TREAT-NMD Neuromuscular Network

Spinal muscular atrophy

EPNS Training course, 6-7 April 2017, Budapest

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Spinal muscular atrophy (SMA):

1. Clinical overview SMA?

2. Genetics of SMA

3. Standards of diagnosis and care for SMA

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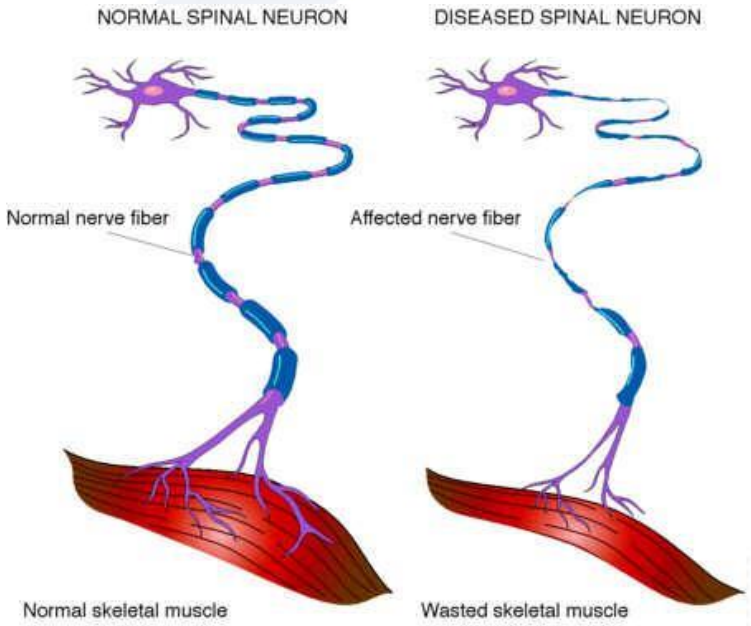
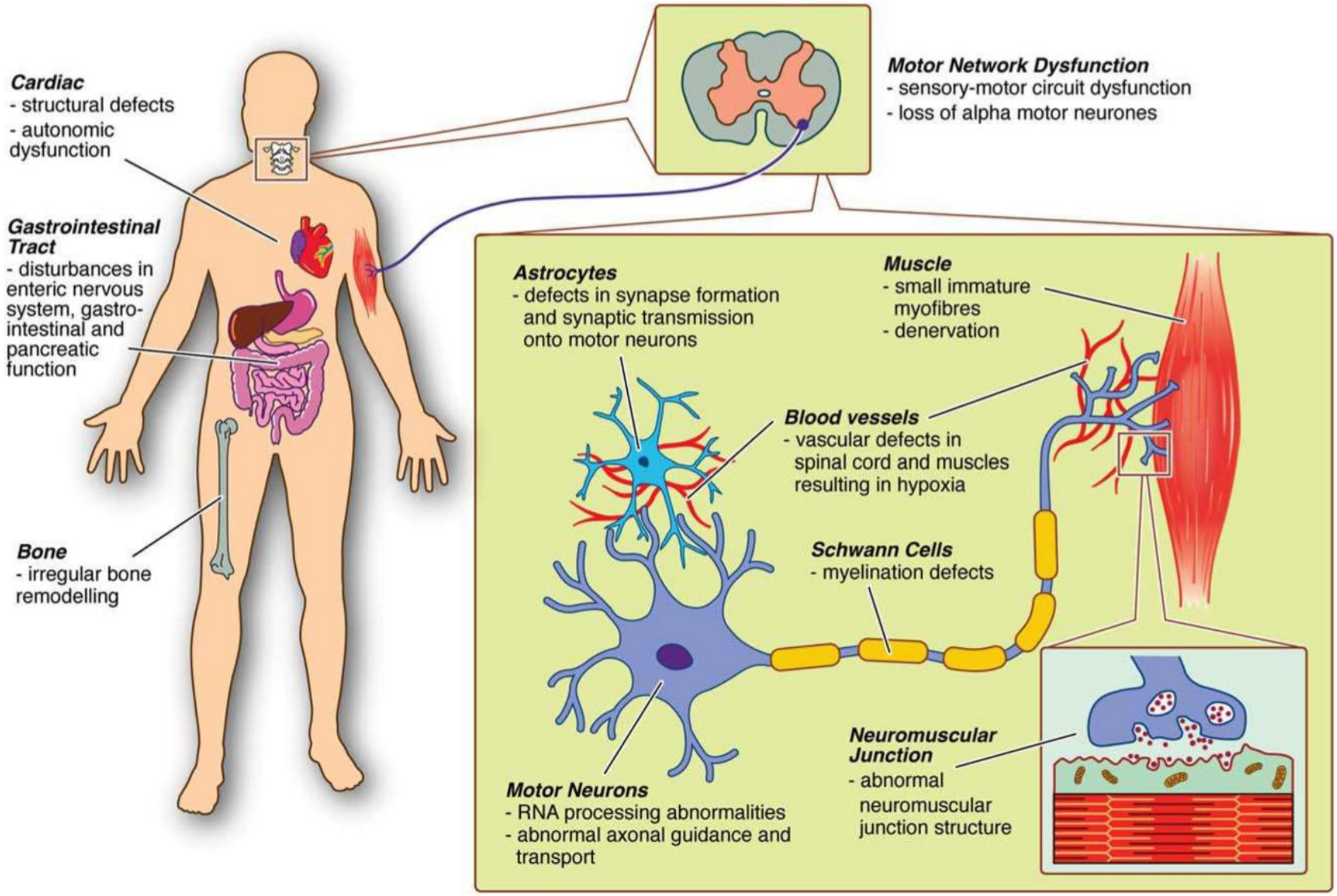
Spinal Muscular Atrophy (SMA)



”Motor neuron degeneration leading to symmetrical muscle weakness and atrophy”



