Spinal Muscular Atrophy: Natural History and Clinical Presentation

MED-MI--00007-US 07/22

Bannockburn, IL 60015

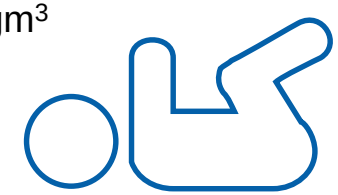
SMA Type 1: Symptoms and Presentation

SMA type 1 can be divided into 3 groups[1,2]

- **Type 1A/0:** presentation at birth with joint contractures, respiratory compromise; typically fatal within 6 months
- **Type 1B:** symptom onset before age 3 months
- **Type 1C:** symptom onset after age 3 months

"Never-sitters"

- Muscle hypotrophy and weakness in bulbar, truncal, and proximal limb muscles more than distal[3]
- Limbs more affected than face[3]
- Chest wall more affected than diaphragm[3]
- Poor motor function and significant electrophysiological motor unit loss[4]
- Mild joint contractures[5]
- Difficulties in sucking and swallowing[5]



Other affected organ systems

- Respiratory[6]
  - Intercostal muscle weakness and thoracic cage deformation
  - Paradoxical breathing
  - Airway obstruction complications and lung damage

- Metabolism[7]
  - Dyslipidemia reported in 37% of patients with SMA

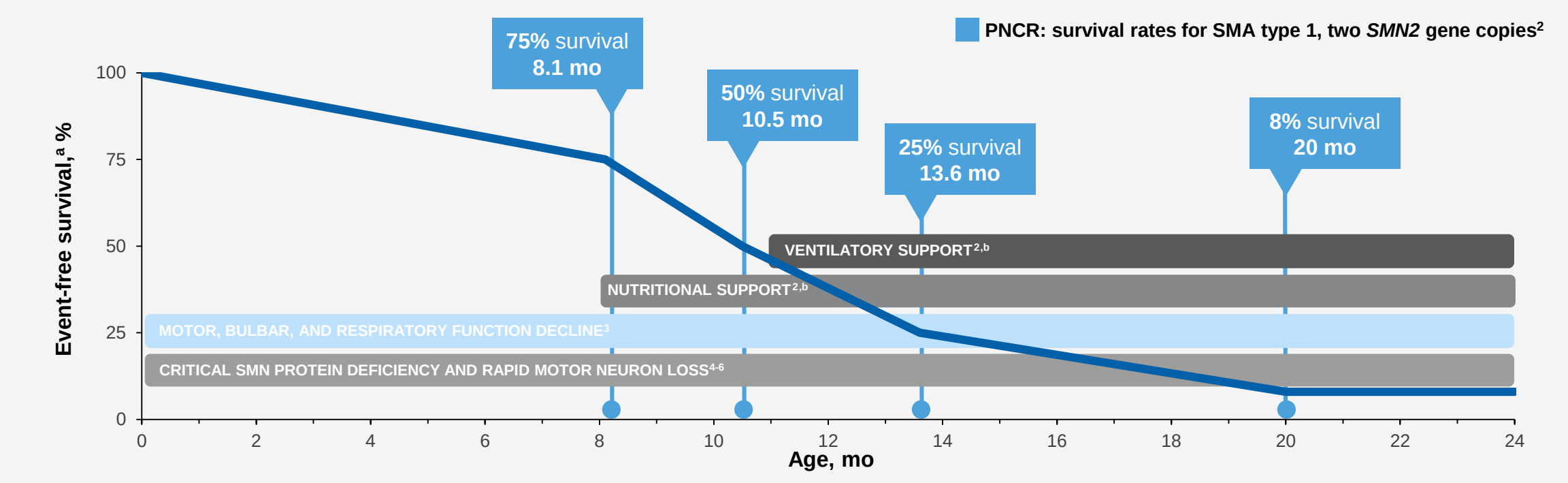
- Cardiovascular[6]
  - Congenital heart malformation defects, primarily in patients with one copy of *SMN2*
- Autonomic nervous system[6]
  - Severe bradycardia in long-term ventilated patients
  - Abnormal blood pressure and temperature regulation

SMA, spinal muscular atrophy; SMN2, survival motor neuron 2 gene.

