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Spinal Muscular Atrophy: The Use of Functional Motor Scales in the Era of Disease-Modifying Treatment

Katarzyna Pierzchlewicz[1], Izabela Kępa[1], Jacek Podogrodzki[1], and Katarzyna Kotulska[1]

Abstract

Spinal muscular atrophy (SMA) is a genetic condition characterized by progressive motoneuron loss. Infants affected by SMA type 1 do not gain developmental milestones and acutely decline, requiring ventilatory support. Several scales are used to assess motor disability and its progression in SMA. Recently, 3 disease-modifying therapies have been approved for SMA patients: nusinersen, an intrathecal antisense oligonucleotide enhancing SMN protein production by the *SMN2* gene, risdiplam, also influencing the *SMN2* gene to stimulate SMN production but administered orally, and onasemnogene abeparvovec-xioi, an *SMN1* gene replacement therapy. Thus, the functional scales should now be applicable for patients improving their motor function over time to assess treatment efficacy. In this paper, we compare different functional scales used in SMA patients. Their usefulness in different SMA types, age groups, and feasibility in daily clinical practice is described below. Some changes in motor function assessments in SMA are also suggested.

Keywords

spinal muscular atrophy, disability, functional scale, treatment

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Spinal muscular atrophy (SMA), a neuromuscular disease affecting about 1 in 7500 live births,[1–5] used to be the most common genetic cause of infant mortality before the introduction of disease-modifying treatment.[1–3,5] It is caused by a loss or mutation of the survival motor neuron 1 (*SMN1*) gene in more than 95% of cases. The disease is inherited in autosomal recessive mode, and carrier frequency varies between 1/47 in the Caucasian population to 1/72 in the African American population.[5,6] In infants, SMA was first described in 1891 by Werdnig and independently by Hoffmann in 1893.[7,8] The hallmark of the disease is the progressive muscle weakness associated with normal cognitive functions. Proximal muscle weakness and atrophy are more prominent than distal weakness, and lower extremities are more affected than upper ones.[9] Based on the age of the first symptom presentation and the patient's motor milestones before the disease's onset, SMA is divided into 5 types.

Spinal muscular atrophy type 1, the so-called Werdnig-Hoffmann disease, is the most frequent (60%).[1,2,7,10] Infants with SMA type 1 are never able to sit independently, and their life expectancy is about 2 years in untreated patients.[9] SMA type 1 can be divided into 3 subtypes:

a. symptoms are present at birth, frequently including joint contractures, and respiratory support is needed within the first weeks of life,
b. the onset of symptoms is after a neonatal period but before 3 months of age and head position control is never achieved,
c. symptoms appear between the third and sixth month of age, and head position control is possible.[9,11]

[1] Department of Neurology and Epileptology, Children's Memorial Health Institute, Warsaw, Poland

Corresponding Author:
Katarzyna Pierzchlewicz, Department of Neurology and Epileptology, Children's Memorial Health Institute, Warsaw 04-730, Poland.
Email: katarzynapierzchlewicz88@gmail.com

Table 1. Types of SMA (Spinal Muscular Atrophy).[2,9,12,13]

SMA type	Natural history of the disease	Age at first symptoms	Life expectancy without treatment
0	Generalized hypotonia present prenatally or in neonates, respiratory insufficiency, failure to swallow, contractures	Prenatal (faint fetal movements) or neonatale	Approximately 6 months
1	Independent sitting never achieved, acute loss of motor functions, respiratory failure before the age of 2, early feeding problems	Before 6 months	Approximately 2 years
2	Independent walking never achieved, subacutely progressing muscle weakness, early development of scoliosis	6-18 months	Shortened, different in various sources
3	Independent walking achieved, slowly progressing muscle weakness,	18 months-18 years	Not affected
4	Mild hypotonia, slowly progressing muscle weakness	After 18 years	Not affected

In SMA type 2, patients gain the ability to sit, but they never walk, and their life expectancy is shortened. Patients with SMA type 3 (SMA3 or Kugelberg-Welander disease) develop the disease after gaining the ability to walk.[2,3,9,12] Type 3 can be divided into 2 subtypes:

- 3a—with first symptoms before the age of 3, and
- 3b—with symptoms onset after the age of 3[8,9] (Table 1).