Farrar et al, Ann Neurol 2017;81:355–368

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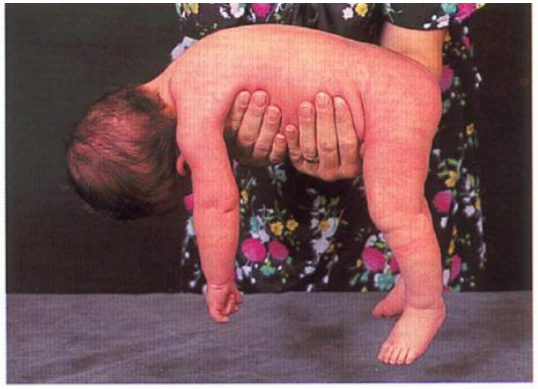
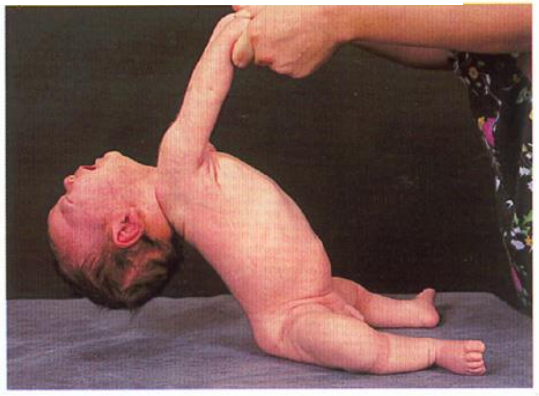
SMA: great variation in severity



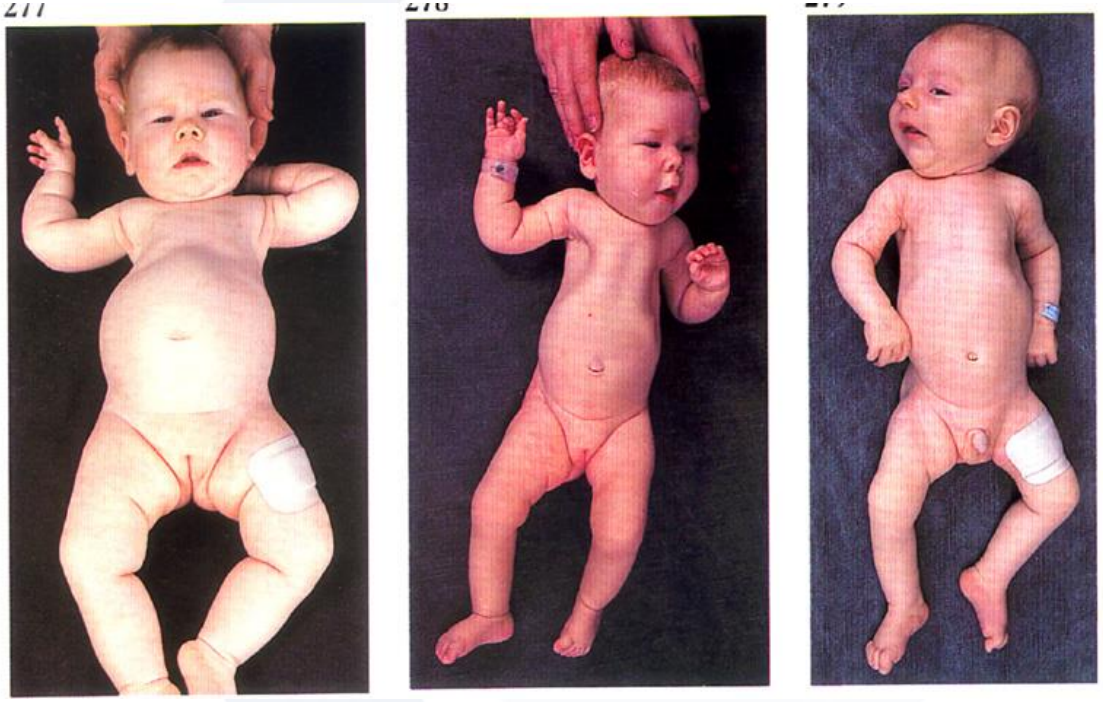


Type 1

Type 2

Type 3

SMA I – double burden on respiration:



- Thorax underdeveloped
- Weak respiratory muscles

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Spectrum of disease severity

The International SMA Consortium classification defined several degrees of severity in the SMA phenotype, depending on the age of onset and maximal motor development achieved

SMA Type	Age of Onset (months)	Motor Milestones	Age of death (years)
I	<6 months	Never sit	<2 years
II	<18 months	Sit, but never stand, non ambulant SMA	>2 years
III	> 18 months	Stand, ambulant SMA	Juvenile, Adult

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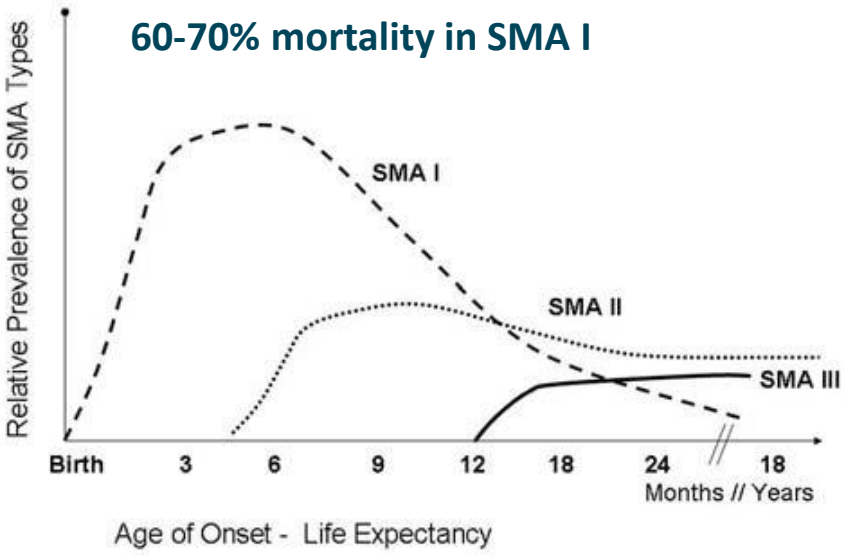
Epidemiology

- Incidence: 1.5 -14.8 X 10^{-5} (~1:6000)
- Prevalence: 1.2 – 6.5 X 10^{-5}
- Carrier prevalence in the general population 1/34 to 1/40.



