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INTRODUCTION

Neuromuscular disorders that present in the newborn period with hypotonia and weakness can be caused by various conditions that affect the central nervous system (brain or spinal cord), peripheral nervous system, or skeletal muscle. Spinal muscular atrophy (SMA) is characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy. This topic will review clinical aspects of spinal muscular atrophy (SMA), with a focus on survival motor neuron 1 (*SMN1*) gene-related SMA.

GENETICS

The inheritance pattern of chromosome 5q-related SMA is autosomal recessive [1]. The different forms of 5q-SMA are caused by biallelic deletions or mutations in the *SMN1* gene on chromosome 5q13.2, resulting in a deficiency of the SMN1 protein [2-5]. The most common mutation of *SMN1* is a deletion of exon 7 [6]. Approximately 94 percent of patients with clinically typical SMA carry homozygous deletions of exon 7. SMN protein appears to play a role in mRNA synthesis in motor neurons and may inhibit apoptosis [7,8].

The differences in SMN protein activity and phenotypic expression are partly related to a modifying gene called survival motor neuron 2 (*SMN2*). The *SMN1* and *SMN2* genes are more than 99 percent identical and lie within an inverted duplication on chromosome 5q13.2 [5]. *SMN1* lies telomeric of *SMN2*. The main difference between them is a C to T transition in exon 7 of *SMN2* [9,10]. This change leads to the production of a truncated, nonfunctional SMN protein from the majority of *SMN2*-derived mRNAs. However, approximately 10 to 15 percent of mRNAs from *SMN2* contain exon 7 and can produce some functional, full-length SMN protein [11]. Thus, the loss of the SMN1 protein is partially compensated by SMN2 protein synthesis (figure 1), a mechanism that explains some but not all of the phenotypic variability in patients with SMA [12]. Disease severity in SMA generally correlates inversely with *SMN2* copy number, which varies from 0 to 8 in the normal population, and to a lesser degree with the level of SMN protein [11,13-17]. The presence of four or more copies of *SMN2* is associated with a milder phenotype [1,14].

While the most common forms of SMA are caused by deletions or mutations in the *SMN1* on chromosome 5q (ie, 5q SMAs), there are many rare non-5q spinal muscular atrophies [15,18,19]. The non-5q SMAs are genetically and clinically heterogeneous (table 1).

EPIDEMIOLOGY

The incidence of spinal muscular atrophy ranges from 5 to 13 per 100,000 live births, and the carrier frequency of disease-causing *SMN1* mutations ranges from 1:100 to 1:45, with marked interethnic variability [1,20-22]. SMA is the most common monogenic cause of infant mortality [23].

CLINICAL FEATURES

SMA disorders are characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy [16,23]. Cognition is unaffected [24]. These diseases were traditionally classified into types 1 to 3, but now they are classified as types 0 through 4, depending upon the age of onset and clinical course (table 2). SMA type 0 (prenatal onset) and SMA type 1 (infantile onset) are the most common and severe types. SMA type 2 and SMA type 3 have a later onset and a less severe course. SMA type 4 (adult onset) is the least severe. While these subtypes are clinically useful for prognostic and therapeutic considerations, it is clear that SMA phenotypes span a spectrum of severity without discrete separation [1]. Disease severity in SMA generally correlates inversely with *SMN2* copy number, which varies in the normal population and, to a lesser degree, with the level of SMN protein. (See 'Genetics' above.)

Patients with all forms of SMA have diffuse symmetric proximal muscle weakness that is greater in the lower than upper limbs, and absent or markedly decreased deep tendon reflexes [25]. In addition, SMA is associated with restrictive, progressive respiratory insufficiency, particularly SMA type 0 and type 1 [26].

Less commonly, sleep disturbances can occur in children with SMA [27], and congenital heart defects may accompany SMA type 0 [28]. While there have been occasional reports of heart rhythm abnormalities in SMA types 1, 2, and 3 [29], these may be coincidental associations [23,30,31].

SMA type 0 — In the expanded classification, SMA type 0 designates prenatal onset of SMA [32-34], although prenatal onset was traditionally classified as SMA type 1. Mothers of affected patients with SMA 0 may recognize a decrease or loss of fetal movement in late pregnancy [35]. At birth, infants with SMA type 0 have severe weakness and hypotonia, often with areflexia, facial diplegia, and congenital heart defects [1,16,28,35,36]. Arthrogryposis (multiple joint contractures) may be present. No motor milestones are achieved. Death occurs from respiratory failure by age six months, and usually by one month. Infants with SMA of neonatal onset may present with signs of fetal hypokinesia deformation sequence, including polyhydramnios, intrauterine growth retardation, skeletal abnormalities with multiple articular contractures, and pulmonary hypoplasia [37].