In SMA type 0, the most severe form of the disease, the symptoms can present prenatally or immediately after birth. Affected newborns present with respiratory failure and severe generalized hypotonia.

SMA type 4 presents in adulthood and is slowly progressing. SMA type 3 and 4 do not affect life expectancy[1,2,9] (Table 1). However, in all SM types, the symptoms progress irrevocably in untreated patients.

Given that all SMA patients decline over time, type 3 patients may at some point present with disability typical for type 2, and type 2 patients may require ventilatory support and lose the ability to sit, similar to SMA 1 patients. Therefore, SMA typing refers only to the patient's best status ever. According to their current neurological status, patients are frequently divided into non-sitters, sitters, and walkers.[14]

In SMA, the causing mutation affects survival motor neuron (SMN) protein production involved in transcriptional regulation, telomerase regeneration, and cellular trafficking.[15,16] In addition to the *SMN1* gene, the human genome contains the *SMN2* gene, which also produces SMN protein, but due to the single nucleotide substitution in exon 7, only 10-20% of *SMN2* transcripts are full-length functional protein.[16] Lack of SMN protein in motor α-neurons results in SMA symptoms. Degeneration of spinal cord motoneurons leads to improper motor innervation and muscle atrophy with axial and bulbar muscles being most severely affected.[8,17] The symptoms of the disease are associated with weakness and atrophy of different groups of muscles. They include scoliosis due to dorsal muscles involvement and other skeletal deformations related to weak muscles of the limbs, breathing difficulties with paradoxical breathing, and bellshaped chest deformation due to the weakness of intercostal muscles (the diaphragm is usually not affected), swallowing and coughing problems related to hypotonia of throat muscles. The onset of symptoms in infants and young children is generally associated with poor weight gain. On the other hand, decreased physical activity results in a high risk of obesity in older patients. Patients are usually at increased risk of developing osteoporosis and frequent bone fractures. Due to breathing effort and autonomic system involvement, SMA patients frequently sweat excessively.[1,18,19] Until recently, only symptomatic treatment of SMA was possible, including orthopedic operations (correction of scoliosis and limb deformities), ventilatory support, antibiotics during frequent respiratory infections (weakness of intercostal muscles and lack of proper coughing), naso-gastric tube or gastrostomy feeding for malnourished patients or those unable to swallow properly. Symptomatic treatment does not change the natural history of SMA and does not influence the loss of motor functions. However, it can extend life expectancy and improve the quality of life.[14]

Molecular Background of SMA

In more than 90% of all SMA cases, individual homozygous deletion of *SNM1* gene located on the telomeric region of chromosome 5 is found.[15,16,20] In a small number of SMA patients, the disease is caused by point mutations in the *SMN1* gene.[9,16,21] About 90% of *SMN2* mRNA lacks exon 7, and protein translated from that transcript (named SMNΔ7) is shorter and non-functional. Thus, only 10-20% of normal SMN protein comes from the *SMN2* gene.[20] However, the number of *SMN2* gene copies varies from 1 to even 8 in some individuals. It is known that the higher *SMN2* copy number is related to the later onset of symptoms and slower disease progression.[17] Patients with SMA 1 usually have 2 *SMN2* copies, while SMA 2 and 3 patients have 3 copies or more.[6,8] However, it is not a rule, and for example, patients with 4 *SMN2* copies may rarely develop SMA type 1.[4]

Disease-Modifying Therapies

There are now 2 SMA treatment strategies: *SMN1* gene replacement and increasingly functional SMN protein