1. Finkel RS et al. *Neurology.* 2014;83(9):810-817. **2.** Wijngaarde CA et al. *Neurology.* 2020;94(15):e1634-e1644. **3.** Ramos DM et al. *J Clin Invest.* 2019;129(11):4817-4831. **4.** Kolb SJ et al. *Ann Neurol.* 2017;82(6):883-891. **5.** Prior TW et al. Spinal muscular atrophy. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. Accessed May 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1352/; **6.** Shababi M et al. *J Anat.* 2014;224(1):15-28. **7.** Deguise M-O et al. *Ann Clin Transl Neurol*. 2019;6(8):1519-1532.

Natural History of SMA Type 1

- Most patients with SMA type 1 will not survive or will need permanent ventilatory support by age 2 years[1,2]
- Nutritional and respiratory support reduces mortality to ~30% at age 2 years, with approximately half of the survivors fully reliant on noninvasive ventilation[3]



PNCR, pediatric neuromuscular clinical research; SMA, spinal muscular atrophy; SMN, survival motor neuron.
[a]Survival for Finkel et al[2] = no death, or no need for ≥16 hours/day ventilation continuously for ≥2 weeks, in absence of an acute reversible illness; n = 23 (two copies of *SMN2*). [b]SMA types 1B and 1C combined.[2]

1. Zerres K et al. *Arch Neurol*. 1995;52(5):518-523. **2.** Finkel RS et al. *Neurology*. 2014;83(9):810-817. **3.** Kolb SJ, Kissel JT. *Neurol Clin*. 2015;33(4):831-846. **4.** Finkel RS. *Neuromuscul Disord*. 2013;23(2):112-115. **5.** Swoboda KJ et al. *Ann Neurol*. 2005;57(5):704-712. **6.** Ramos DM et al. *J Clin Invest*. 2019;129(11):4817-4831.

SMA Type 2: Symptoms and Presentation

SMA type 2 presents at 6 to 18 months[1]

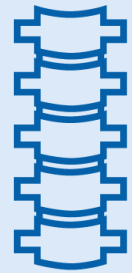
- Poor muscle tone may be observed at birth or within the first few months of life
- Patients slowly gain motor milestones through age ~5 years

"Sitters"

- Developmental delay with loss of motor skills[1]
- Diminished/absent deep tendon reflexes[1]
- Proximal muscle weakness[1]
- Postural finger tremor[1]
- Will sit but will never walk[2]
- With supportive care only, motor function declines and ability to sit independently is lost by mid-teens[1]

Other affected organ systems

- Respiratory[2]
  - Respiratory muscle weakness
- Metabolism[3]
  - Abnormal fatty acid metabolism, with dyslipidemia reported in 37% of patients with SMA[4]
  - Mild to moderate dicarboxylic aciduria
  - Occasional diabetes and glucose metabolism abnormalities
- Skeletal[1]
  - Most patients with SMA type 2 develop scoliosis



SMA, spinal muscular atrophy.

1. Prior TW et al. Spinal muscular atrophy. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. Accessed May 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1352/; **2.** Bowerman M et al. *Dis Model Mech.* 2017;10(8):943-954. **3.** Shababi M et al. *J Anat.* 2014;224(1):15-28. **4.** Deguise M-O et al. *Ann Clin Transl Neurol.* 2019;6(8):1519-1532.

Natural History of SMA Type 2

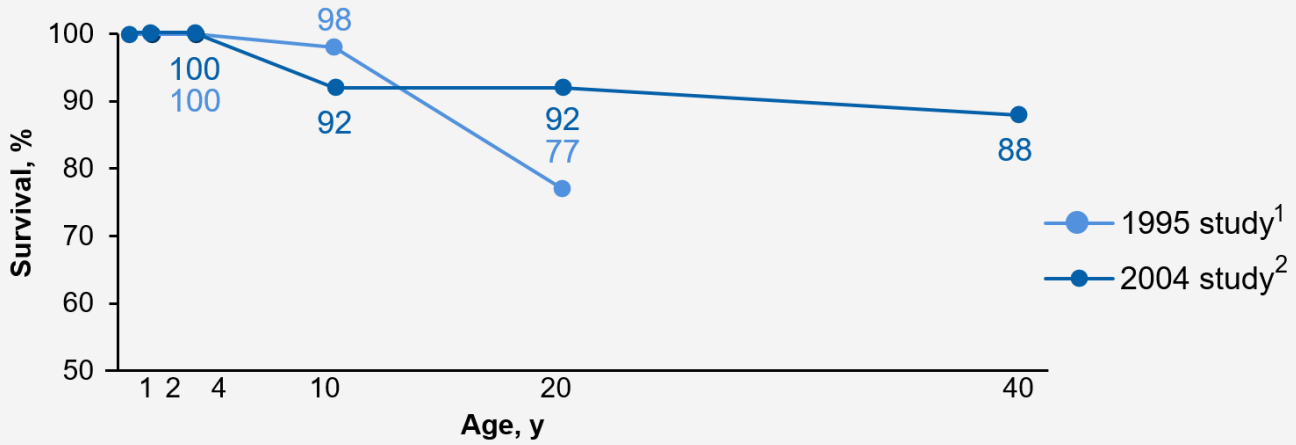
The majority of patients with SMA type 2 survive into adulthood. More recent studies demonstrate increased survival, presumably due to improved treatment[1,2]