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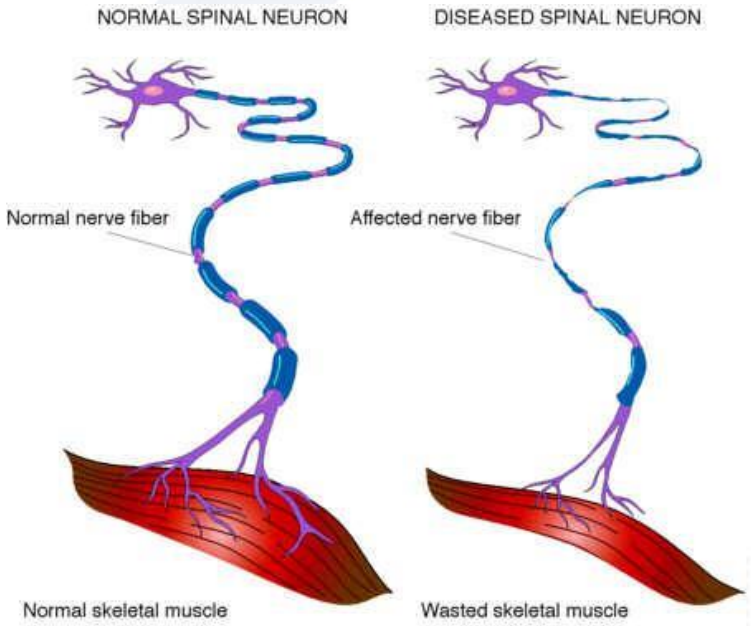


”Motor neuron degeneration leading to symmetrical muscle weakness and atrophy”

Deletion SMN1-gene chr 5

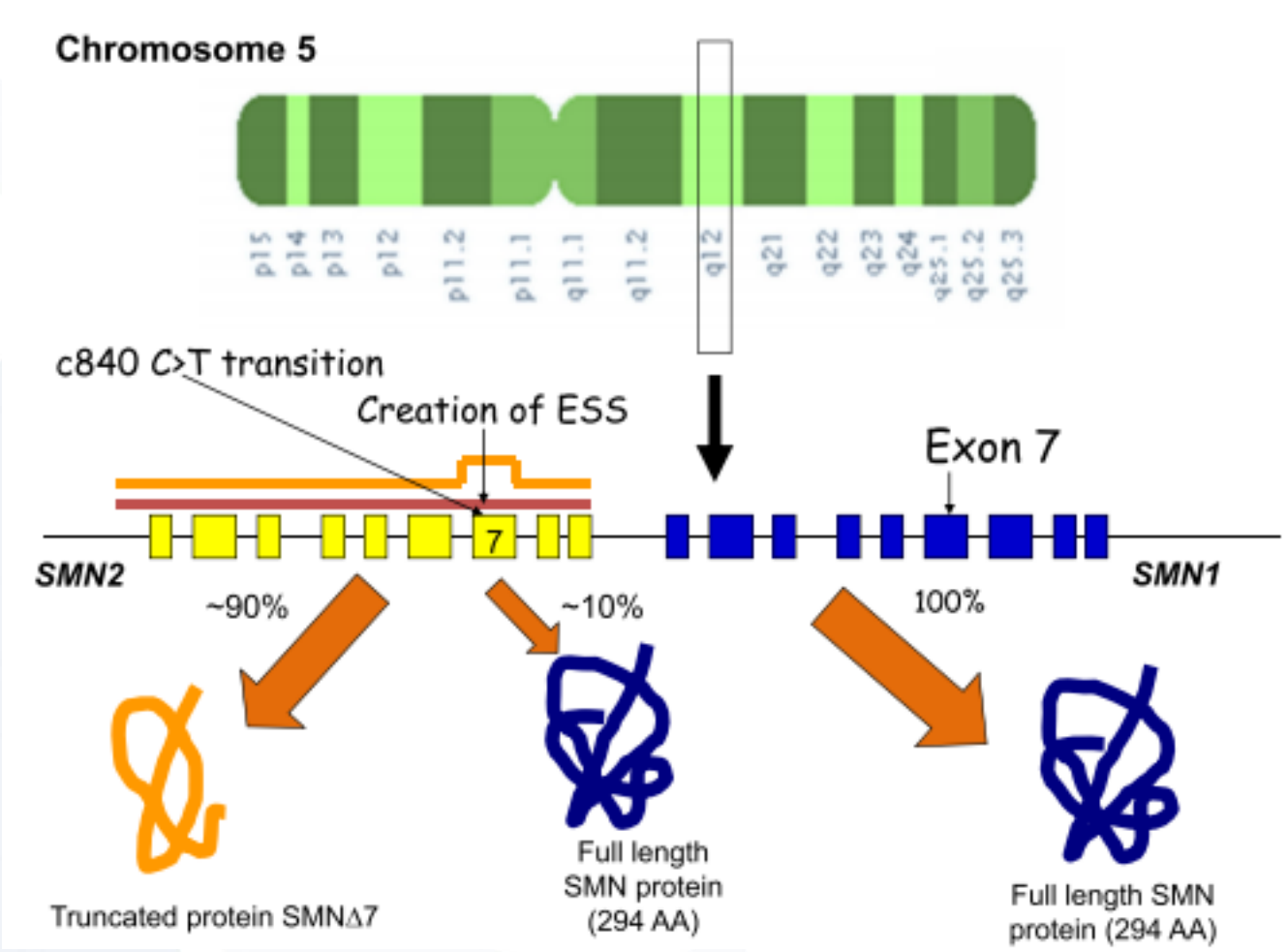
Incidence 1:6000

2nd most common autosomal recessive disorder

Diagnosis

- The absence of *SMN1 exon 7 is used* for molecular diagnosis of the disease.
- Homozygous *SMN2* deletion is found in 5-9% of normal controls, and is not considered to be pathological.

