Spinal muscular atrophy

A guide to the early referral and diagnosis of spinal muscular atrophy (SMA) and other paediatric neuromuscular disorders

What is SMA?

SMA is a genetic neuromuscular disorder characterised by progressive muscle weakness and wasting, due to the degeneration of motor neurons.[1,2] Untreated, it is the most common genetic cause of infant mortality and an important cause of motor delay or regression in children that should not be missed.[2]

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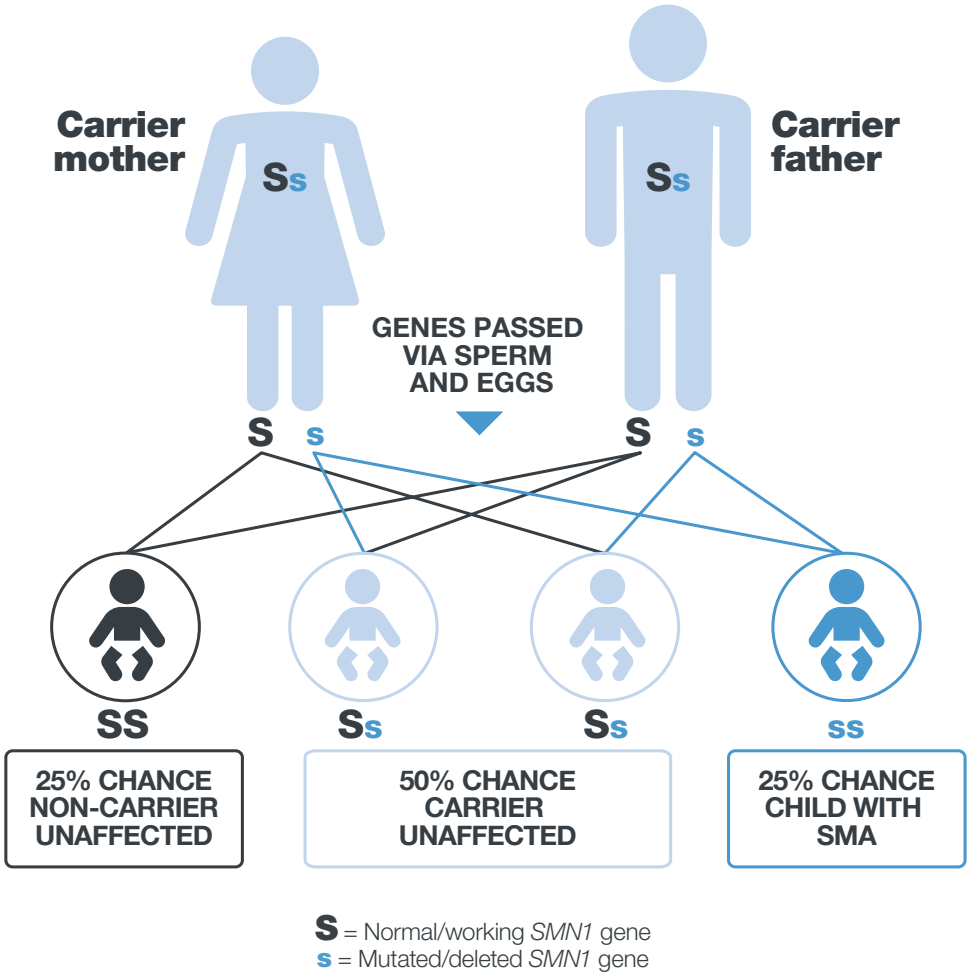
Putting SMA in context: The clinical imperative

Doctors often adopt a 'wait-and-see' approach when children show signs of delayed motor development. However, recent advances in therapy have made previously untreatable diseases, like SMA, treatable. Timely treatment initiation may delay disease progression and improve outcomes. This highlights the need for proactive, early intervention when clinical suspicion arises.

What causes SMA?