production by the *SMN2* gene. In 2016, the first disease modifying treatment for SMA—nusinersen—was approved by the FDA, initiating a new SMA therapy era.[22] Nusinersen is an antisense oligonucleotide which modulates splicing of the *SMN2* mRNA transcript, thus increasing inclusion of exon 7 and production of full-length SMN protein. The drug is administered intrathecally with 3 loading doses given every 2 weeks, the fourth dose after 1 month, and then the maintenance doses are given every 4 months.[22–24,25,26] Risdiplam, approved by the FDA in 2020, is an oral antisense oligonucleotide increasing the SMN protein production by the *SMN2* gene. A similar agent, called branaplam, is still in clinical trials.[27,28] In 2019, gene replacement therapy with onasemnogene abeparvovec-xioi (AVXS-101, trade name Zolgensma®) was approved by the FDA.[29] It employs the AAV9 (adeno-associated virus type 9) vector to deliver the normal copy of the *SMN1* gene. Due to its ability to cross the blood-brain barrier, it can be administered intravenously.[20,29] Nusinersen, risdiplam, and onasemnogene showed their efficacy in SMA.[20,23,24,29] Treatment with either of the compounds resulted in the disease activity stabilization not seen in the untreated cohorts. Moreover, a significant improvement in motor functions was observed in many cases.[30] Both in clinical trials and now in clinical practice, different scales are used to assess the patients' functional status objectively.[20,24]

Motor Assessment Scales in SMA

According to the recommendations published in 2018, all SMA patients should undergo neurologic examinations every 6 months.[14] Such examinations should include the assessment of motor functions according to an appropriate functional scale. The choice of a scale should be based on the patient's age, SMA type, and current neurological status (Tables 2 and 3).[14] The examinations using scales should be carried out by physiotherapists or physicians, employing tests based on the standard neurological examination.[14]

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)

The scale contains 16 items addressing the spontaneous movements, hand grip, head stabilization, flexion, and extension of the limbs. The state of the patients should be rated using the Brazelton Neonatal Behavioral Assessment Scale prior to examination with the CHOP-INTEND scale. It gives information on whether the patient's abilities are state-dependent.[34] The test should not be performed in hungry or tired patients. If the patient requires respiratory support, the test must not interrupt it.[34] Every item is rated from 0 to 4 points in the CHOP-INTEND scale, and the maximum score is 64 points. In cases of asymmetric motor functions, the better side result should be reported. The complete CHOP-INTEND usually takes 10 to 15 minutes, but the exact time may vary according to the patient's cooperation. The scale is relatively easy to use. It does not require any sophisticated equipment (only a toy to draw the patient's attention and test the grip and a mirror useful in placing the child correctly on a caregiver's lap) or special training.[34] The CHOP-INTEND is the most popular scale used worldwide to assess SMA patients, and, therefore, may be used to compare the results obtained in different centers.[34–36] It is used in daily clinical practice and clinical trials in SMA type 1 and non-sitting patients with other types of the disease.[34–36] One of its limitations is relatively poor reliability in the youngest newborns and infants.

The Hammersmith Infant Neurologic Examination (HINE)

The Hammersmith Infant Neurologic Examination is a scale designed for children between 2 and 24 months of age. It is used to evaluate their ability to achieve motor milestones. The scale includes examining cranial nerves, posture, movements, tone, and reflexes. The maximum score is 26 points.[33] The scale was invented to assess healthy children's motor milestones and was validated in healthy populations only.[37] The significant advantage of this scale is its simplicity and the short time required for the examination. However, the scale is not sensitive enough in the case of patients with a more severe disability.[11]

The Hammersmith Infant Neurological Exam—Part 2 (HINE-2)

Like HINE, HINE-2 also evaluates motor milestones but is more focused on rating patients' increments in each item.[37] Thus it is more suitable for SMA patients who make no or very modest improvements in gaining the milestones.[11] An examiner evaluates the patient's head control, sitting, voluntary grasp, ability to kick, roll, crawl, stand, and walk. Points for every item are given for functions described in detail; for example, ability to kick gets 0 points for no kicking, 1 point is given for kicking horizontally, 2 for kicking upward, 3 for touching legs, and 4 for touching the toes.[11] Every item has a different number of descriptive achievements (for example, for head control only 3), and the maximum score is 56 points.[37] HINE-2 can be used as a tool to compare milestones achieved by non-SMA children and SMA patients.[37]

It is widely used in SMA patients, but it still needs validation.[11,37]

The Motor Function Measure-20 (MFM-20)

The Motor Function Measure (MFM) was validated in various neuromuscular disorders.[38] It was initially designed for children aged 7 or more and has 32 items divided into functional domains.[39] However, it was too strenuous for the majority of SMA patients.[38] MFM-20 is a modified version of the MFM scale with some difficult items removed, making it suitable for younger children. The scale is composed of 20 items.[39] It can be used in patients aged 2 or more.[40]

Table 2. Comparison of the Most Popular Motor Scales.