- This genetic test is highly reliable having 100 % specificity and 95% sensitivity



B Darras, Pediatr Clin N Am 62 (2015) 743–766

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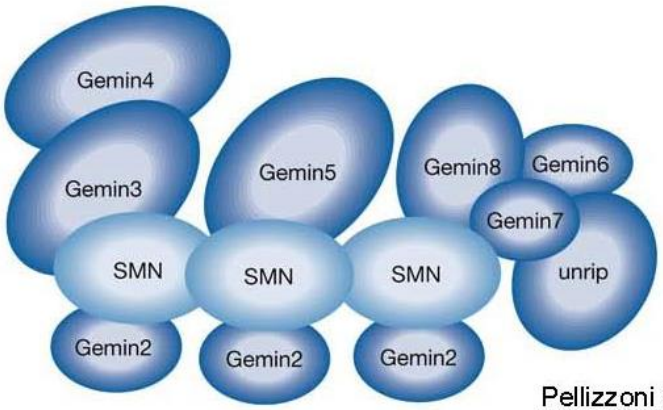
The SMN Complex



Pellizzoni 2007

SMN binding proteins

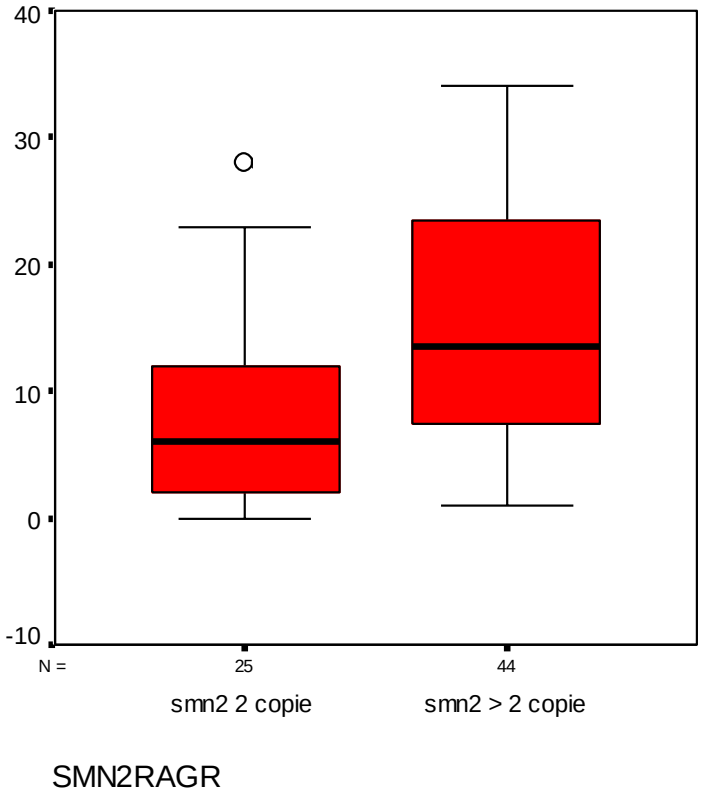
- Gemin 2-8 and unrip-complex binds Sm proteins
- Fibrillarin
- Nuclear transcritional activator E2
- mSin3A (transcriptional corepressor
- Heterogeneous nuclear ribonucleoprotein-R (hnRNP-R)
- Profilin
- α-actinin

SMN: Proposed functions

- Assembly of snRNPs
- Transcription
- Neurite outgrowth and pathfinding
- Profilin binding & actin dynamics
- Axonal transport of messenger RNPs
- NMJ formation
- Muscle cytoskeleton

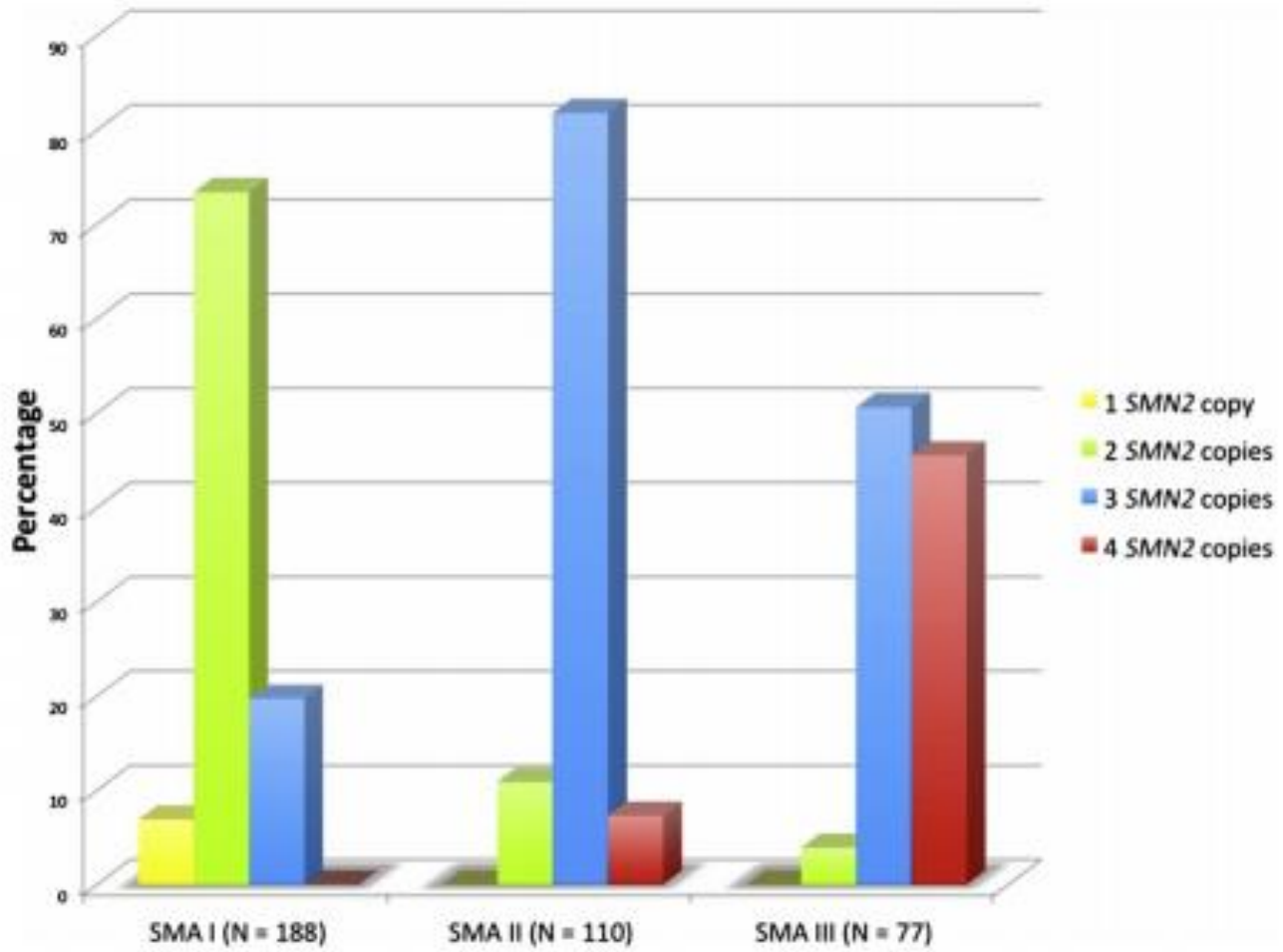
SMN2 copy number correlates with disease severity in humans

