubations. Although efficacy of stretching, for example using devices to restore jaw mobility, has not been investigated, it is probably pragmatic to initiate stretching if maximum mouth opening is smaller than 30–35 mm, if only to facilitate oral hygiene, eating and

chewing and communication. Other contractures, such as the elbow, may complicate venous access in emergency situation. From the patient's perspective, **Chapter 2**, contractures in (acute) care scenarios may be a primary source of pain. For instance, when cast immobilization for fractures, which is a frequently occurring complication in individuals with SMA, necessitates joint extension beyond the range permitted by the contracture it can result in considerable discomfort. Moreover, prolonged joint stretching on an operating table or with medical imaging may lead to extended periods of pain. Health care professionals involved in the management of SMA should ensure that both patients and colleagues are appropriately informed to prevent such situations, for example by providing an additional instruction to an existing emergency card. A sentence could be added to the fracture section of the current Dutch SMA emergency card: "*when applying a cast: avoid excessive stretch on contractures*".

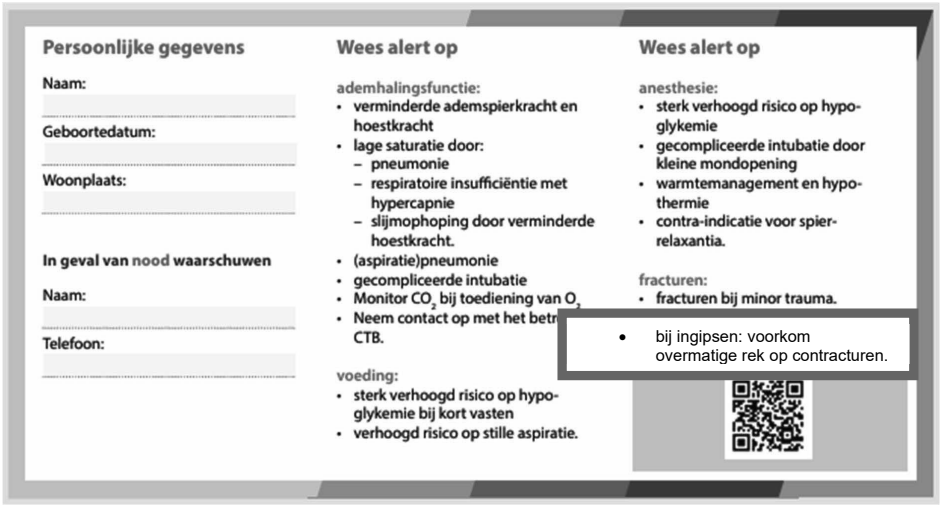


Figure 7.1. Dutch emergency card. The left column lists personal data, the middle covers advice on respiratory and feeding awareness, and the right discusses anaesthesia and fracture considerations.

Appearance was mentioned by AYA as an important aspect, which is in accordance with the findings of Willig et al. (1995)[22]. AYA also mentioned priorities with hindsight, in particular regarding appearance and sexuality. They highlighted the importance of early goal setting as a key aspect of contracture management, which may seem to conflict with the priorities (for example more time for leisure) of their younger selves. Being able to wear regular shoes rather than orthopedic shoes was mentioned as an important part of the desired appearance. More notably, AYA with severe contractures

report that contractures hindered during intimacy and sexuality in particular by limiting the variety of comfortable positions. Pediatric rehabilitation physicians, however, tend to prioritise setting functional treatment goals rather than focusing on future appearance and self-esteem (**Chapter 3**). As AYAs highlight the importance of goals related to appearance and sexuality, we recommend that these goals, although difficult to explain to younger children, remain 'at the back of the mind' of pediatric rehabilitation professionals.

Moreover, during our discussions about sexuality, two participants also brought up challenges related to pregnancy. It was not possible to recruit additional participants to strengthen its representation in our qualitative study, but I would strongly recommend that the themes of sexuality and pregnancy receive further attention in future research. The legs of individuals with severe neuromuscular conditions are often not functional and the first thought may be that contracture management is therefore not necessary. The feedback provided by AYA indicates that, while caring for younger children, we should find ways to discuss long-term goals with parents such as appearance and the possibility to explore sexuality in adulthood.

As a first step, incorporating hip abduction into routine contracture monitoring for children with SMA is important. This approach would not only facilitate personal hygiene but could ultimately also improve satisfaction related to intimacy and sexuality.

To our surprise, AYA did not mention pain in daily life as a main concern of contractures. Previous studies reported that contractures may result in pain and impair functional abilities in patients with SMA[14,23–25]. For example, a 1995 study by Willig et al.[22] found a correlation between flexion contractures and upper extremity pain in SMA. More recently, another study reported that lower limb contractures are positively associated with greater pain[26]. Steiner et al.[27] also concluded that the presence of contractures increases the likelihood of experiencing pain. However, this latter study did not provide a detailed definition of contractures beyond noting their presence in the lower limbs. Although a person with contractures might experience chronic pain, the direct connection between the two remains uncertain. What is described as pain in literature may also reflect stiffness rather than pain. AYA reported deriving significant benefit from passive mobilization by a physiotherapist due to stiffness. Notably, pain was observed to be significant in acute emergency situations or surgical procedures, particularly when limbs were maintained in a static position for longer periods of time. Pain is an important factor that negatively influences quality of life and has a clear impact on participation[28]. The fact that pain was, with the exception of casting for fractures

etc., not mentioned as an important symptom of contractures might otherwise be explained by our cohorts' age. Pain may occur as a late complication of contractures and AYA may experience pain later in life. Furthermore, within rehabilitation care in the Netherlands, substantial attention is devoted to pain, seating, and comfort (e.g., through specialized seating teams), which may potentially contribute to this outcome.