Name of the scale	Age	Target group	What does the test determine in particular	Advantages	Disadvantages	Validation in SMA
CHOP-INTEND	No lower or upper limit established[30]	Non-sitters[30]	The strength of the axial and peripheral muscles[30]	The child's behavioral state is taken into account[30]	Not sensitive enough	Yes[30,31,32]
HINE	2-24 months[19]	Non-sitters, sitters, and walkers[19]	Achieved milestones and cranial nerves[19]	Harmonizes with physiological motor development[19]	Age limit[19]	No
HINE-2	2-24 months[33]	Non-sitters, sitters, and walkers[33]	Focused on achieved milestones[33]	Rates the patient's increments[10,33]	Age limit[34]	Not enough data[10,33]
MFM-20	>2 years	Sitters and walkers	Different patterns of weakness and different functional levels	Sensitive enough to distinguish between proximal and distal muscle weakness	Time-consuming	Yes (validated in neuromuscular disorders in general)
GMFM	>5 years	Non-sitters, sitters, and walkers	A detailed assessment of muscle strength during motor development	Sensitive to distinguish even small changes in muscle strength	Too much focused on strength asymmetry	Yes
HFMS	>30 months	Sitters and walkers	Upper and lower extremities and trunk muscles strength	Correlates with *SMN2* copy number and age	Does not assess small muscles strength	No
HFMSE	>2 years	Sitters and walkers	Gross motor function	Correlates with *SMN2* copy number, CMAP, and FVC	Patient's cooperation is needed	Yes
RHS	>1 year	Sitters and walkers	Gross motor function and motor milestones	Can be used when the patient achieves the ceiling effect on the HFMSE	Not enough data assessing test utility	No
6-MWT	>4 years	Walkers	Gait and fatigue	Assessment of different organs	Aggravating for weaker ambulant patients	Yes
RULM	>30 months	Non-sitters, sitters, and walkers	Strength of upper limbs and precise movements	Assess abilities useful in everyday living	Assess only upper limbs	No
QMT	>3 years	Non-sitters, sitters, and walkers	Strength of limbs muscles	The test is objective	Rates only a limited number of muscles	No
Neuromuscular GRO	No upper or lower limit	Non-sitters, sitters and walkers	Muscle strength and motor development	Detailed items	Can cause fatigue	No

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurologic Examination; HINE-2, Hammersmith Infant Neurologic Examination Section 2; MFM-20, Motor Function Measure 20; GMFM, Gross Motor Function Measure; HFMS, Hammersmith Functional Motor Scale; HFMSE, Expanded Hammersmith Functional Motor Scale; RHS, Revised Hammersmith Scale; 6MWT, 6-Minute Walk Test; RULM, Revised Upper Limb Module; QMT, Quantitative Muscle Testing; SMN2, Survival Motor Neuron Gene 2; CMAP, Compound Muscle Action Potential; FVC, Forced Vital Capacity; GRO, Gross Motor Outcome.

Table 3. Tests Recommended in Different Types of SMA.[14]

Patient's best functional status	Recommended functional scale
Non-sitter	CHOP-INTEND, HINE
Sitter	HFMSE, RULM, MFM
Walker	6-MWT, RULM, HFMSE

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurologic Examination; HFMSE, Expanded Hammersmith Functional Motor Scale; RULM, Revised Upper Limb Module; MFM, Motor Function Measure; 6MWT, 6-Minute Walk Test.

Functional domains of MFM-20 include:

D1—standing and transfers,
D2—axial and proximal motor function,
D3—distal motor function, thus, capturing different patterns of weakness (such as proximal or distal) and other functional levels (including the ability to walk).

