

# Interventions for Spinal Muscular Atrophy

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## Case Summary

An adult with type 1 spinal muscular atrophy, with initial onset of symptoms at 5 months of age, including delayed milestones and the inability to sit independently. The diagnosis was confirmed by genetic testing. The patient had limited motor skills and had difficulties with activities necessary for independent daily living. Additionally, the patient was ventilator dependent. Spinal fixation from C4-S1 was performed for severe levoscoliosis.

Nusinersin (Spinraza, Biogen, Inc, Cambridge, Massachusetts) is an antisense oligonucleotide inhibitor that increases the amount of SMN protein, needed for normal nerve and muscle function.<sup>1</sup> Intrathecal (IT) nusinersen was instituted at 17 years of age. Since beginning the IT therapy, hand movement and voice quality have improved, resulting in an improved quality of life.

## Imaging Findings

There are no pathognomonic imaging findings diagnostic of spinal muscular atrophy. However, over time patients may develop scoliosis because of the imbalance between the flexor and extensor muscles of the

trunk, typically leading to a C-shaped curvature of the spine (Figure 1). If the scoliosis is severe or progressive, spinal fusion is often necessary, as in this patient. The severity of the curvature, the vertebral rotation, and spinal fixation may make traditional approaches for IT medication administration challenging for radiologists performing these procedures.

## Diagnosis

Spinal muscular atrophy (SMA). The clinical differential diagnosis is extensive and includes many conditions that present with severe hypotonia, including congenital muscular and neuropathic disorders.<sup>1</sup>

## Discussion

Spinal muscular atrophy is an inherited, autosomal recessive, neuromuscular disorder most often caused by a homozygous deletion or mutation of the *SMN1* gene on chromosome 5q13 with absent *exon 7*, resulting in absent or deficient levels of survival motor neuron (SMN) protein. A second and nearly identical gene, *SMN2*, produces low levels of functional SMN protein, however this fails to compensate for the loss of *SMN1*.<sup>2</sup> SMN facilitates the assembly of spliceosomal small nuclear ribonucleoprotein (snRNP) particles, which are thought to function in motor neuron growth and neuromuscular maturation.<sup>3</sup> Over time, SMA results in the degeneration of anterior

horn cells in the spinal cord with associated destruction of alpha motor units in lower motor neurons.

SMA presents with varying clinical phenotypes and is classified into five main subtypes based on severity and age of onset. All are characterized by progressive muscle weakness, reduced tone, and atrophy. However, cognition is not affected. Type 0 is congenital SMA, which presents early in neonatal life as severe hypotonia, early respiratory failure, and severe weakness, with death occurring at birth or within the first month of life. Type 1, also known as Werdnig-Hoffman disease, presents in the first 6 months of life with limited head control, hypotonia, areflexia, weakness of intercostal muscles, swallowing difficulties, and tongue fasciculations.

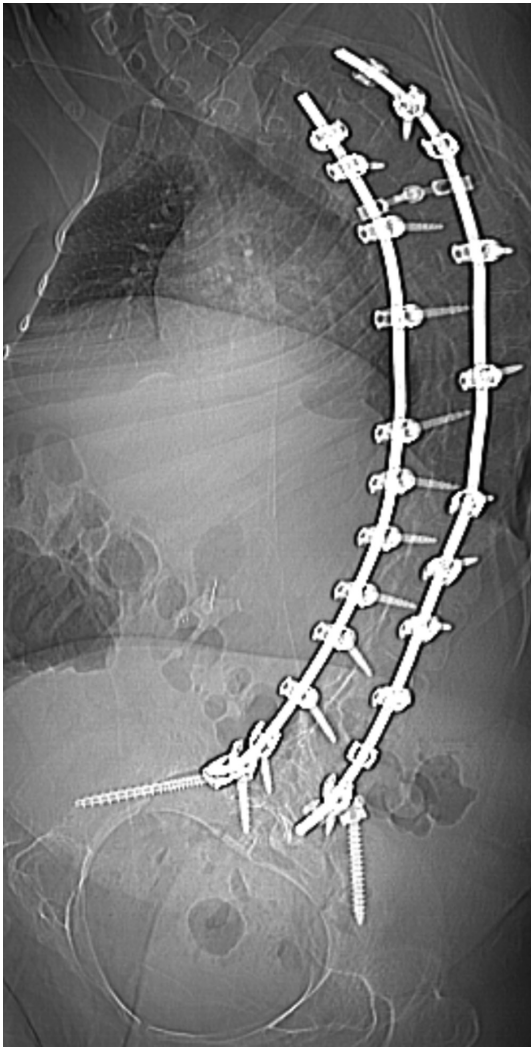
Type 2, Dubowitz disease, is of intermediate severity, presenting at 6-18 months of age. Children with SMA 2 are able to sit but have hypotonia, areflexia, progressive scoliosis, and restrictive lung disease. Mortality is most commonly due to respiratory compromise, but 70% of patients survive until age 25.