Dutch rehabilitation physicians emphasize the importance of personalized contracture management, taking into account variations in disease characteristics and contextual factors (i.e. personal and environmental factors). Estimating a child's functional prognosis is essential for personalized approaches. This remains complex, with no other predictors of efficacy of DMT (in terms of improved functional outcome) than (1) age at start of DMTs, (2) baseline (motor) function, and (3) *SMN2* copy number. Understanding disease progression and its impact on motor function is essential for designing appropriate rehabilitation strategies and therapeutic interventions aimed at slowing or halting decline. This was also described in a 2025 review on rehabilitation management in patients with SMA[29]. **Chapter 3** provides an overview of pediatric rehabilitation physicians' vision on postural management strategies for contracture management, including the use of orthoses and standing frames. One of the conclusions is that posture management is important to reduce contractures but that the lack of evidence complicates rational choices. Mortenson et al.[30] concluded that rehabilitation professionals require updated guidelines and improved knowledge-sharing mechanisms to effectively adapt to evolving SMA care practices. While their study covers rehabilitation care broadly and ours focuses on contracture management, the themes identified are closely related. Both studies underscore the importance of incorporating contextual factors (environmental and personal factors) in the care for children with SMA. Each child with SMA faces unique challenges, underscoring the necessity of adopting a child-centred approach that aligns rehabilitation objectives with everyday functioning. Current care standards advise contracture management purely based on motor function: 'non-sitters', 'sitters', or 'ambulant'. This study highlights the need to incorporate the comprehensive and holistic ICF-framework, including various domains of functioning alongside functional mobility. For instance, when considering overnight orthoses for young children, understanding their sleep patterns is crucial. If a child experiences sleep difficulties, prioritizing sleep as a short-term goal may be more important for rehabilitation physicians than focusing solely on functional level as a long-term goal. It is essential to incorporate the child's perspective. Goal setting should be a central outcome in clinical practice, requiring active engagement with the child and integration of both the caregivers and the child/families perspective in the rehabilitation process[31,32]. This approach expands rehabilitation beyond just physical

impairments to also consider activities, participation, and contextual influences. Figure 7.2, adapted from a figure illustrating the multidisciplinary approach in the current standards of care, may assist care professionals internationally in implementing the ICF-framework in SMA care, fostering a more holistic and goal-oriented practice.

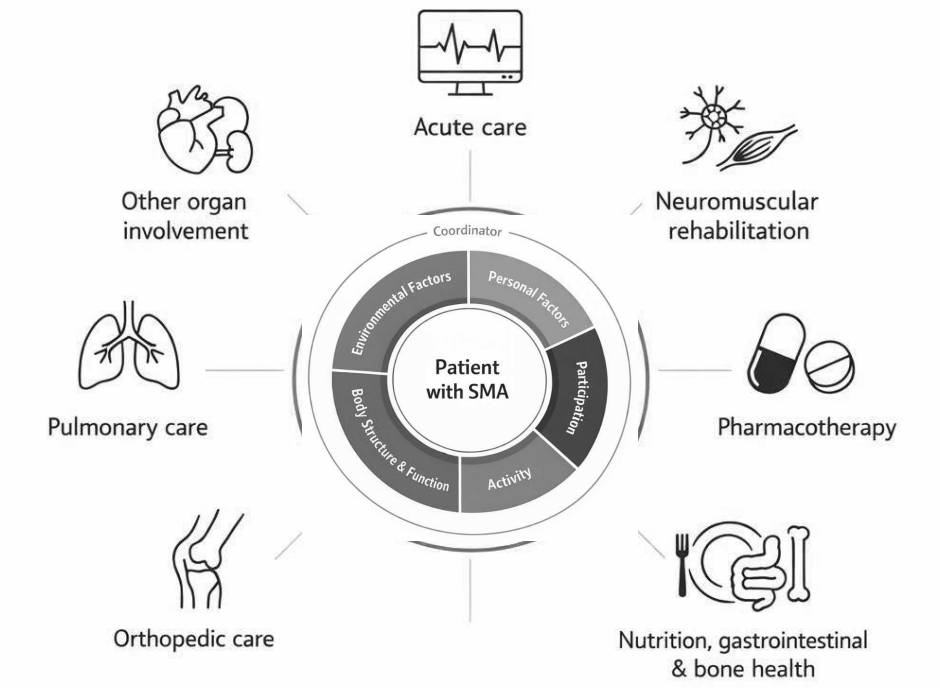


Figure 7.2. Integrated ICF-framework for children with SMA receiving multidisciplinary care.

Part 2: Development of joint range of motion in the era of DMTs

A key observation from this thesis is a possible change in the development of contractures in the current group of children with SMA receiving DMTs. In both longitudinal studies, we found that elbow extension ROM is stable over a 3-year follow-up period and the knee extension ROM decreases by 2–3° per year.

Identification of children at risk

These findings indicate that intensive monitoring and contracture prevention/management may no longer be necessary for all patients, highlighting the importance of a more individualized approach based on risk profiles. A critical challenge is the accurate identification of children at risk that require both closer monitoring and intensified contracture management. Part two of this thesis provides insight in parts of the assessments that may help in the identification of children at risk:

1. Joint ROM measurements,
2. Muscle strength assessments, and
3. Agonist-antagonist ratio assessments as a tool for risk identification in contracture follow-up protocols.