87 patients with SMA II
Hammersmith score
versus SMN2 copies



Tiziano et al.. 2007

Smn2-kopior vid SMA1-3:



B Darras, Pediatr Clin N Am 62 (2015) 743–766

Genetisk diagnos SMA:

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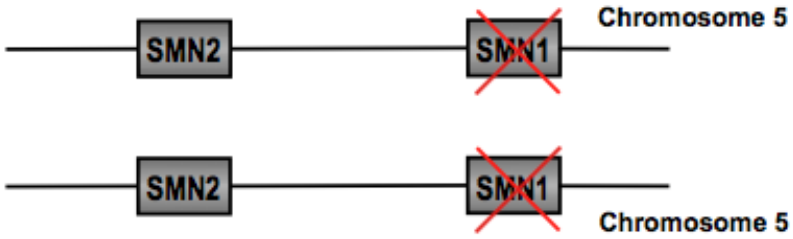
Genetic diagnostic testing in spinal muscular atrophy

Type of Mutation	Test Applied	Mutation Detection Rate
Homozygous deletion of exon 7[a]	*SMN1* Targeted mutation analysis PCR/restriction enzyme analysis or MLPA methodologies	~95%–98%
Compound heterozygosity (deletion of *SMN1* exon 7 [allele 1] and an intragenic mutation of *SMN1*[b] [allele 2])	Targeted mutation analysis combined with *SMN1* gene sequence analysis[c]	2%–5%
SMN2 copy number[d]	Quantitative PCR analysis and other methodologies[e]	N/A



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Standards of Diagnosis and Care

1. A joint basis for diagnostics and care improves quality of multinational treatment studies

2. Low prevalence necessitates expert advice being collated on a multinational level

3. Families should be offered the most informed treatment and counselling regardless of where in Europe they live

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Standards of care in SMA

- **ICC Consensus statement for SOC in SMA**

  TREAT-NMD/ICC précis

  ICC Family guide

www.treat-nmd.eu/soc/eng/sma

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ICC Consensus statement for SOC in SMA

Journal of Child Neurology
http://jcn.sagepub.com

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, Richard S. Finkel, Enrico S. Bertini, Mary Schroth, Anita Simonds, Brenda Wong, Annie Aloysius, Leslie Morrison, Marion Main, Thomas O. Crawford, Anthony Trela and Participants of the International Conference on SMA Standard of Care

J Child Neurol 2007; 22; 1027
DOI: 10.1177/0883073807305788

The online version of this article can be found at:
http://jcn.sagepub.com/cgi/content/abstract/22/8/1027

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ICC Consensus statement for Standards of care in SMA

Standard of care committee (SCC) formed 2005 to establish guidelines

12 core members, 56 experts

How to reach consensus?

Delphi technique

ICC Consensus statement for Standards of care in SMA

Five areas adressed:

diagnosis

pulmonary care

GI and nutritional care

orthopedics and (re)habilitation

palliative care

Three functional levels:

non-sitter

sitter

walker

ICC Consensus statement for Standards of care in SMA

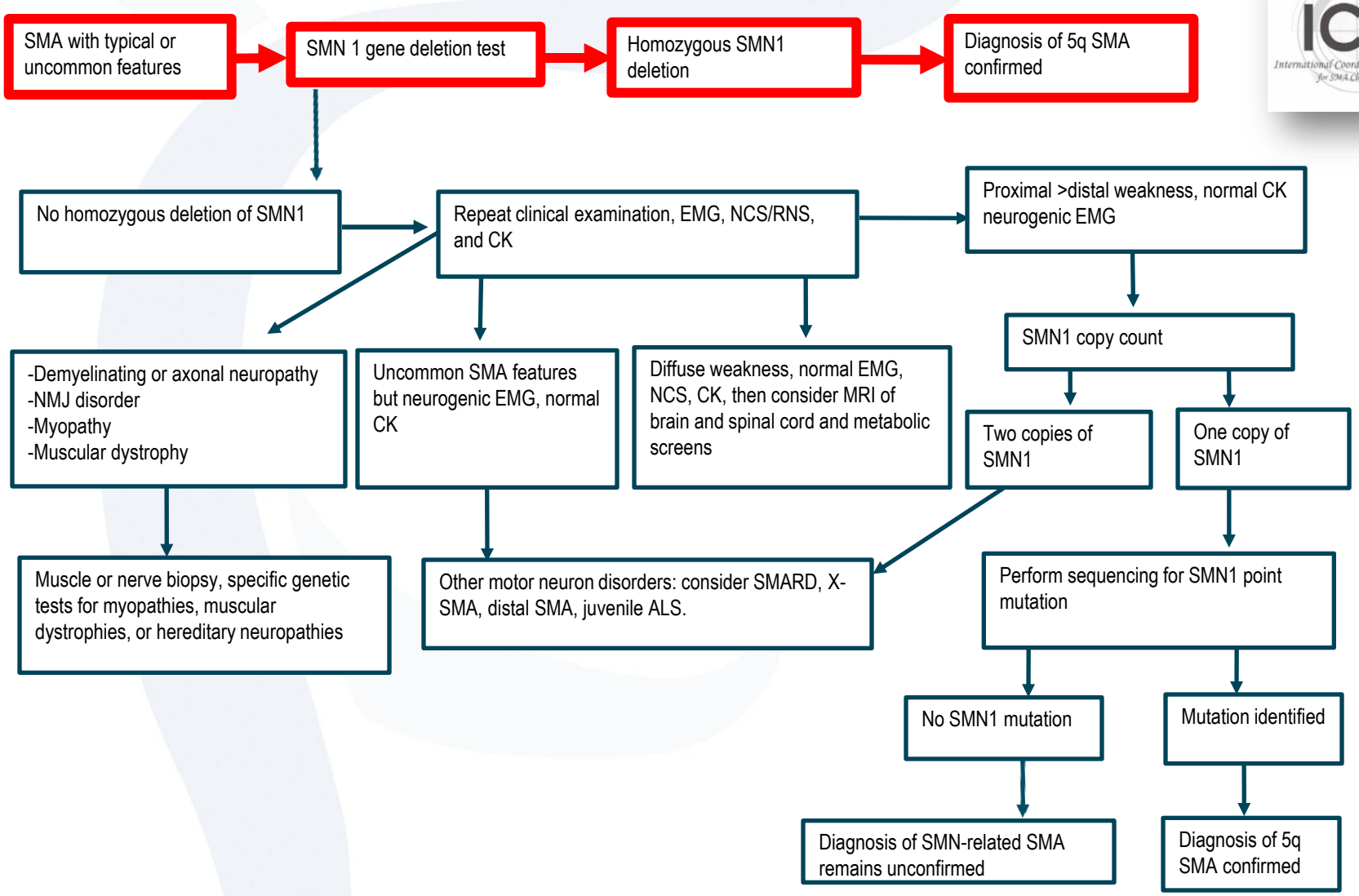
Five areas adressed:

- diagnosis
- pulmonary care
- GI and nutritional care
- orthopedics and (re)habilitation
- palliative care

Three functional levels:

- non-sitter
- sitter
- walker

Diagnosis


SMA with typical or uncommon features
SMN 1 gene deletion test
Homozygous SMN1 deletion
Diagnosis of 5q SMA confirmed
No homozygous deletion of SMN1
Repeat clinical examination, EMG, NCS/RNS, and CK
Proximal >distal weakness, normal CK neurogenic EMG
-Demyelinating or axonal neuropathy
-NMJ disorder
-Myopathy
-Muscular dystrophy
Uncommon SMA features but neurogenic EMG, normal CK
Diffuse weakness, normal EMG, NCS, CK, then consider MRI of brain and spinal cord and metabolic screens
SMN1 copy count
Two copies of SMN1
One copy of SMN1
Muscle or nerve biopsy, specific genetic tests for myopathies, muscular dystrophies, or hereditary neuropathies
Other motor neuron disorders: consider SMARD, X-SMA, distal SMA, juvenile ALS.
Perform sequencing for SMN1 point mutation
No SMN1 mutation
Mutation identified
Diagnosis of SMN-related SMA remains unconfirmed
Diagnosis of 5q SMA confirmed

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Pulmonary care - assessment

- **Physical examination:** monitor cough effectiveness, chest walll deformity, work of breathing, respiratory rate, paradoxical breathing, and skin color.
- **Polysomnography:** to document signs of hypoventilation.
- **Pulse oximetry:** to monitor oxygen saturation
- **Pneumonias:** monitor frequency of infection and antibiotic treatments over past 6 months.
- **Chest x-ray:** baseline and during respiratory deterioration.
- **Swallow studies:** in unexplained acute respiratory deterioration and recurrent pneumonia.

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Pulmonary - anticipatory care

- Provide families with **information about options** for **chronic care, acute illness management, and perioperative care.**
- Non-sitters are the most fragile group and early discussions should include the option of **noninvasive ventilation (NIV) and secretion management** due to the rapid progression of the disease.
- Ongoing discussion of the family's desires for support should occur, and the result should be a negotiated care plan with **maximums and minimums outlined.**

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Pulmonary - day to day management

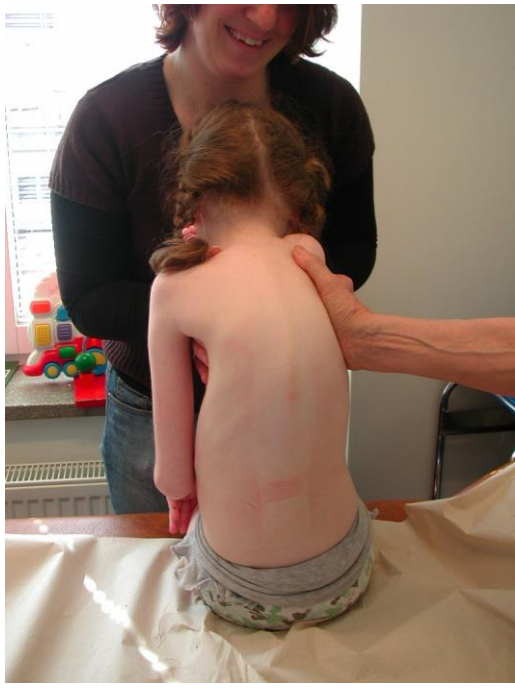
- Understanding the child's **baseline** and deviations from his/her baseline
- Understanding **hypoventilation** and intervention
- **Acute illness management** including rapid access to specialty medical care providers
- **Airway clearance** and secretion management techniques
- **Respiratory support** including NIV
- **Nutrition and hydration**
- A low threshold to start **antibiotics**
- Routine **immunizations** including influenza vaccine, pneumococcus vaccine, and RSV prophylaxis (palivizumab)

Pulmonary - acute care

The goal of management during acute illness is to **normalize gas exchange** by reducing atelectasis and enhancing airway clearance where possible by non-invasive respiratory support. Blood gas monitoring may be of benefit.