Each item is scored from 0 (not able to initiate movement) to 3 (full performance of a task), and thus, 60 points are the maximum score on this scale.[39]

This scale's major advantage is its relatively high sensitivity to differentiate changes in proximal and distal muscles.[39] MFM-20 is most useful for children who can sit without support.[40]

The Gross Motor Function Measure (GMFM)

The Gross Motor Function Measure (designed at McMaster University) is a scale intended initially for children with cerebral palsy. Its validity was established by correlation with muscle strength—assessed by the Quantitative Muscle Testing (QMT) in patients from 5 (QMT is only valid from that age) to 18 years of age.[38,41] It consists of 5 domains of items:

1. lying and rolling,
2. sitting,
3. crawling and kneeling,
4. standing,
5. walking, running, and jumping.[38,41]

The scale includes 88 items, and each item is scored from 0 to 3 points.[38,41] The advantages of this scale include the discriminatory increments for small changes in strength and its flexibility as eliminating some items is allowed.[41] It is essential for patients with hip contractures for whom the prone position is difficult or impossible to perform.[41] Moreover, low scores correlate well with the use of ventilation support.[41] The main disadvantage of GMFM is the relatively long time to perform the examination. Moreover, the scale is better suited for children with cerebral palsy (even though it is validated for SMA) and focused on asymmetry.[41,42]

The Hammersmith Functional Motor Scale (HFMS)

The Hammersmith Functional Motor Scale was designed in 2003 for children with SMA type 2 or 3 and aged >30 months.[43] It consists of 20 items, each rated from 0 to 2 points, where 2 points are given when the activity is unaided, 1 when assistance is needed, and 0 when the patient is unable to perform the task.[43] The maximum score is 40.[43] Items are ordered from the easiest to the most difficult one.[42] It takes about 15 minutes and tests the child's ability to control the head, roll, achieve prop position, kneel, crawl, stand, and take at least 4 steps unaided.[43] The high scores in HFMS were reported to correlate with a higher *SMN2* copy number and patient's age.[31] Main at al. proposed to classify the HFMS results into decimals to describe the functional abilities of an SMA type 2 patient: a child with grade 2.7-2.9 should walk well in orthoses and be able to operate a manual wheelchair on even surfaces, grades of 2.8-2.9 indicate the ability to transfer to and from the wheelchair, whereas a child graded 2.1-2.3 can only stand in standing frames and needs assistance in daily activities.[13,43] This scale is focused on patients with impaired ambulation, thus, in practice, it was suitable for mainly SMA type 2 patients.[43] It has been modified several times as described below.

The Modified Hammersmith Functional Motor Scale (MHFMS)

There were several attempts to extend the HFMS to include both weaker and stronger patients. The Modified Hammersmith Functional Motor Scale was designed in 2006.[32] It differs from the classic HFMS by making it easier for patients to perform and thus is suitable for children younger than 30 months and weaker, non-ambulant patients. Each item is scored from 0 to 2 points on a 20-item scale.[32] The MHFMS allows the elimination of fatigue effects and postural changes on the results in the HFMS by changing the order of items.[32,44] Notably, the intrarater, but not interrater, reliability of this scale in a group of non-ambulant patients with SMA type 2 and 3 and aged 2-12 is very good.[43]

The Expanded Hammersmith Functional Motor Scale (HFMSE)

The first version of this most commonly used modification of the HFMS, called the Expanded Hammersmith Functional Motor Scale (HFMSE), was presented at the Families of SMA meeting in 2005.[38] This modification's primary goal was to adapt HFMS for both SMA 2 and 3 patients to enable its use in clinical trials recruiting patients with both types of SMA.[38] Since then, it has been upgraded. The scale is a fusion of HFMS with some items from the Gross Motor Function Measure (GMFM). The GMFM items were chosen to eliminate the ceiling effect in SMA 3 patients observed in the case of the GMFM test.[38] The GMFM items included in the new scale were required to meet all of the following criteria:

1. at least one subject had to be scored in 3 of 4 scoring grades,
2. no ambiguous items,
3. items requiring no or minimal equipment,
4. clinically meaningful items,
5. not duplicated in HFMS.[38]

As a result, 13 GMFM and 20 HFMS items were incorporated, making the 33-item HFMSE. The scoring was unified to 0-2 points, so the maximum score is 66 points.[38,41] This scale rates gross motor functions.[38,42] The score of the HFSME was reported to be positively correlated with the *SMN2* copy number, forced vital capacity (FVC), and muscle strength in SMA patients.[42] The advantage of the HFMSE over the HFMS is omitting the ceiling effect in the case of some SMA 3 patients.[38,42] The validity and reliability of HFMSE in SMA 2 and 3 patients were confirmed in numerous studies.[38,42,45]