1. Joint ROM measurements

It is now known that DMT improve muscle strength and motor function[18,33], but do they also prevent contractures? Two key points may indicate that DMTs positively affect joint ROM. Historically, in children with SMA type 2 aged 3–5, 11.5% of assessments showed a decline in elbow extension with an average contracture of 10°[12,13]. In contrast, we did not find elbow contractures in this age group. Secondly, combining data of elbow ROM assessments from **Chapters 5** (green) **and 6** (blue) shows effects of age (Figure 7.3). In **Chapter 5**, we showed that only few children showed elbow extension below 0 degrees. In contrast, in **Chapter 6** several children had limited elbow extension (ROM <0°) at baseline, suggesting that these children already had contractures at younger ages. The most important difference between these cohorts is the median age at start of treatment, i.e. 2 months [IQR 0–8] in **Chapter 5** and 74 months [IQR 55–124] in **Chapter 6**. Because **Chapter 6** includes children with greater strength (MRC grade ≥3), these results indicate that there is, at minimum, a delay in the development of contractures.

Regarding knee ROM there was a decline observed in knee extension ROM in both **Chapter 5** (-3° [95% CI: -3.96; -2.04]) and **Chapter 6** (-2° [95% CI: -3.85; -0.18]), even though these groups differ in the following respects:

- The children in **Chapter 5** received an earlier initiation of treatment (2 months [IQR 0–8]) in comparison to the children in **Chapter 6** (77 months [IQR 58–123]), which could lead to the assumption that these children would have a milder course of contractures.
- However, in the cohort assessed in **Chapter 6**, selection bias regarding contracture formation likely occurred because only children with an MRC grade ≥3 were eligible for inclusion, which probably resulted in the exclusion of children with more severe contractures as well as a higher risk on progression of contractures.
- Additionally, the number of children included in the longitudinal study in **Chapter 6** (n=18), was much smaller than in **Chapter 5** (n=42), resulting in less assessments in **Chapter 6**.

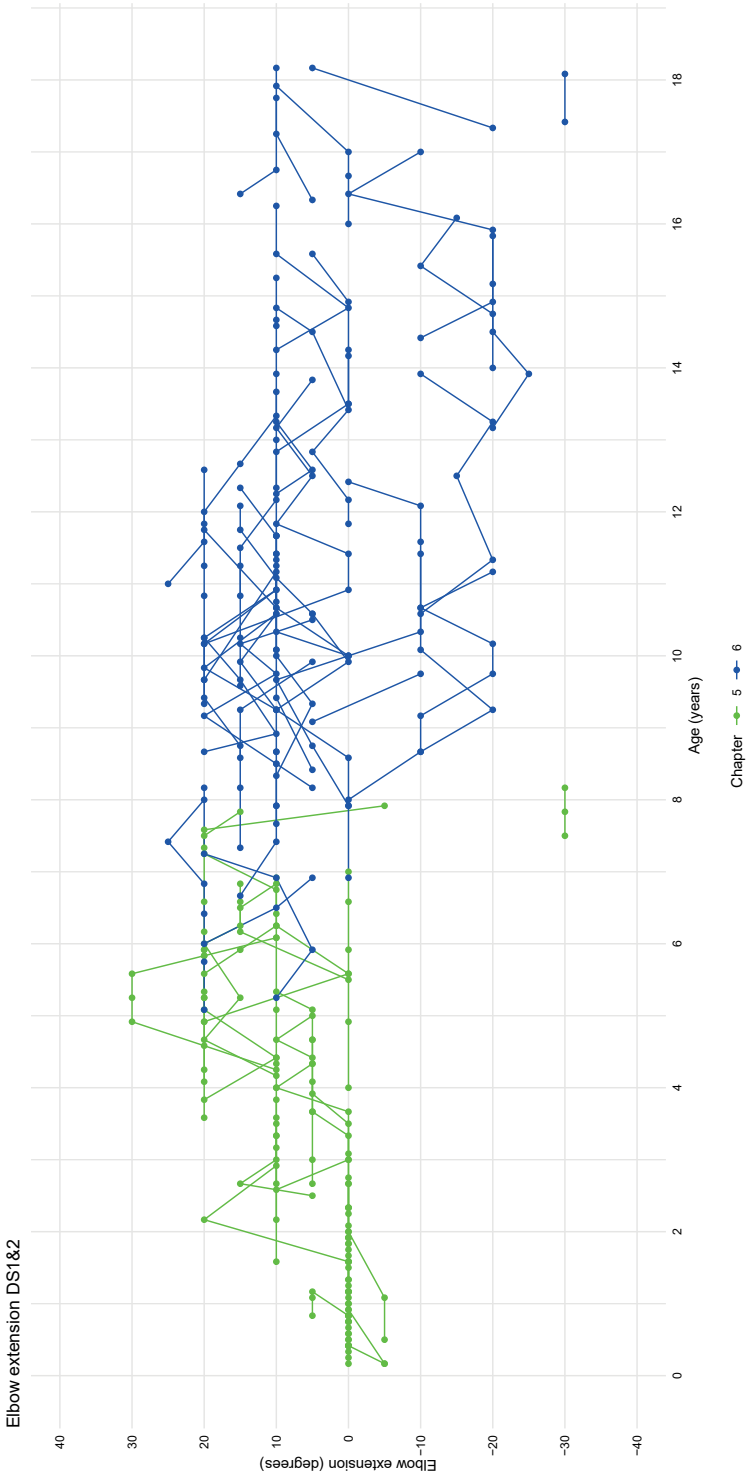


Figure 7.3. Combined elbow extension ROM data of Chapter 5 and Chapter 6.