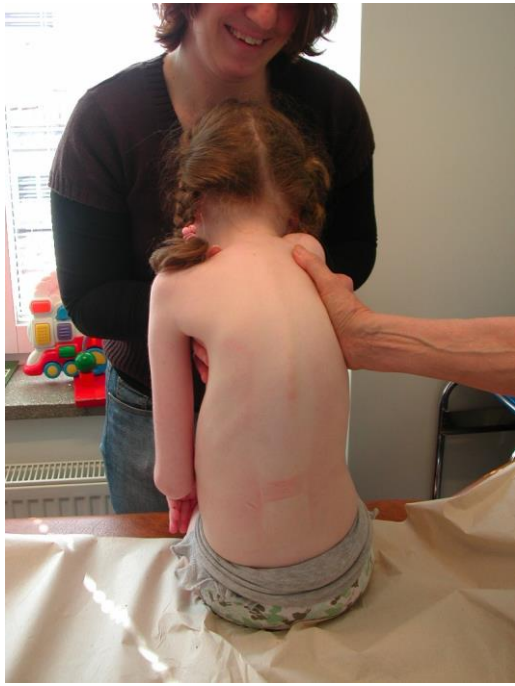
Airway clearance: manual cough or cough assist, oral or airway suctioning. Assisted cough techniques preferred.

Respiratory support: acute use of NIV, oxygen, short-term intubation and mechanical ventilation



Pulmonary - acute care

- Decision-making about escalation to intubation should be carried out in advance as part of **anticipatory care planning.**
- **Tracheotomy and ventilation** can be considered in case of frequent acute pulmonary infections in non-sitters, but may not improve quality of life or reduce hospitalizations.
- With deteriorating function it may be appropriate to redirect care to a **palliative approach**, particularly for non-sitters.



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GI and nutritional care

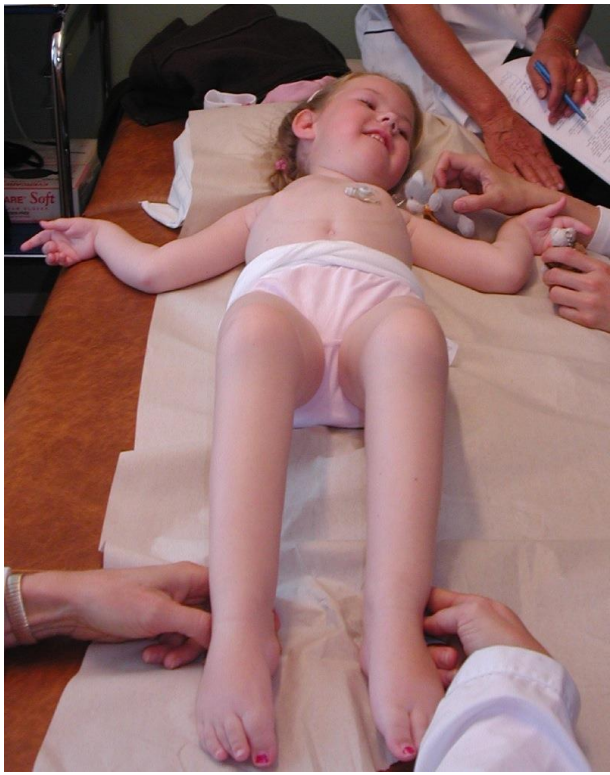
Key clinical problems related to:

I. Feeding and swallowing problems

II. Gastrointestinal dysfunction (constipation, delayed gastric emtying, GE reflux)

III. Under-/overnutrition

IV. Respiratory problems



GI and nutritional care

Management of feeding and swallowing difficulties:

- Changing **food consistency**, e.g semi-solid diet.
- **Positioning** and seating alterations and orthotic devices, e.g. elbow support, valved straw
- Proactive **nutritional supplementation**
- Nasogastric/nasojejunal feeding, **G-tube** feeding

GI and nutritional care

***Management of GE reflux**:*

- Acid neutralizers / inhibitors od acid secretion
- Prokinetic agents if diminished motility
- Probiotics, e.g. lactobacillus
- Anti-reflux Nissen fundoplication

GI and nutritional care

***Management of under or over nutrition**:*

- Goal for child to follow own growth velocity
- Nutritional intake assessment by dietician
- Document appropriate intake of Ca and Vit D
- Adequate protein status may be checked by pre-albumin levels

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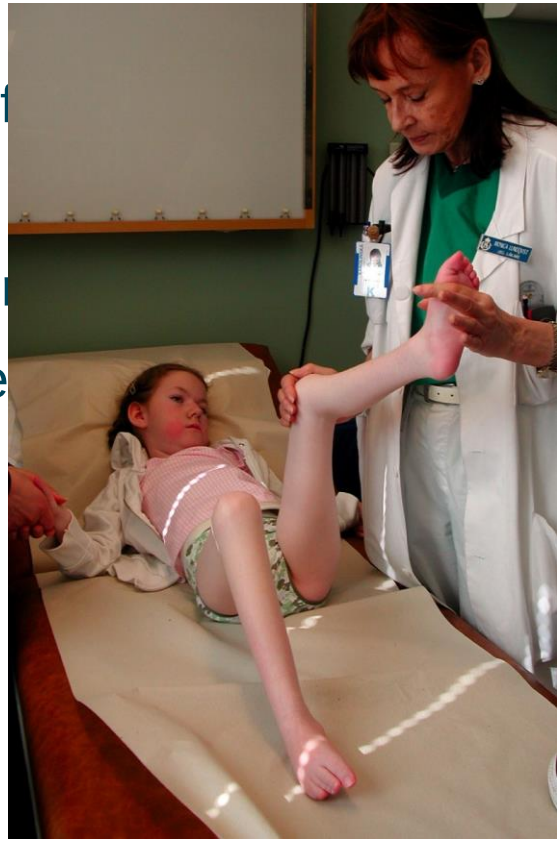
Orthopedics and (re)habilitation

