Early diagnosis and intervention in spinal muscular atrophy

Daniella Villano

Neuromuscular nurse consultant Royal Children's Hospital Melbourne

Biography

Ms Daniella Villano

Neuromuscular nurse consultant, Melbourne VIC

Ms Villano has been working as a paediatric nurse as part of the Children's Neuroscience Centre since 2004. In 2007 she commenced her role as the nurse consultant working with patients and families affected by neuromuscular conditions. Her role encompasses overall coordination of the clinical research and clinical care program through the Royal Children's Hospital Neuromuscular service. Ms Villano is one of Australia's leading neuromuscular nurses and is passionate about supporting patients and families in achieving the best quality of life and health outcomes.

Declarations: Ms Villano received honorarium from Novartis Australia for this talk

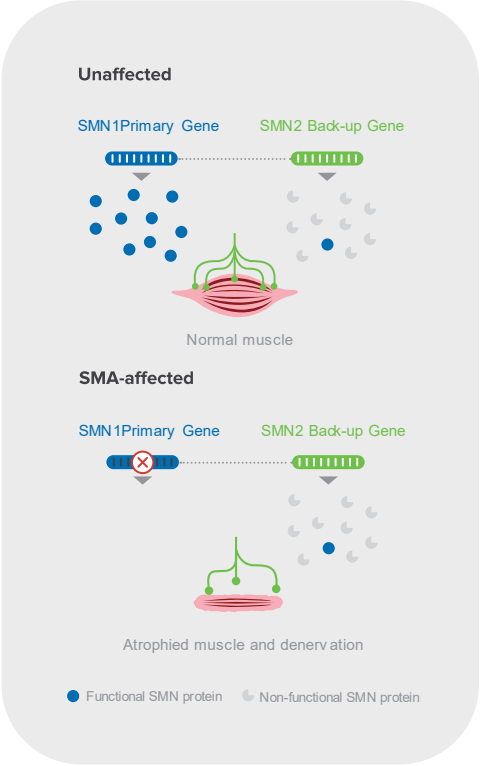
An introduction to spinal muscular atrophy

- Spinal muscular atrophy (SMA) is an autosomal recessive genetic disorder[1,2]
- Characterised by progressive proximal muscle weakness and atrophy with no effect on cognition[1,2]
- Caused by progressive dysfunction and loss of motor neurons in the spinal cord[1]
- Untreated, SMA is the 2nd most common fatal autosomal recessive genetic disorder after cystic fibrosis[3,4]

1. Glascock J, et al. J Neuromusc Dis. 2018; 5: 145–158. **2.** Farrar MA, et al. Ann Neurol. 2017; 81: 355–368. **3.** Armstrong EP, et al. J Med Econ. 2016;19(8):822–826. **4.** Lally C, et al. Orphanet Journal of Rare Diseases. 2017; 12: 175.

The pathophysiology of SMA

- Most cases of SMA are caused by deletion or mutation of the gene *SMN1*[1,2]
- *SMN1* is responsible for the production of the protein Survival Motor Neuron (SMN) [1,2]
- SMN protein is critical to health and development of motor neurons[1,2]
- SMN protein is also produced by the 'back-up' gene *SMN2* but in lower concentrations[1,2]
- SMA severity is influenced by the number of copies of *SMN2* that a patient has[1,2]



Farrar MA, et al. Neurotherapeutics. 2015 Apr; 12(2): 290–302. **2.** Chaytow H, et al. Cell Mol Life Sci. 2018 Nov; 75(21): 3877–3894.

SMA in Australia

- SMA affects around 1 in 10,000 live births and can impact any race or sex[1]
- Approximately 1 in 40–60 people is a SMA carrier[1,5]
- Around 30 births are affected by SMA per year in Australia*[2]
- Approximately 17 of those patients have SMA Type 1*[2–4]

*Based on Australian birth statistics (2020)

1. Mendell JR, et al. N Engl J Med. 2017; 377(18): 1713–1722. **2.** Australian Bureau of Statistics (ABS). Available at: https://www.abs.gov.au/statistics/people/population/births-australia/2020. Date accessed: February 2023. **3.** Ali HG, et al. Gene Ther. 2021 Nov; 28(10-11): 676-680. **4.** Spinal Muscular Atrophy: epidemiology and Genetics. Available at: https://hcp.smanewstoday.com/spinal-muscular-atrophy-epidemiology-and-genetics/. Date accessed: February 2023. **5.** Govoni A, et al. Mol Neurobiol. 2018; 55(8): 6307–6318.