2. Muscle strength

There are two key reasons why the assessment of absolute muscle strength adds value in identifying children at risk for contractures. First, absolute muscle strength provides information beyond that available through motor function tests, especially in clinical situations where contractures can influence motor function scale outcomes. However, strength assessment is impossible in infants and at least challenging in toddlers and young children. In newborns, muscle strength assessment therefore starts with functional observation using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). Motor function scales, such as the Hammersmith Functional Motor Scale Expanded (HFSME), Motor Function Measure (MFM), and Revised Upper Limb Module (RULM), are commonly used from age 3 onwards, but often display plateau effects within a few years after the start of DMTs[19]. These scales measure a child's ability to perform specific tasks, but small changes in strength may not affect scores unless a functional threshold is crossed, which can mask gradual improvement or decline. In contrast, quantitative muscle strength assessments capture strength as a continuous variable, enabling the detection of trends in changes over time, even when these changes do not alter observable motor task performance. Our study found that muscle strength continued to increase throughout the treatment trajectory, supporting the value of routinely measuring absolute muscle strength, especially in children older than six years and those with muscle strength preceding MRC grade 3. Secondly, the AAR alone may be insufficient for reliably identifying at-risk children. For example, two children may have the same AAR, even though one is very weak and the other is very strong; this ratio does not distinguish between overall muscle strength levels. Furthermore, static posture may play an additional role beyond the AAR in predicting contracture risk. By including absolute muscle strength assessments, not just AAR, clinicians can more effectively identify children who may be at risk. For instance, consider a hypothetical scenario: child A and child B both have an AAR of 2, but child A's muscle strength is significantly lower. Child A is at higher risk for developing contractures, a risk that might not be apparent from AAR alone. In summary, combining absolute muscle strength measurements with traditional motor function scales and AAR assessments provides a more comprehensive understanding of a child's risk profile. This approach allows clinicians to detect subtle changes and make more informed decisions about interventions. Future development of assisted protocols, such as Biodex testing, will further enable children with reduced muscle strength to undergo more detailed assessment and enrich future analyses.

3. Agonist-antagonist ratio as objective tool for risk identification

The need for objective tools to evaluate contracture risk is underscored by the ongoing contracture susceptibility of the knee in children treated with DMTs. An elevated AAR at the knee in children with SMA, relative to normative values, may indicate reduced knee extension despite increases in muscle strength. Integrating the AAR into clinical practice could be advisable. However, the restricted number of assessments precluded analysis of possible relationships. These topics require further research to clarify their clinical benefits. First, future studies should determine if a correlation exists. Secondly, determining a threshold ratio that signals heightened risk could help in detecting issues early and provide timely guidance for initiating contracture prevention strategies.

METHODOLOGICAL CONSIDERATIONS

Goniometry is an important tool for the collection of data presented in this thesis. Currently, goniometry is considered the most effective method for evaluating joint ROM in various (pediatric) patient groups, despite the obvious limitations and concerns regarding validity and reliability[34–36]. A systematic review of the literature highlighted the high intra- and interrater reliability of the universal goniometer for elbow measurements[37]. Similarly, ICC values for knee ROM are also very high[38]; however, literature on the smallest detectable difference remains scarce. This thesis demonstrates a decline in knee extension of 9° and 6°, respectively, over 3 years of time. Given the setup of the LMMs analysis, I find it very unlikely that the reduction in ROM observed is caused by a measurement error.

Even though joint range of motion assessment by trained clinicians is a reliable method to determine the quantitative range of motion in neuromuscular disorders[39–41], performing goniometry in young children, aged 0–2 years old, is challenging (**Chapter 5**). ROM assessments in children within this subgroup displayed variability; some presented with hyperextension while others exhibited contractures. However, by the age of two years, both typically transitioned to a neutral position. Normative reference values for joint ROM starts by the age of 3 years old[42]. Therefore, it can be discussed whether these results are contributed to a normal distribution or whether this has to do with SMA.

In clinical practice, where the assessment of multiple joints is required, rapid and precise assessment is essential. The inclusion of additional joints, such as the ankle, hip, and forearm (pronation and supination), with measurements across different planes

(such as an ankle with valgus and equinus deformity), may introduce considerable complexity. Therefore, I believe it is crucial in this field to consider alternative solutions, such as digital inclinometers. One study found digital inclinometers more accurate for knee assessment than universal goniometers[38]. Keijsers et al. also recommend using digital photographs and goniometry smartphone apps[43]. These alternative measurement methods may further enhance the reliability and accuracy of ROM assessments and could therefore be valuable for use in both clinical and research settings.

FUTURE RESEARCH DIRECTIONS

I would like to outline six additional research questions and directions to bring this discussion to a close.

The first question is: how can we develop individual prognostic models? Long-term studies should determine if wrist and elbow joint ROM in children with SMA on DMT remains stable or declines with age, as age has historically influenced joint ROM[12,13]. International data registries on joint range of motion can improve our knowledge on the accuracy of goniometry (when assessed using a standardized protocol), highlight factors that affect outcomes (including disease duration, progression prior to DMT initiation and SMN copy number), and contribute to developing individual prognostic models.

Second, is the observed high AAR associated with a reduction in knee joint ROM? The elevated agonist–antagonist ratio observed around the knee in children with SMA, compared with ratios in the reference group, may predispose these children to a reduction in knee extension ROM, even in the presence of increasing muscle strength. Therefore, we recommend future longitudinal studies to determine whether a high AAR precedes a decline in joint ROM.