SMA is an autosomal recessive condition caused by a deficiency in SMN protein due to a mutated or deleted *SMN1* gene.[3] This protein is required for the survival of motor neurons. Without the SMN protein, motor neuron loss in the brainstem and spinal cord occurs, leading to subsequent denervation and atrophy of muscles.[2,4]

SMA AUTOSOMAL RECESSIVE INHERITANCE



S = Normal/working *SMN1* gene
s = Mutated/deleted *SMN1* gene

Source: Delatycki MB, Laing NG, Moore SJ, et al. Preconception and antenatal carrier screening for genetic conditions: The critical role of general practitioners. Aust J Gen Pract 2019;48(3):106–10. doi: 10.31128/AJGP-10-18-4725.[5]

SMA has a broad spectrum of clinical severity, related in part to the number of *SMN2* gene copies an individual has.[6] *SMN2* is nearly identical to *SMN1*, but only 10–15% of protein derived from *SMN2* is functional.[3]

How common is SMA?

SMA affects one in 10,000 live births and the carrier frequency for *SMN1* mutations is estimated to be between one in 38 and one in 70.[1,2] Unlike other genetic conditions, SMA affects individuals of all ethnic groups.[6]

Why is early referral and diagnosis important?

While there is no cure for SMA, a pharmacological treatment option is now available. Nusinersen was listed on the Pharmaceutical Benefits Scheme in 2018 and has demonstrated dramatic benefit in regard to motor function and survival. Clinical trials indicate that earlier treatment initiation leads to better clinical outcomes, due to reduced motor neuron loss.[7–9]

Delays in referral may delay drug treatment, leading to further loss of motor neurons and, in turn, motor function.

How does nusinersen work?

Nusinersen is an antisense oligonucleotide drug administered via intrathecal injection. It promotes increased production of functional SMN protein. This protein reduces the loss of motor neurons, resulting in altered disease progression – specifically, improved survival and motor function.[7–9]

Beyond the prompt initiation of drug treatment, timely diagnosis also aids early intervention and support measures, including the set-up of a multidisciplinary care team for the child and family. This ensures adequate support structures are in place prior to disease progression or the onset of complications, which can help to ease the family's burden.[10]

While first-line clinicians (eg general practitioners [GPs], obstetricians, maternal child health nurses) are not expected to formally diagnose SMA, they should recognise that an infant or child presenting with motor weakness and delay requires urgent specialist assessment.

How does SMA present?

SMA presents with progressive proximal muscle weakness and atrophy in the setting of unaffected cognition.[2,11,12] Due to the wide variation in the age of onset and clinical course of the disease, SMA is classified into five different types.[12,13]

Summary table of SMA types 0–4[2,12–15]

TYPE	AGE OF ONSET	MOTOR MILESTONES	SIGNS AND SYMPTOMS	DISEASE COURSE (UNTREATED)
Type 0	**Prenatal**	Respiratory support at birth	Severe weakness and hypotonia Background of decreased fetal movements	Death occurs by respiratory failure. Life expectancy is less than two months.
Type 1	**0–6 months**	Unable to independently sit	Muscle weakness and hypotonia Poor suck and swallow reflexes Tongue fasciculations 'Frog leg' posture when lying Reduced or absent tendon reflexes Failure to thrive	Symptoms progress rapidly, with development of breathing difficulties. Life expectancy is less than two years.
Type 2	**6–18 months**	Able to independently sit	Muscle weakness (affects proximal legs more than arms) Joint contractures Progressive scoliosis Respiratory insufficiency	Never stand or walk independently. Life expectancy is variable. However, the majority reach young adulthood.
Type 3	**18 months – adulthood**	Able to independently stand and walk	Muscle weakness (affects proximal legs more than arms) Joint contractures Joint or muscle pain	The ability to stand or walk may be lost over time. Life expectancy is unaffected.
Type 4	**Adulthood**	Achieve all motor milestones	Mild muscle weakness	Ambulation is usually maintained throughout life. Life expectancy is unaffected.

What are the red flags for SMA?