The Revised Hammersmith Scale (RHS)

The Revised Hammersmith Scale is the modified version of HFMSE and also adapted for SMA 2 and 3 patients.[44] The idea of this modification emerged when Rasch analysis revealed that the original scale takes into consideration too dissimilar abilities and assesses patients bilaterally what makes the results less reliable.[44,45] Item grouping removed the impact of position change in an order complying with the patient's orientation.[44] The RHS incorporated some modules from the World Health Organization (WHO) motor milestones.[44] Those milestones include: sitting without support, hands- and- knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone.[46] It contains some modified elements from CHOP-INTEND, such as hip flexion from supine, in order to address the needs of frailer patients. It also takes elements from the North Star Ambulatory Assessment (NSAA), a test developed for patients with Duchenne muscular dystrophy (revised timed items included lifting the head from prone for a count of 3).[44] The test consists of 36 items, and the maximum score is 69 points.[44] However, further investigation is necessary to assess its validity.[44]

The Revised Upper Limb Module (RULM)

The Revised Upper Limb Module is a modification of the Upper Limb Module (ULM), which was used in SMA patients aged >30 months who had low HFMSE scores due to advanced weakness or contractures in the lower limbs.[47] The ULM, however, showed the ceiling effect. In order to modify it, some items from the Performance of Upper Limb (PUL)—a test used in Duchenne muscular dystrophy—were taken and subjected to Rasch analysis.[47] The RULM rates only the upper limb, but it correlates very well with the ability to perform everyday activities. It consists of such items as putting a coin into a cup or elevating a cup to lips, picking a coin, bringing hand to shoulder, lifting weights, opening a zip lock, drawing a line on paper, and other tasks reflecting daily activities.[47] The test is very sensitive in rating distal muscle strength. It contains 20 elements with a maximum score of 37 points. The patient chooses the preferred limb, and exercises are performed unilaterally. It takes approximately 20 minutes.[47] The RULM can assess motor functions in non-walking SMA patients.[47]

The 6-Minute Walk Test (6-MWT)

The 6-Minute Walk Test is applicable to SMA patients who can walk. It requires the patient's cooperation, so it is not suitable for very young children.[48] The patient is asked to walk 25 meters on a flat surface for 6 minutes as many times as possible. At least 10-minute rest is obligatory before the start of the test. No jogging or running is allowed. One can rest during the test but without sitting. Assistive devices such as orthoses or canes are not allowed.[48] The analysis concerns:

- the distance covered during the 6 minutes of the tests,
- the distance covered during each minute of the test,
- time to complete each 25-meter walk,
- the number of falls,
- the difference between the distance walked in the first and last minute of the test.[48]

Results are compared to those achieved by healthy participants matched according to gender, age, weight, and height.[49] It should be noted that the result depends not only on muscle strength but also on the cardiopulmonary system's functions.[48,49]

Quantitative Muscle Testing (QMT)

Quantitative Muscle Testing (QMT) is an objective method to assess a patient's muscle strength.[41,50] It uses a dynamometer to examine different muscle groups (both flexors and extensors and both proximal and distal ones). Active contractions should be isometric and held for 5 s with a 10-15 s resting period.[41,50]

Each motion is repeated 3 times, and the best result is taken into account. The examiner measures the strength of each muscle group.[41,50] Results are compared to those achieved in a healthy population.[50]

The test is objective and reliable but requires the patient's full cooperation with the examiner and is not suitable for feeble patients.[50]

Neuromuscular Gross Motor Outcome

Neuromuscular Gross Motor Outcome (GRO) was designed for patients with neuromuscular diseases.[51] It assesses whole body strength, motor development and function across the lifespan. It consists 50 items, each scored from 0 to 2 points.[51] If asymmetry occurs only best side is considered. Examination starts from tasks requiring minimal muscle strength (like finger movements) to complicated complex movements (like ascending stairs or fast walk).[51] It could be proper for different SMA patients.

Table 4. The Proposition of a Scale for Patients With a Very Low Number of Points in CHOP-INTEND.