Third, what is the exact relation between contractures and pain? We did not find contractures to be related to pain or impaired functional abilities in AYAs with SMA. Is pain a late complication of contractures, explaining its absence among AYA, or do contractures co-exist with, rather than cause pain? Pediatric rehabilitation physicians emphasize that ‘pain prevention’ is a key goal in managing contractures, which greatly influences how they set goals and make decisions in contracture management. Future studies should evaluate the effects of secondary orthopedic complications on functioning, with a specific focus on (different types and causes of) pain across various age groups.

Fourth, what is the contributing role of static posture? When flexion strength surpasses extension strength, even when flexion and extension muscle strength increases over time, static posture could play a contributing role. Exploration of movement patterns in greater depth could enhance our understanding of how static posture may contribute to the development of contractures. For instance, the analysis of movement patterns using video observation or wearable technology may provide valuable insights. Additionally, observing muscle activation, potentially via electromyography (EMG), could help discern whether muscle strength is present but not utilized during the activities children perform. This would suggest that static posture, rather than muscle weakness or AAR per se, is a key factor.

Fifth, which interventions are most efficacious for the treatment and prevention of contractures? Contracture management is a fundamental aspect for pediatric rehabilitation physicians, aiming to maintain proper body alignment and prevent or reduce contractures. There is an urgent need for more robust clinical recommendations, which in turn requires the use of alternative research designs capable of capturing the complexity of multicomponent rehabilitation interventions.

Lastly, could there be an alternative view on contracture pathophysiology? Joint ROM in SMA is affected by soft tissue extensibility and muscle changes. MRI studies show increased fat in thigh muscles without strength loss, highlighting a disconnect between clinical scoring and pathology, which may explain decreased knee extension despite stable muscle strength[44]. While SMN protein deficiency causes motor neuron loss, it also impacts other systems, for example (but not exclusively) kidney and cognitive function[45–48]. Future research should further assess the relation between contractures and SMN deficiency causing muscle and connective tissue changes.

CLINICAL IMPLICATIONS

The findings of this thesis emphasize the need to pay attention to individual trajectories of joint ROM and the shared-decision making of contracture management in the era of DMTs. Main implications are:

- The chance of developing elbow and wrist contractures appears to be reduced among children with SMA who are receiving disease-modifying treatment compared to those who are treatment-naïve.
- The development of knee extension contractures, though possibly reduced compared to the natural course, persists in children receiving DMTs.

- The impact of contracture management can be significant; personalized goal setting in contracture management is crucial, incorporating the ICF-framework.
- Appearance and sexuality are important for AYA and should therefore be goals that are kept in mind in rehabilitation programs that start at a younger age. Therefore, incorporating hip abduction into routine contracture monitoring for children with SMA may enhance both shorter term and long-term outcomes.
- Health care professionals involved in the management of SMA should ensure that both patients and colleagues are appropriately informed about the influence of contractures in acute care situations.

CONCLUSIONS

Although adolescents and young adults tend to perceive the impact of contractures as minor, they do negatively influence their appreciation of their appearance and self-image, the possibility to explore and enjoy sexuality, and may pose a risk or inconvenience in situations of acute care. Contracture treatment is time consuming and young individuals emphasize the importance of clearly defined, personalized treatment goals for effective management. Dutch pediatric rehabilitation physicians highlight the complexities of managing children with SMA who present novel phenotypes following DMT treatment. They stress the need for improved prognostic models, the use of the ICF-framework, and transparent discussions with parents about uncertainties surrounding contracture interventions.

A stable joint ROM was observed for the wrist and elbow, indicating a low risk of contracture formation in these joints in children, receiving DMTs before the age of 18 months. However, knee extension declined by 2–3° per year. Which supports the need for continuous routine joint ROM assessments in children with SMA receiving DMTs, at least until predictive models (incorporating factors such as age at treatment initiation, disease status, agonist-antagonist muscle strength ratios and possibly *SMN2* copy number) are available.

We recommend using the ICF-framework when updating contracture management guidelines for individuals with SMA, especially as DMTs evolve. The ICF-framework supports more effective, tailored rehabilitation plans. Setting child-specific treatment goals can enhance participation and improve quality of life for children with SMA.

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APPENDICES

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NEDERLANDSE SAMENVATTING

Spinale musculaire atrofie (SMA) is een zeldzame, ernstige en erfelijke spierziekte. In Nederland worden jaarlijks 15–20 kinderen geboren met aanleg voor deze aandoening en zijn er naar schatting tussen de 450 en 700 mensen met SMA. SMA kenmerkt zich door het afsterven van motorische zenuwcellen aan de voorzijde van het ruggenmerg, wat leidt tot het dunner worden van spieren (‘atrofie’) en het afnemen van de spierkracht, waarbij vooral houdingsspieren en de spieren in de bovenste delen van de ledematen zijn aangedaan. In de loop van de ziekte ontstaat vaak ook een verminderde beweeglijkheid van specifieke gewrichten, de zogenaamde contracturen. Uit de literatuur blijkt dat contracturen vaak leiden tot pijnklachten en beperkingen in het dagelijks functioneren.

De ernst van SMA vertoont grote verschillen. Dit wordt enigszins weergegeven door de klinische classificatie van SMA in verschillende types (0–4), waarbij SMA type 0 tot en met 3 op de kinderleeftijd voorkomen. SMA-typering gebeurt op basis van behaalde motorische mijlpalen en de leeftijd waarop de eerste tekenen van spierzwakte optreden.