SMA type changes prognosis

- SMA is classified into a variety of phenotypes that range in severity and age of onset[1–3]
- *SMN2* copy number is the primary influence on the type of SMA[1–3]
- SMA Type 1 is the most common phenotype and the most severe post-natal form[4]
- Approximately 60% of SMA patients have Type 1[4]

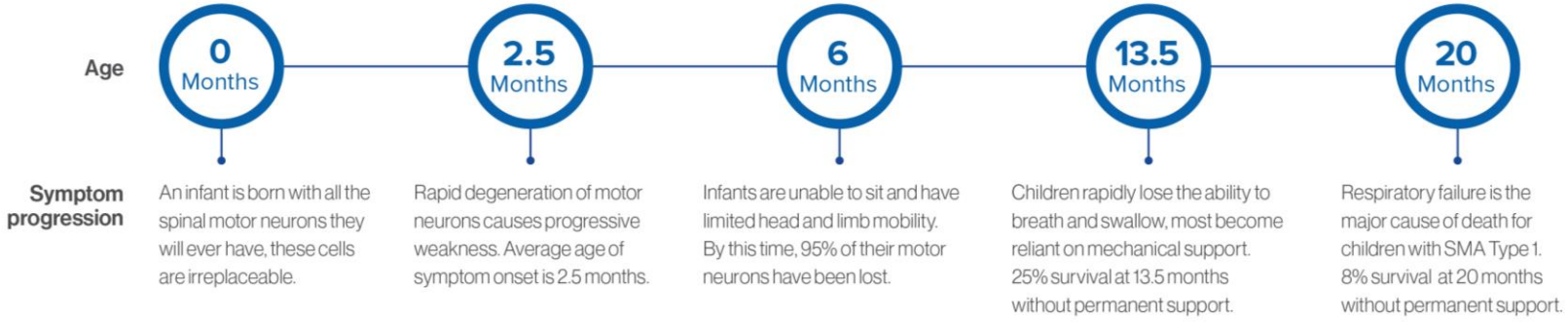
SMA Type	*SMN2* copy number	Age of onset	Natural history prognosis
Type 0 Prenatal-onset SMA	≤1 copy	Congenital	Severe weakness and hypotonia at birth; patients do not survive past 6-months old
Type 1 Werdnig-Hoffman disease	1 or 2 copies	<6 months	Never able to sit without support; most patients will not survive beyond 2 years without ventilation
Type 2 Dubowitz disease	2 or 3 copies	6–18 months	Able to sit independently; may survive to early adulthood
Type 3# Kugelberg-Welander disease	3 or 4 copies	>18 months	Able to walk but many lose the ability in early teenage years; life expectancy not affected
Type 4 Adult-onset SMA	4+ copies	Adulthood	Many lose the ability to walk around 60 years old; life expectancy not affected

#SMA type 3 is subdivided into type 3a and 3b based on onset of symptoms before or after the age of 3 years.

1. Farrar MA, et al. Ann Neurol. 2017; 81: 355–368. **2.** Mendell JR, et al. N Engl J Med. 2017; 377(18): 1713–1722. **3.** Verhaart IEC, et al. Orph. J Neurol. 2017; 264: 1465–1473. **4.** Ali HG, et al. Gene Ther. 2021 Nov; 28(10-11): 676-680.

Rapid progression in SMA Type 1

- SMA Type 1 is the most severe and rapidly progressing form, symptoms start within the first 2–2.5 months[1]
- By 6 months of age 95% of motor neurons are irreversibly lost[2,3]
- Respiratory failure leads to death before the age of two in more than 90% of children with SMA Type 1[4]



1. Mendell JR, et al. N Engl J Med. 2017; 377(18): 1713–1722. **2.** Glascock J, et al. J Neuromusc Dis. 2018; 5: 145–158. **3.** Govoni A, et al. Mol Neurobiol. 2018; 55(8): 6307–6318. **4.** Finkel RS et al. Neurology. 2014; 83: 810–817.

New treatments in SMA

- The first treatment for SMA in Australia was TGA approved in 2017 and PBS listed in 2018
- There are now 3 treatments indicated for SMA in Australia:[1–3]
  - Nusinersen
  - Risdiplam
  - Onasemnogene abeparvovec
- All three work by increasing the amount of SMN protein available to motor neurons[1–3]

Treatment	Nusinersen (Spinraza® [Biogen])	Risdiplam (Evrysdi® [Roche])	Onasemnogene abeparvovec (Zolgensma® [Novartis])
Mechanism of action	Increases amount of SMN produced by SMN2	Increases amount of SMN produced by SMN2	Gene therapy that provides new functioning SMN1
Dose	intrathecal injection 4 loading doses then maintenance dose every 4 months	oral solution given by syringe daily	A single IV infusion providing ongoing SMN production

1. Spinraza Australian approved Product Information. **2.** Evrysdi Australian approved Product Information **3.** Zolgensma Australian approved Product Information.

Why is early treatment important?