Type 3, Kugelberg-Welander disease, is mild SMA, presenting after 18 months of age with more progressive proximal weakness in the legs than in the arms. Type 3 patients are ambulatory and typically do not have restrictive lung disease. Additionally, their life expectancy is not affected.

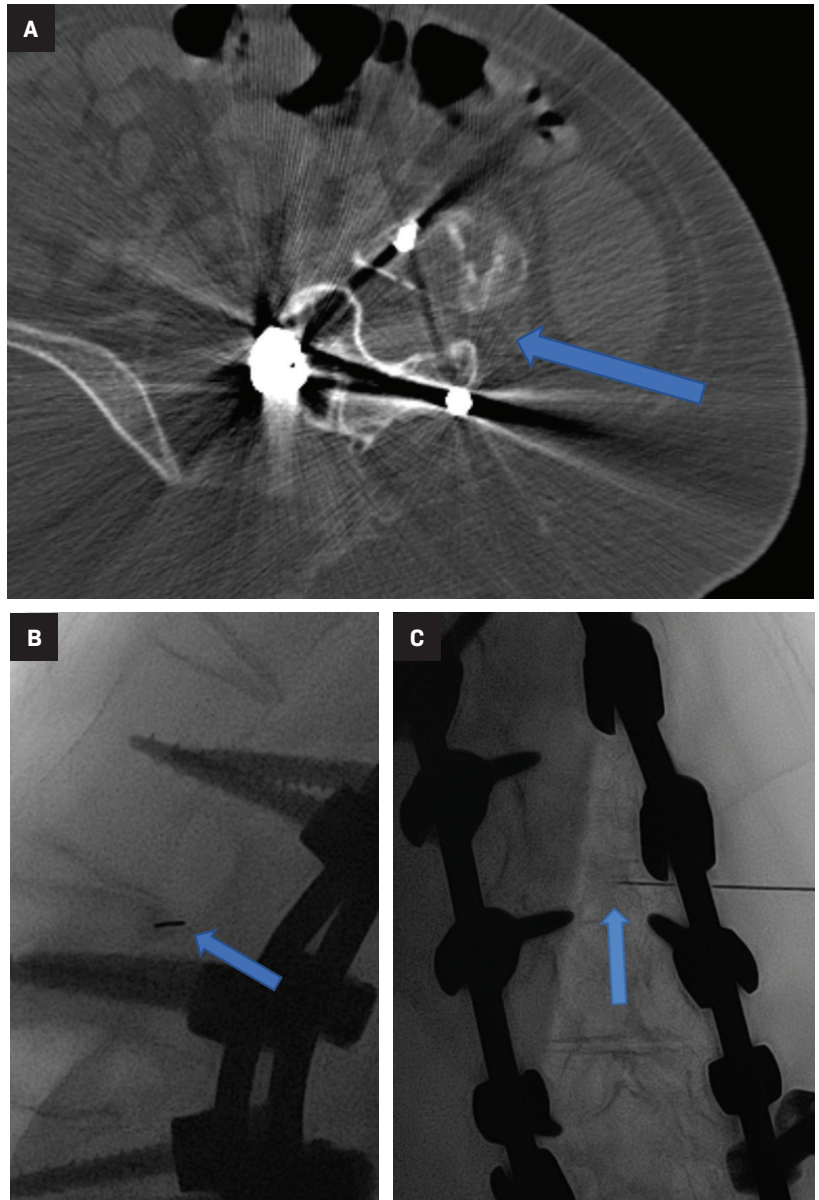
Finally, type 4 is adult-onset SMA. It has the mildest phenotype and presents

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**Figure 1.** Scout image of CT of the spine demonstrating the presence of a severe levoconvex rotary scoliosis of the thoracolumbar spine with posterior spinal construct.