Poor muscle tone
(first few months of life)[3]

Symptom onset
(age 6 to 18 months)[3]

Slow motor milestone gains
(through age ~5 years)[3]

With supportive care only, the maximum motor milestone attained by patients with SMA type 2 is independent sitting[3]



Slow decline in motor function, losing the ability to sit independently by mid-teens[3]:

- Hand tremor and scoliosis may be present
- Deep tendon reflexes are decreased or absent
- Cognition is normal
- Cardiac abnormalities are unlikely
- Progressive respiratory muscle weakness may lead to restrictive lung disease and subsequent mortality

SMA, spinal muscular atrophy.

1. Zerres K, Rudnik-Schöneborn S. *Arch Neurol*. 1995;52(5):518-523. **2.** Chung BHY et al. *Pediatrics*. 2004;114(5):e548-e553.
3. Prior TW et al. Spinal muscular atrophy. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. Accessed May 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1352/

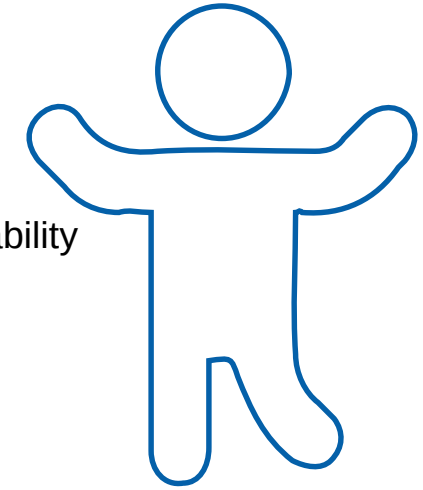
SMA Type 3: Symptoms and Presentation

SMA type 3 presents at age >18 months[1]

- Typically causes less severe motor disability compared with SMA type 1 and 2[2]
- Patients typically have three to five copies of *SMN2*[3]

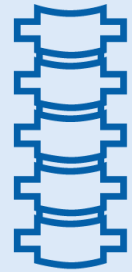
"Walkers"

- Proximal muscle weakness[1]
- Ability to walk but difficulty with stairs and running[1]
- With supportive care only, walking ability lost over time[1]
- Postural finger tremor[1]
- Fatigue[1]
- With supportive care only, gains in motor function lost after childhood[1]



Other affected organ systems

- Metabolism
  - Occasional diabetes and glucose metabolism abnormalities[4]
  - Nonambulatory individuals at risk of developing obesity[1]
- Skeletal[1]
  - Approximately half of the patients with SMA type 3 develop scoliosis[1]



SMA, spinal muscular atrophy; SMN2, survival motor neuron 2 gene

1. Prior TW et al. Spinal muscular atrophy. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. Accessed May 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1352/; **2.** Kaufman P et al. *Neurology*. 2012;79(18):1889-1897. **3.** Bowerman M et al. *Dis Model Mech.* 2017;10(8):943-954. **4.** Shababi M et al. *J Anat.* 2014;224(1):15-28.

Natural History of SMA Type 3

- The life expectancy of individuals with SMA type 3 is no different than that of the general population[1]

Symptom onset
(age >18 months)[1]

With supportive care only, patients may walk independently but stumble frequently or have difficulty with stairs[1]

Motor milestones are reached
(through age ~6 years)[1]

Slow decline in motor function through puberty
(age ~20 years), at which point a
more rapid decline in function **may** occur[1]

Adulthood brings a slower decline in motor function, likely leading to a loss of ambulation by age 30 to 40 years[1] and a decline in independent living[2]

SMA, spinal muscular atrophy.

1. Prior TW et al. Spinal muscular atrophy. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. Accessed May 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1352/; **2.** Klug C et al. *Orphanet J Rare Dis*. 2016;11:58.