An infant presenting with motor weakness and delay in the setting of normal cognition should raise a high index of suspicion for SMA. This suspicion should be maintained regardless of whether the infant appears superficially normal, as infants with SMA often look bright and alert with normal facial expression.[12,14]

Parents may additionally report that their child seems floppy like a rag doll, struggles to lift their head up or do 'tummy time', isn't on par with other kids of the same age, or simply that something is not quite right – all of which should augment suspicion.[16–18] It is important to take the report of parents seriously, as studies indicate that parental concern is a fairly accurate predictor of developmental problems.[19,20]

Other characteristic red flags to be aware of include:[12,14]

- muscle weakness (with or without atrophy)
- hypotonia (relaxed tone, 'floppy')
- poor head control (eg head lag when pulled to sit, if age >5 months)
- tongue fasciculations
- 'frog leg' posture when lying
- reduced or absent tendon reflexes.

Infants with SMA are not dysmorphic. This may lead clinicians to dismiss the significance of other signs such as relaxed tone and delayed motor milestones.

Other causes of motor weakness and delay

There are other conditions that may present somewhat similarly to SMA.[14] These include the muscular dystrophies (eg Duchenne, Becker), congenital myotonia and Charcot–Marie–Tooth disease. Narrowing the differential diagnosis requires specialist input and genetic testing.

When should you refer?

Given the importance of early diagnosis, children suspected of having SMA or other neuromuscular disease should be urgently referred for specialist assessment – hypotonia and motor weakness in a child aged <2 years always requires urgent investigation, especially if accompanied by delay.

Ideally, you should refer the patient to a paediatric neurologist or tertiary paediatric neuromuscular clinic, indicating the urgency of your referral. If access to subspecialty care is limited, refer urgently to a general paediatrician for further assessment, stating that you are concerned about a possible SMA diagnosis.

A common cause of diagnostic delay is initial referral to a paediatric allied health service, physiotherapist or general paediatrician rather than to a paediatric neurologist.[17]

If SMA is confirmed, the patient and family will require multidisciplinary care from providers across a range of disciplines. This may include neurology, respiratory medicine, orthopaedics, physiotherapy, occupational therapy, psychology and palliative care, depending on the type and severity of the condition.

Do not take a 'wait and see' approach with a concerning clinical impression. Do take a 'let's play it safe and refer early' approach.

Can SMA be prevented?

Carrier screening (ie genetic testing) can identify individuals and couples at increased risk of having a child with SMA.[6] Currently, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommends that information about carrier screening – including the three-panel screen for SMA, fragile X syndrome and cystic fibrosis – be provided to all women and couples planning a pregnancy or in their first trimester. GPs, fertility specialists and obstetricians are ideally placed to have this conversation with patients. If further information is desired, a detailed discussion with a genetic counsellor should follow.[21]

For more information on carrier screening and the role of healthcare professionals in informing and counselling patients, please refer to this guide **Genetic carrier screening: A guide to preconception and early pregnancy carrier screening for hereditary rare diseases.**

The Australian Reproductive Genetic Carrier Screening Project

Currently, a government-funded research trial called the Australian Reproductive Genetic Carrier Screening Project ('Mackenzie's Mission') is screening 10,000 Australian couples for more than 700 serious genetic conditions. The project aims to evaluate the outcomes of screening, the psychosocial impacts reported by couples, the economic impact of screening, as well as the potential benefits and limitations of population-wide screening.[22]

Where can you direct patients and families for support?

- Genetic Alliance Australia, **geneticalliance.org.au**
- Genetic and Rare Disease Network, **gardn.org.au**
- Spinal Muscular Atrophy Australia, **smaaustralia.org.au**
- Together in SMA, **togetherinsma.com.au**
- Rare Voices Australia, **rarevoices.org.au**

Further information for healthcare professionals

- Australian Genomics Health Alliance, **Australian Reproductive Genetic Carrier Screening Project (Mackenzie's Mission)**
- Standing Committee on Screening, ***Population based screening framework***

Key takeaway points

Even though inherited neuromuscular diseases like SMA are rare, you must keep them on your clinical radar. You are likely to encounter at least one of these conditions over the course of your career.