- SMA treatments can slow or prevent progressions but they can't reverse prior damage[1]
- Infants treated early in the disease course reach more motor milestones than those treated later[2]
- Early diagnosis and treatment is critical to ensuring the best possible patient outcomes[1,2]

Adapted from Lowes 2019[2]

1. Govoni A, et al. Mol Neurobiol. 2018; 55(8): 6307–6318. **2.** Lowes LP, et al. Pediatr Neurol. 2019; 98: 39–45.

Newborn screening for SMA

- Newborn screening (NBS) is the gold standard for identifying infants with SMA[1]
- SMA patients identified with NBS can receive treatment before developing symptoms[1]
- SMA NBS has been approved by the Federal government but has not been implemented in all Australian States/Territories[2]

1. D'Silva AM. Dev Med Child Neurol. 2022; 64(5): 625–632 **2.** www.health.gov.au/our-work/newborn-bloodspot-screening/what-is-screened-in-the-program [accessed February 2023]

Identifying symptomatic patients

- Without newborn screening, early treatment relies on healthcare providers recognising the signs of SMA
- Patients with SMA Type 1 often appear normal at birth with symptoms developing over time[1]
- Diagnostic delay is common, the average age of Type 1 diagnosis is 6 months[2]
- Remaining vigilant for common signs can help with early identification[1,3]

1. Wang CH, et al. J Child Neurol. 2007;22:1027–49. **2.** Lin, CWL, et al. Ped. Neurol. 2015; 53: 293–300. **3.** De Sanctis R, et al. Neuromuscul Disord. 2016; 26(11): 754–759.

Think 3 for SMA at 3 months of age

Three signs of possible SMA at 3 months of age

Head lag[1]

Head lag can be seen when baby is being held or when placed on their stomach for tummy time.

Hypotonia (floppy baby)[1]

A baby with hypotonia is often described as ‘floppy.’ They will likely feel limp when held and may be unable to move their arms, legs or neck.

Inability to reach[2]

A baby not raising their arms or reaching for things. When laying baby on their back, hold a toy above them to see if they reach for it.

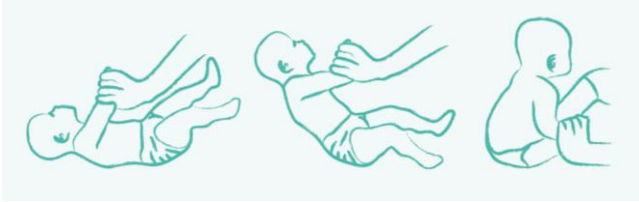
THINK 3 FOR SMA

1. Wang CH, et al. J Child Neurol. 2007;22:1027–49. **2.** De Sanctis R, et al. Neuromuscul Disord. 2016; 26(11): 754–759.

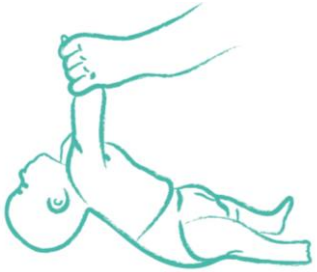
Using the the pull-to-sit test

- The pull-to-sit test can help identify head lag and hypotonia[1,2]
- with the baby lying flat on their back – grasp their hands and pull them into the sitting position[1,2]
- Typically a baby will hold their head in line with their torso and brace arms when hip flexion is initiated[1,2]
- Atypical signs in the pull-to-sit test:
  - Head lagging behind torso
  - No bracing in arms and shoulders pulling forwards
  - No bend in hips

Typical response



Atypical response



1. Hammersmith Infant Neurological Examination (v 07.07.17). 2. Great Ormond Street Hospital for Children NHS. Brief Developmental Assessment (BDA). Available at: www.gosh.nhs.uk/file/1841/download?token=oTvMwb9q [accessed February 2023]

What to do if you suspect SMA

- SMA progresses rapidly and any delay in treatment can have a life-long impact[1]
- Most States have paediatric neuromuscular centres with referral processes for SMA
- In Victoria, children displaying signs of SMA should be directed to their GP for emergency referral to the RCH neuromuscular department

Australian paediatric neuromuscular centres

1. Queensland Children's Hospital
2. John Hunter Children's Hospital
3. Sydney Children's Hospital, Randwick
4. The Children's Hospital at Westmead
5. Royal Children's Hospital
6. Monash Children's Hospital
7. Women's and Children's Hospital
8. Perth Children's Hospital

1. Govoni A, et al. Mol Neurobiol. 2018; 55(8): 6307–6318.

Summary

- SMA is a rapidly progressing and devastating genetic disease[1]
- Modern treatments have made SMA a manageable condition but early treatment is critical for the best outcome[1]
- Newborn screening is the gold standard for early identification of SMA; however it is not universally available
- Healthcare provides should remain vigilant for children 3 months or older displaying head lag, hypotonia and inability to reach[2,3]
- These children must be urgently referred to a paediatric neurologist for assessment

1. Govoni A, et al. Mol Neurobiol. 2018; 55(8): 6307–6318. **2.** Wang CH, et al. J Child Neurol. 2007;22:1027–49. **3.** De Sanctis R, et al. Neuromuscul Disord. 2016; 26(11): 754–759.

Daniella Villano
Neuromuscular Nurse Consultant
daniella.Villano@rch.org.au
03 9345 4633