Het afgelopen decennium is er veel veranderd in de behandeling voor kinderen met SMA. Sinds 2017 zijn er drie soorten medicamenteuze therapieën beschikbaar gekomen (Spinraza®, Evrysdi® en Zolgensma®). Elk van deze therapieën heeft een positief effect aangetoond op de overleving van kinderen met SMA type 1 en op de motorische functie van kinderen met SMA type 1–3. Omdat vroeg starten met medicatie beter resultaat geeft, is SMA sinds 2022 opgenomen in het Nederlandse neonatale screeningsprogramma (hielprikscreening). Vroege opsporing vergroot de kans dat de behandeling kan starten wanneer er nog geen of slechts weinig symptomen van SMA zijn, en verbetert daarmee de vooruitzichten voor kinderen met SMA.

Contracturen zijn de meest voorkomende orthopedische complicaties bij spierziekten zoals SMA. Ondanks het feit dat er weinig wetenschappelijk bewijs bestaat voor specifieke behandelingen van deze contracturen, is er op basis van klinische kennis en ervaring in 2018 een internationale richtlijn opgesteld voor het voorkomen en behandelen van contracturen bij kinderen met SMA. In deze richtlijn worden adviezen gegeven om spieren zoveel mogelijk op lengte te houden, onder andere door het toepassen van rekoefeningen, het dragen van spalken en het gebruik van een statafel. Het doel van deze adviezen is het behouden van de beweeglijkheid van de gewrichten en daarmee het voorkomen van beperkingen in het dagelijks functioneren. De precieze ontstaanswijze van contracturen is nog niet opgehelderd. Ook is er beperkt inzicht in de impact van contracturen zelf en de gevolgen van de behandeling die hiervoor worden

ingezet en het beloop van contracturen bij kinderen die medicamenteuze therapie krijgen. Deze kennishiaten maken het lastig om door wetenschappelijk onderzoek onderbouwde behandelkeuzes te maken.

Samenvattend laat de bestaande literatuur en klinische praktijk zien dat contracturen het dagelijks functioneren beïnvloeden en dat er, ondanks beschikbare richtlijnen, nog veel onzekerheid bestaat over hun ontstaan, beloop en optimale behandeling in het tijdperk van medicamenteuze therapieën.

Doel proefschrift

Het doel van dit proefschrift is om verschillende aspecten rondom contracturen te onderzoeken binnen de veranderende context van SMA-behandeling, dat wil zeggen de implementatie van medicamenteuze therapieën. Het eerste deel van dit proefschrift bevat studies die tot doel hadden de kennis over de impact van contracturen op het dagelijks functioneren te vergroten en de manier waarop kinderrevalidatieartsen aankijken tegen contractuurbehandeling vast te leggen. Het tweede deel richt zich op het inzichtelijk maken van het beloop van de gewrichtsmobiliteit bij jonge kinderen met SMA die vroeg, dat wil zeggen vóór de leeftijd van 18 maanden, zijn gestart met medicamenteuze therapie. Daarnaast wordt het beloop van de gewrichtsmobiliteit, spierkracht van de buigers (agonisten) en strekkers (antagonisten), de agonist-antagonist disbalans in de loop van de tijd en de eventuele samenhang tussen deze factoren onderzocht.

Deel 1: Impact van contracturen en contractuurbehandeling

Hoofdstuk 2 beschrijft de ervaringen van adolescenten en jongvolwassenen (AJV) met contracturen en de impact daarvan op hun dagelijks functioneren. Hiervoor vonden interviews plaats met 14 rolstoelgebonden AJVs met SMA (10 vrouwen en 4 mannen, leeftijd 16–30 jaar). Uit de interviews kwam naar voren dat zij minder last hebben van hun contracturen dan van het verlies van spierkracht. Ze benoemen dat ze zich in de loop van de tijd aangepast hebben aan de contracturen. Behandeling van contracturen werd als zinvol ervaren wanneer doelen betekenisvol en haalbaar waren. AJV geven bijvoorbeeld aan dat het dragen van normaal schoeisel bijdraagt aan hun zelfvertrouwen en uitstraling en dat het handhaven van een normale voetstand daarom een belangrijke doelstelling is. Meerdere AJV gaven aan dat het staan aan de statafel negatieve gedachten opriep, omdat ze dit als een onrealistisch doel zagen: '*Ik ga toch nooit staan in de toekomst*'. Negatieve gevolgen van contracturen die door AJV werden benoemd, zijn onder andere veranderingen in het uiterlijk (bijvoorbeeld

de stand van hun handen op een foto) en houdingsbeperkingen die belemmerend kunnen zijn op het gebied van intimiteit/seksualiteit. Bij momenten van acute zorg hebben AJV regelmatig problemen ervaren van pijnklachten (bijvoorbeeld bij gipsbehandeling waarbij een contractuur continu op rek wordt gebracht of bij langdurig in eenzelfde houding moeten liggen). Fysiotherapeutische behandelingen, met name het passief mobiliseren, worden over het algemeen als waardevol en prettig ervaren. Behandelingen met orthesen en statafels daarentegen worden vaker als belastend en minder zinvol omschreven. Van belang is dat kinderen en hun ouders geïnformeerd worden over de mogelijke gevolgen van contracturen, maar ook over de voordelen en mogelijke bijwerkingen van de contractuurbehandeling. Deze informatie kan het gezamenlijke besluitvormingsproces ondersteunen. Hierdoor kunnen zij, op basis van wat kinderen en ouders zelf belangrijk vinden, kiezen voor het starten en voortzetten van contractuurbehandeling die hen helpt in het dagelijks functioneren en participatie.