Assessments:

- Physical and occupational therapy evaluation of f
- (CHOP-INTEND)
- Speech therapy evaluation if swallowing is impai
- speech affected by jaw contracture or inadequate



Orthopedics and (re)habilitation

- **Posture management:** Patient's primary posture should direct choice of equipment that supports function. Ensure comfortable seating.
- **Contracture management:** Splinting to preserve ROM and prevent pain may be indicated.
- **Pain management**
- **Therapy for ADL and assistive equipment:** e.g. lightweight toys and assistive technology with variable controls and a myriad of activation systems.

Orthopedics and (re)habilitation

- **Wheelchair:** Ensure optimal independence and seating comfort
- **Limb orthotics:** Upper extremity (UE) orthotics to aid in function, e.g. mobile arm supports or elastic slings that augment active range of motion and functional abilities.
- **Environmental controls and home modifications** to allow for safe accessibility and optimal independence.

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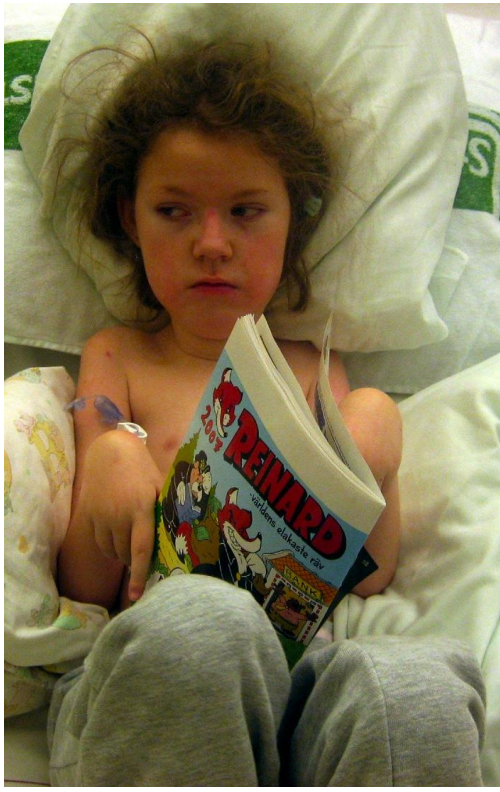
Palliative care

- Care should be mindful of potential conflict of therapeutic goals
- Present care options in open, fair, balanced manner
- Supportive care is not a single binary choice
- G-tube is better done relatively early
- Discuss and determine early response to potential life-threatening respiratory insufficience
- End of life care decisions need to be defined
- Multi-specialty team approach
- Appropriate management od terminal dyspnea if choice againt ventilatory support



Patient Care

ABOUT US
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MEETINGS & EVENTS
GET INVOLVED
PARTNERS
WHAT WE DO
OUTCOME MEASURES
PATIENT REGISTRIES
PATIENT CARE
Care standards
» SMA
DMD
DOWNLOADS

Standards of care for spinal muscular atrophy

TREAT-NMD has been working with the authors of the recently published consensus statement on care for patients with spinal muscular atrophy to create useful summary factsheets based on the full published document. A TREAT-NMD working group is continuing to develop the standards for care on SMA in areas such as physical and occupational therapy, orthopaedics, nutrition and psychosocial implications. We will be looking for volunteers from amongst the partners and others to help with the generation of these further guidelines soon.

We are very interested in talking with patients and clinicians about these recommendations and suggestions for their future improvement. If you're interested, please email the TREAT-NMD team at info@treat-nmd.eu.

Translations

We believe it is crucial to have this type of information about standards of care available in patients' and clinicians' **native languages**, and we are therefore in the process of translating it into a number of languages with the generous help of multilingual staff within the TREAT-NMD network and colleagues from patient organisations. If you are interested in translating our factsheets into your language for hosting on our website, please **contact the TREAT-NMD team** at **info@treat-nmd.eu** - we'd love to hear from you!

Translations that are currently in progress include: Polish, Dutch, Italian, Turkish and Slovenian

Downloads

- SMA précis - English
- SMA précis - German
- SMA précis - Dutch
- SMA précis - Russian
- SMA précis - Bulgarian
- Full consensus statement - English
- Family guide to the consensus statement

SMA care recommendations -a summary:

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Care Area	Recommendations for Clinicians
Diagnosis and Care for the Newly Diagnosed Patient	o If SMA is suspected, order a blood test to confirm or rule out the disease (SMN gene deletion test can confirm 95% of all SMA cases) o If SMA is confirmed, develop a care plan with the patient and family and collaborate with a multidisciplinary care team
Pulmonary Care	o Routinely perform pulmonary assessments o Teach caregivers techniques to assist with airway clearance o Practice vigilance and plan carefully to prevent problems o Work with the family to develop a plan for routine care & care for acute respiratory illness
GI and Nutritional Care	o Monitor growth velocity o Evaluate patient for swallowing difficulties and problems with reflux or constipation o Work with family to develop personalized feeding plan
Orthopedic Care and Rehabilitation	o Develop a physical/occupational therapy plan to help patient achieve and maintain highest level of function and independence o Consider use of assistive devices, tools, and exercise to support breathing, eating, work, and play and slow or prevent complications of SMA o Evaluate and treat scoliosis before severe respiratory complications develop
Palliative Care	o Work with patient and family to develop a plan for medical emergencies o Connect families with hospice and bereavement support

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Thank you!