**Figure 2.** (A) CT axial image of the lumbar spine demonstrating planned left transforaminal access (blue arrow) for intrathecal nusinersen administration. (B) Lateral fluoroscopic view of the lumbar spine with the spinal needle (blue arrow) entering the inferior-most aspect of the neural foramen to avoid the neurovascular structures typically traversing the upper 2/3 of the foramen. (C) Frontal fluoroscopic image demonstrating the spinal needle tip (blue arrow) near the midline of the thecal sac.



in patients older than 21 years, with progressive, mild proximal weakness typically not impairing ambulation or affecting life expectancy.<sup>4</sup>

If clinical history and physical exam findings raise the suspicion for SMA, the diagnosis can be confirmed by molecular genetic testing to detect homozygous exon 7 deletion in the *SMN1* gene, which is 100%

specific for diagnosis. Around 5% of patients with SMA are compound heterozygotes with a single *SMN1* deletion and a frameshift, nonsense, or missense mutation in the other *SMN1* copy. *SMN2* differs from *SMN1* by a single nucleotide that disrupts a splice enhancer in exon 7, producing an unstable protein that is unable to compensate for the loss of *SMN1*.

However, approximately 10-20% fully functional, full-length transcripts are generated from *SMN2*.

There are zero to eight *SMN2* copies in the genome, which is inversely correlated with disease severity. A higher number of *SMN2* copies is often able to produce a milder type 2 or type 3 phenotype of SMA. In the normal population, the *SMN2* copy number

varies from zero to three, with 15% of normal individuals having no *SMN2*. An analysis of 625 unrelated Spanish patients with SMA showed that the majority of individuals with type 1 SMA had one or two *SMN2* copies; most of those with type 2 SMA had three gene copies; and those with type 3 had three or four *SMN2* copies.<sup>5</sup>

Therapeutic approaches are multi-fold, including splicing modification of *SMN2* via antisense oligonucleotides (ASO), small molecules which modulate *SMN2* gene splicing, and *SMN1* gene replacement therapy. Nusinersen, the first molecular drug to treat SMA, is an intrathecally administered ASO which promotes inclusion of exon 7 in mRNA transcripts of *SMN2*, resulting in translation of a higher level of fully functional SMN protein in liver, kidney, skeletal muscle, and central nervous system tissues. SMA patients have experienced significant improvement in motor function and extension in life expectancy after receiving nusinersen.<sup>7</sup>

Intrathecal access in patients with SMA may be challenging based on whether patients have simple or complex spinal anatomy (neuromuscular scoliosis, spinal fusion, and/or instrumentation, Figure 2). Several approaches can be used to facilitate drug injection into the subarachnoid space. In children with uncomplicated spines, a midline lumbar puncture is performed. In those with complex spines, lumbar transforaminal or C1-2 approaches may be required. Although either approach can deliver IT therapy, it is believed that the lumbar approach provides a higher drug concentration to the target lower motor neurons.

The authors prefer the transforaminal approach, as it is reported to be safer and technically easier than the C1-2 approach.<sup>8,9</sup> Multiple reviews have shown that the complex anatomy commonly present in patients with SMA usually requires preprocedural imaging for careful planning, as well

as intraprocedural guidance to access the subarachnoid space via a transforaminal approach.<sup>8,9</sup>

A newer, orally administered small molecule called risdiplam (Evrysdi, Genentech) has also been developed to treat SMA. This drug modulates *SMN2* gene splicing by binding two pre-mRNA splice sites in exon 7, increasing levels of full-length SMN mRNA and protein. Risdiplam crosses the blood-brain barrier, achieving systemic distribution with suitable half-life and predictable pharmacokinetics.<sup>10</sup>