Een studie met vragenlijsten onder kinderrevalidatieartsen in Nederland naar het contractuurbeleid bij kinderen met SMA (**hoofdstuk 4**) richtte zich op het in kaart brengen van de doelen/strategieën ten behoeve van preventie/behandeling van contracturen en hoe dit zich verhoudt tot landelijke en internationaal geldende richtlijnen. Alle 151 geregistreerde kinderrevalidatieartsen in Nederland ontvingen een vragenlijst die twee hoofdonderwerpen behandelde: (1) indicatie, doel en interventies, en (2) overwegingen bij het contractuurbeleid in relatie tot het moment van starten met medicamenteuze therapieën bij SMA. Om beter inzicht te krijgen in het besluitvormingsproces rond contractuurbehandeling in de huidige tijd van medicamenteuze therapieën, organiseerden we een bijeenkomst met een adviesgroep van kinderrevalidatieartsen. Van de kinderrevalidatieartsen vulde 56% de vragenlijst in. Alle respondenten noemden optimale zithouding als belangrijk behandeldoel; 95% vond pijnpreventie belangrijk en 87% hechtte waarde aan behoud van functioneren. Nederlandse kinderrevalidatieartsen vinden klinische besluitvorming bij contractuurbehandeling voor SMA lastig vanwege veranderende behandelperspectieven. Op basis van dit onderzoek adviseren we enkele kernprincipes te gebruiken ter ondersteuning van de gezamenlijke besluitvorming bij contractuurbehandeling:

1. Een inschatting maken van de functionele prognose;
2. Het vaststellen van doelen voor deelname in het dagelijks leven;
3. Het meenemen van persoonlijke en omgevingsfactoren bij het maken van keuzes over contractuurbeleid.

Tijdens de opstartfase van de in dit proefschrift beschreven studies, bevond Nederland zich in de uitzonderlijke omstandigheden van de COVID-19 pandemie. Daarom worden in **hoofdstuk 3** de ervaringen, uitdagingen en behoeften van ouders (die kinderen met SMA verzorgen) in de vroege stadia van de pandemie belicht. Tijdens de COVID-19 pandemie moesten ouders van kinderen met SMA voortdurend een balans vinden tussen het beschermen van hun kind (tegen COVID-19 blootstelling) en het waarborgen van het welzijn van het hele gezin. Ouders van kinderen met SMA ervaren een hoge zorglast en voelen zich verantwoordelijk voor zowel de fysieke als mentale gezondheid van hun kind. Tijdens de COVID-19 pandemie werd deze zorglast versterkt door onzekerheid, beperkte toegang tot therapieën en het wegvallen van sociale contacten. Deze ervaringen onderstrepen het belang van medische zorg, waarin niet alleen puur medische, maar ook psychosociale factoren aandacht krijgen. Gezinnen geven daarnaast aan het contact en de dialoog met zorgprofessionals als essentieel te hebben ervaren voor besluitvormingsprocessen en het omgaan met onzekerheden, zelfs wanneer zorgprofessionals niet op alle vragen een antwoord konden geven.

Deel 2: Beloop van gewrichtsmobiliteit in het tijdperk van medicamenteuze therapieën

Hoofdstuk 5 beschrijft onderzoek waarin we de gewrichtsmobiliteit van drie gewrichten hebben gemeten bij jonge kinderen met SMA die in de eerste 18 maanden van hun leven gestart zijn met medicatie. De metingen vonden plaats tussen april 2021 en augustus 2024 en werden uitgevoerd tijdens reguliere controles in het Spieren voor Spieren kindercentrum in het Wilhelmina Kinder Ziekenhuis (UMC Utrecht). De tijd tussen de metingen varieerde van vier tot twaalf maanden. Voor de analyse van deze studie waren gegevens beschikbaar van 39 kinderen (20 jongens, 19 meisjes) met gemiddeld vier metingen per kind. In totaal zijn er data beschikbaar van 165 meetmomenten. De mediane follow-up was 16 maanden. De bewegingsuitslagen van pols en elleboog bleven stabiel over de tijd. Bij de knie zien we een langzame afname van de strekking (met ontstaan van contractuur) gedurende de studie. De gemiddelde afname per jaar is 3 graden. Regelmatige controle van de bewegingsuitslag is belangrijk om (knie)contracturen bij kinderen met SMA tijdig op te sporen en behandeling in te zetten om achteruitgang te voorkomen of te behandelen, vooral bij kinderen die voldoende spierkracht hebben om te kunnen/gaan staan en/of lopen.

Bij SMA wordt verondersteld dat een disbalans in spierkracht tussen de buig- en strekspieren ertoe kan leiden dat een gewricht, naarmate de ziekte voortschrijdt, langdurig in een gebogen positie blijft staan. Hierdoor kan uiteindelijk een bewegingsbeperking