Action	0	1	2
Elevating eyebrows	No movement	Elevates with difficulty	Elevates high
Grinning	No movement	Teeth barely visible	Teeth exposed
Protruding tongue	No protrusion	Tongue to the teeth line	Tongue crossing teeth line
Moving fingers	No movement	<5 finger can move	>5 fingers can move
Moving toes	No movement	<5 toes can move	>5 toes can move
Moving the head to the side	No movement	Able to move the head to the one side	Able to move the head to both sides
Speech	Cannot speak	Speech difficult to understand	Speaks normally
Salivation	Marked drooling	Moderately excessive saliva	Normal
Swallowing	Cannot swallow, difficulty even with swallowing saliva	Choking when swallows, needs a change of food consistency	Normal
Respiratory insufficiency	Requires permanent invasive ventilation	Requires intermittent non-invasive ventilation	No respiratory support needed

The Use of the Scales in the Era of Treatment

None of the scales currently used in SMA patients alone is designed to assess everyday living functions, gross motor functions, and small muscle skills together, and none can be applied in all SMA individuals, including walkers, sitters, and non-sitters. Moreover, each scale rates patients in a different way, and it is not possible to translate the results from one scale to another.[14]

Until now, all scales have been used only to monitor a patient's deterioration. In the era of disease-modifying treatments in SMA, there is a need for a reliable motor function scale enabling functional improvement assessment. It is of particular importance both in clinical trials and clinical practice, for example, when a justification for a change in therapy is required.

The clinical practice shows that the change in the CHOP-INTEND score frequently does not correspond with the improvement reported by the patients and their families. For example, the fingers' fine movements or the ability to turn the head to the side are not included in the CHOP-INTEND scale. However, those small changes make a difference for many patients, as movements of the head make the observation of the environment possible, and finger movements can allow better communication using electronic devices. No scale includes the assessment of breathing and feeding of the patient despite the fact that it is known that any changes in time the mechanical ventilation is required or the time spent on eating meals may have a substantial effect on the quality of life. In daily practice, we frequently see patients who benefit from the therapy, but it cannot be reported using the scales. Therefore there is an unmet and urgent need to create a tool that could bypass the ceiling effect of the CHOP-INTEND scale.

Similar to SMA, amyotrophic lateral sclerosis (ALS) is also characterized by a progressive loss of motor function, therefore, some scales used in ALS might also be useful in SMA. The most popular functional scale used in ALS patients is the Tufts Quantitative Neuromuscular Exam (TQNE).[52] It comprises 4 categories: assessment of pulmonary function, oropharyngeal function, timed motor activities, and isometric strength.[52] However, those items require a patient's cooperation and are too difficult for young children.

Manual Muscle Testing (MMT) is an example of a different approach to functional assessment in ALS and intensive care unit patients.[53] This method relies on assessing the proximal and distal muscle strength performed by physiotherapists using palpation during a particular motor task.[53] It cannot be applied in frail patients as it requires at least minimum muscle strength.

The Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) is a modification of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) used widely in clinical trials in ALS.[54] The ALSFRS is a list of questions assessing the patient's functions: speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking and climbing stairs. Each item is rated from 4 (normal function) to 0 (very advanced disability).[54] The scale was validated for ALS patients and showed to correlate with the predicted survival of patients. The ALSFRS-R also includes questions about dyspnea, orthopnea, and respiratory insufficiency.[54] This questionnaire may be of use in severely disabled patients with SMA. We suggest adding it as a sub-scale in patients with a very low CHOP-INTEND score, together with the assessment of cranial nerves. To be included in the CHOP-INTEND scale, the ranks for items from the ALSFRS should be changed to 0 for no function and 2 points for normal function. Table 4 presents our proposed subscale for severely affected SMA patients. The usefulness and reliability of this potential new scale require verification.

Conclusions

The progression of SMA symptoms can be assessed using different functional scales, but none is applicable to the whole spectrum of patients. In the era of disease-modifying therapies, the functional scales should evaluate the improvement in various SMA-related symptoms, including subtle changes in severely affected patients. Further efforts to establish a new

tool that could be used both in clinical trials and daily practice are necessary.

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ORCID iD

Katarzyna Pierzchlewicz https://orcid.org/0000-0001-5084-8083

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