Onasemnogene abeparvovec (Zolgensma, Novartis) is an *SMN1* gene replacement therapy, which uses a non-replicating, adeno-associated virus capsid carrying *SMN1* complementary recombinant DNA to efficiently deliver wild-type *SMN1* to motor neuron cells. The drug cannot reverse any pre-existing damage to motor neurons and is currently approved for children under age 2 years.<sup>11</sup> To achieve the best results it is important to give the drug early in the disease course before there is injury to the motor neurons.

## Conclusion

Spinal muscular atrophy is an inherited neuromuscular disorder characterized by progressive muscle weakness. It has varying clinical severity ranging from mild proximal muscle weakness to death from restrictive lung disease. The diagnosis is confirmed by genetic testing. Treatment includes the *SMN2* splicing modulator nusinersen, facilitated by interventional radiologists. This may be challenging to administer intrathecally as patients develop scoliosis over time, making midline or paramedian lumbar punctures more challenging. Patients with complex spinal anatomy may benefit from pre- and intraprocedural imaging to allow for a transforaminal approach to the thecal sac.

## References

- 1) Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 Dec 3]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1352/>
- 2) Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol Clin.* 2015 Nov;33(4):831-46. doi: 10.1016/j.ncl.2015.07.004. PMID: 26515624; PMCID: PMC4628728.
- 3) Fan L, Simard LR. Survival motor neuron (SMN) protein: role in neurite outgrowth and neuromuscular maturation during neuronal differentiation and development. *Hum Mol Gen.* 2002; 11(14) 1605-1614. <https://doi.org/10.1093/hmg/11.14.1605>
- 4) Burr P, Reddivari AKR. Spinal Muscle Atrophy. 2021 Jan 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. PMID: 32809522.
- 5) Calucho M, Bernal S, Aliás L, et al. Correlation between SMA type and *SMN2* copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord.* 2018;28(3):208-215. doi:10.1016/j.nmd.2018.01.003
- 6) Rouzier C, Chaussonnet A, Paquis-Flucklinger V. Molecular diagnosis and genetic counseling for spinal muscular atrophy (SMA). *Arch Pediatr.* 2020 Dec;27(7S):7S9-7S14. doi: 10.1016/S0929-693X(20)30270-0. PMID: 33357600.
- 7) Paton DM. Nusinersen: antisense oligonucleotide to increase SMN protein production in spinal muscular atrophy. *Drugs Today (Barc).* 2017;53(6):327-337. doi: 10.1358/dot.2017.53.6.2652413. PMID: 28799578.
- 8) Mousa MA, Aria DJ, Schaefer CM, Kaye, RD, Abruzzo TA, Bernes, SM, Willard SD, Riemann MC, Towbin, RB. A comprehensive institutional overview of intrathecal nusinersen injections for spinal muscular atrophy. *Pediatr Radiol.* 2018;48(12):1797-1805. doi:10.1007/s00247-018-4206-9
- 9) Towbin R, Schaefer C, Kaye R, Abruzzo T, Aria DJ. The complex spine in children with spinal muscular atrophy: the transforaminal approach—a transformative technique. *AJNR Am J Neuroradiol.* 2019; 40(8):1422-1426. doi: 10.3174/ajnr.A6131. Epub 2019 Jul 11. PMID: 31296522; PMCID: PMC7048480.
- 10) Ratni H, Ebeling M, Baird J, et al. Discovery of risdiplam, a selective survival of motor neuron-2 (*SMN2*) gene splicing modifier for the treatment of spinal muscular atrophy (SMA). *J Med Chem.* 2018; 61(15):6501-6517. doi: 10.1021/acs.jmedchem.8b00741. Epub 2018 Jul 25. PMID: 30044619.
- 11) Messina S, Sframeli M. New treatments in spinal muscular atrophy: positive results and new challenges. *J Clin Med.* 2020;9(7):2222. doi: 10.3390/jcm9072222. PMID: 32668756; PMCID: PMC7408870.