van het betreffende gewricht ontstaan. Omdat er nooit is onderzocht of deze hypothese klopt, beschrijft **hoofdstuk 6** de verandering in spierkracht en gewrichtsmobiliteit van de elleboog en knie in de loop van de tijd. Spierkracht wordt gemeten op de Biodex, een gespecialiseerd meet- en trainingstoestel dat veel wordt gebruikt in revalidatie- en sportgeneeskunde. Met behulp van het apparaat kunnen we spierkracht en krachtverhoudingen rond gewrichten, zoals knie, heup, schouder en enkel, goed meten. Met de Biodexgegevens kunnen we ook een analyse maken van de spierbalans. Voor de elleboog kijken we naar de verhouding tussen biceps (buigspier) en triceps (strekspier) en voor de knie naar de verhouding tussen hamstrings (buigspier) en quadriceps (strekspier). Deze verhouding noemen we agonist-antagonist ratio (AAR). De gegevensverzameling voor deze studie vond plaats tussen april 2021 en januari 2025, waarbij de kinderen iedere acht maanden werden gemeten. In totaal konden voor deze groep de metingen van 42 kinderen (24 meisjes en 18 jongens) worden meegenomen in de analyses van de elleboog. Voor de knie werd de spierkracht bij 18 kinderen op verschillende momenten gemeten. Het eerste doel was het beloop van gewrichtsmobiliteit, spierkracht en AAR te bestuderen. Het tweede doel was om de mogelijke samenhang tussen deze verschillende factoren te onderzoeken. Uit de analyse van het beloop van de gewrichtsmobiliteit blijkt dat de beweeglijkheid van de elleboog over tijd stabiel blijft, terwijl de strekking van de knie langzaam afneemt (gemiddeld 2 graden per jaar). De spierkracht voor zowel de buigers als strekkers van de knie én elleboog nam toe gedurende de onderzoeksperiode. De AAR van de elleboog steeg. De AAR van de knie was weliswaar hoger, maar bleef gelijk gedurende de studieperiode. We vonden geen duidelijke verbanden tussen verandering in spierkracht en de ratio enerzijds en de bewegingsuitslag van het gewricht anderzijds. Voor de knie kwam dit waarschijnlijk doordat de aantallen te laag waren; een hoge AAR kan mogelijk wel bijdragen aan het geleidelijke verlies van kniestrekking. Door een hoge AAR blijft een gewricht langdurig in een gebogen stand en dit kan na verloop van tijd resulteren in een verkorte positie waardoor het gewricht minder kan bewegen en er een contractuur ontstaat.

Tenslotte heb ik in **hoofdstuk 7** de belangrijkste bevindingen samengevat, de resultaten bediscussieerd en belangrijke conclusies en aanbevelingen voor de praktijk weergegeven. Zo begrijpen we dankzij dit onderzoek beter hoe de beweeglijkheid van bepaalde gewrichten zich ontwikkelt bij kinderen die medicatie krijgen voor SMA. De achteruitgang van de gewrichtsmobiliteit bij de elleboog en pols lijkt verminderd bij kinderen met SMA die met medicatie behandeld worden in vergelijking met kinderen die niet behandeld werden. Het risico op het ontstaan van een beperking in het strekken van de knie blijft echter bestaan in deze kinderen die met medicatie behandeld worden.

Dit onderzoek benadrukt het belang van een blijvende goede zorg voor contracturen en het afstemmen van specifieke en persoonlijke doelen samen met het kind en/of de ouders. Hierbij dient ook gedacht te worden aan aspecten als zelfvertrouwen, uiterlijk en seksualiteit. Het regelmatig monitoren van de beweeglijkheid van de heupspreiding bij kinderen met SMA kan bijdragen aan zowel de verzorging en persoonlijke hygiëne als in overwegingen voor revalidatieartsen op het gebied van toekomstige intimiteit en seksualiteit. In tegenstelling tot bevindingen uit eerder onderzoek werd in dit onderzoek geen duidelijke relatie gevonden tussen contracturen en pijn. Het is mogelijk dat pijn door contracturen pas later in het leven ontstaat of de revalidatiezorg tussen landen verschillend is. Zorgprofessionals die betrokken zijn bij de SMA-zorg moeten zowel patiënten als collega's adequaat informeren over de invloed van contracturen in acute zorgsituaties (bij een breuk waarvoor gips nodig is of bij een operatie). Het hoofdstuk wordt afgesloten met een aantal aanbevelingen voor toekomstig onderzoek dat ons moet helpen om zicht te krijgen of de beweeglijkheid van de elleboog en pols ook op langere termijn stabiel blijven én dat helpt om beter te voorspellen welke kinderen meer risico lopen op het ontstaan en toenemen van contracturen.

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CURRICULUM VITAE



Irene Busstra-Oude Lansink was born on October 10th, 1989, in Eindhoven, the Netherlands, and grew up in the village of Wierden. She studied Medicine at Radboud University Nijmegen, where she developed an early interest in both Rehabilitation Medicine and scientific research. During her medical training, she undertook a research internship at St James's University Hospital in Leeds, United Kingdom, and completed her final clinical internship at the Department of Rehabilitation Medicine at the University Medical Center Groningen.

After obtaining her medical degree, she started her residency in Rehabilitation Medicine at UMC Groningen. As part of her residency training, she completed a research internship at the CanChild Centre for Childhood Disability Research in Canada, further strengthening her interest in pediatric rehabilitation and international research collaboration.

Since January 2018, Irene has been working as a pediatric rehabilitation physician at University Medical Center Utrecht, with a clinical focus on neuromuscular disorders. Her work integrates patient-centered care with clinical research aimed at improving outcomes and quality of life for children and adolescents with neuromuscular conditions.

In July 2019, she initiated her PhD research at the Department of Rehabilitation, University Medical Center Utrecht. Her doctoral research focused on contracture development in children with spinal muscular atrophy (SMA) in the era of disease-modifying therapies. The PhD project was supervised by Prof. Dr. Jan Willem Gorter, Prof. Dr. Ludo van der Pol, and Dr. Anita Beelen. The research presented in this thesis reflects the close integration of her clinical practice and academic interests.

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