An infant or child presenting with motor weakness and delay in the setting of normal cognition always requires urgent investigation, regardless of whether they appear superficially normal.

In most cases, patients experience superior outcomes with timely diagnosis and early intervention. A concerning clinical impression should be referred urgently for specialist input.

Resources for healthcare professionals

Visit **bewaretherare.com.au** for useful clinical resources including a video library and an RACGP-accredited CPD (Cat. 2) Activity suitable for GPs, practice nurses, obstetricians, fertility specialists, general paediatricians and maternal child health nurses.

References **1.** Farrar M, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol 2017;81(3):355–68. **2.** Darras B. Spinal muscular atrophies. Pediatr Clin N Am 2015;62(3):743–66. **3.** Kolb S, Kissel J. Spinal muscular atrophy. Arch Neurol 2011;68(8):979–84. **4.** Friesen W, Massenet S, Paushkin S, Wyce A, Dreyfuss G. SMN, the product of the spinal muscular atrophy gene, binds preferentially to dimethylarginine-containing protein targets. Mol Cell 2001;7(5):1111–17. **5.** Delatycki MB, Laing NG, Moore SJ, et al. Preconception and antenatal carrier screening for genetic conditions: The critical role of general practitioners. Aust J Gen Pract 2019;48(3):106–10. **6.** Sugarman E, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: Clinical laboratory analysis of >72400 specimens. Eur J Hum Genet 2012;20(1):27–32. **7.** Finkel R, Mercuri E, Darras B, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377(18):1723–32. **8.** De Vivo D, Bertini E, Swoboda K, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the phase 2 NURTURE study. Neuromuscul Disord 2019;29(11):842–56. **9.** Mercuri E, Darras B, Chiriboga C, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378(3):625–35. **10.** Lin C, Kalb S, Yeh W. Delay in diagnosis of spinal muscular atrophy: A systematic literature review. Pediatr Neurol 2015;53:293–300. **11.** von Gontard A, Zerres K, Backes M, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. Neuromuscul Disord 2002;12(2):130–36. **12.** Kolb S, Kissel J. Spinal muscular atrophy. Neurol Clin 2015;33(4):831–46. **13.** Russman B. Spinal muscular atrophy: Clinical classification and disease heterogeneity. J Child Neurol 2007;22(8):946–51. **14.** D'Amico A, Mercuri E, Tiziano F, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71. **15.** Foead A, Yeo WWY, Vishnumukkala T, Larvin M. Rehabilitation in spinal muscular atrophy. J Int Soc Phys Rehabil Med 2019;2(1):62–70. **16.** Lurio J, Peay H, Mathews K. Recognition and management of motor delay and muscle weakness in children. Am Fam Physician 2015;91(1):38–45. **17.** Lawton S, Hickerton C, Archibald A, McClaren B, Metcalfe S. A mixed methods exploration of families' experiences of the diagnosis of childhood spinal muscular atrophy. Eur J Hum Genet 2015;23(5):575–80. **18.** National Task Force for Early Identification of Childhood Neuromuscular Disorders. Signs of weakness by parent report. US: National Task Force for Early Identification of Childhood Neuromuscular Disorders, 2020. Available at www.childmuscleweakness.org/know-the-signs/signs-of-weakness-by-parent-report [Accessed 13 January 2020] **19.** Oberklaid F, Drever K. Is my child normal? Milestones and red flags for referral. Aust Fam Physician 2011;40(9):666–70. **20.** Glascoe F. Evidence-based approach to developmental and behavioural surveillance using parents' concerns. Child Care Health Dev 2000;26(2):137–49. **21.** The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Genetic carrier screening. East Melbourne, Vic: RANZCOG, 2019. **22.** Victorian Clinical Genetics Services. Budget 2018 confirms the importance of genomic healthcare. Parkville, Vic: VCGS, 2018. Available at www.vcgs.org.au/news/budget-2018-confirms-importance-genomic-healthcare [Accessed 10 January 2020].

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