Infants with SMA type 0 generally have only one copy of *SMN2* [11,16].

SMA type 1 — SMA type 1 is also known as infantile spinal muscular atrophy or Werdnig-Hoffmann disease. It typically presents after birth but before age six months [25]. Affected infants may appear normal before the onset of symptoms, but soon develop a severe, symmetric flaccid paralysis and never achieve the ability to sit unsupported. Because the upper cranial nerves are mostly spared, patients with SMA type 1 usually have an alert expression, furrowed brow, and normal eye movements. However, weakness of the bulbar muscles results in a weak cry, poor suck and swallow reflexes, pooling of secretions, tongue fasciculations, and an increased risk of aspiration and failure to thrive [16]. Respiratory muscle weakness leads to progressive respiratory failure. The intercostal muscles typically are more affected than the diaphragm, resulting in paradoxical breathing (inspiratory efforts cause the rib cage to move inward and the abdomen to move outward) and the development of a characteristic bell-shaped chest deformity. The severe hypotonic leg weakness often manifests as a "frog-leg" posture when lying. Cardiac muscle does not appear to be affected, since SMA is not associated with dilated cardiomyopathy.

Symptoms progress rapidly, and the majority of infants die before two years of age from respiratory failure [38-40]. Nevertheless, long-term survivors have been reported [41-43]. This is perhaps due, in part, to advances in the care of chronic respiratory insufficiency and to more aggressive care. (See 'Supportive therapy' below.)

Patients with SMA type 1 generally have two or three copies of the *SMN2* gene [11,16].

SMA type 2 — SMA type 2 (intermediate form; Dubowitz disease) accounts for approximately 20 percent of cases and has a less severe course than type 1. SMA type 2 most often presents between 3 and 15 months of age [1,16,25,42,44]. The ability to sit unassisted is attained at some point but may be delayed. However, independent standing and walking are never achieved. Weakness is predominately proximal and affects the legs more than the arms. Common features include sparing of face and eye muscles, tongue atrophy with fasciculations, areflexia, a fine tremor-like form of myoclonus (minipolymyoclonus) affecting distal limbs, dysphagia, and respiratory insufficiency. Muscular weakness leads to progressive scoliosis in nearly all affected individuals; the combination of respiratory muscle weakness and scoliosis may result in restrictive lung disease. Some develop joint contractures and ankylosis of the mandible. The ability to sit independently is usually lost in the teenage years. Life expectancy is variable; one report found that approximately two-thirds of individuals with SMA type 2 were alive at age 25 years [42].

Patients with SMA type 2 generally have three copies of the *SMN2* [11,16,45,46].

SMA type 3 — SMA type 3 (juvenile form; Kugelberg-Welander disease) accounts for approximately 30 percent of cases [1,16,25]. Onset usually occurs between age 18 months and adulthood. Affected individuals achieve independent ambulation. Presenting symptoms usually reflect proximal weakness affecting the legs more than the arms, such as falls and trouble climbing stairs. Many lose the ability to stand or walk independently with time and progression of weakness, becoming wheelchair dependent [47]. Ambulatory patients may develop foot deformity [48]. However, most do not develop scoliosis or debilitating respiratory muscle weakness. SMA type 3 is associated with a normal lifespan [42,49].

Patients with SMA type 3 generally have three or four copies of *SMN2* [11,16].

SMA type 4 — SMA type 4 (late onset) accounts for less than five percent of cases [16,25]. Age of onset is not strictly defined; some experts use onset at age ≥30 years to separate SMA type 4 from SMA type 3, and others accept juvenile onset [16,42,50]. SMA type 4 is on the mild end of the SMA spectrum; all motor milestones are achieved, ambulation is usually maintained throughout life, and lifespan is normal [1,49,51-53]. Patients with SMA type 4 generally have four to eight copies of *SMN2* [11,16].

DIAGNOSIS

The diagnosis of SMA should be suspected for any infant with unexplained weakness or hypotonia [25]. Additional clues suggesting the diagnosis in infants, children, or adults include a history of motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia or areflexia, tongue fasciculations, and signs of lower motor neuron disease on examination [1]. Molecular genetic testing with targeted mutation analysis can confirm the diagnosis of SMA by detection of homozygous deletions of exons 7 of *SMN1* [1,25,32]. The exon 7 deletion is by far the most common mutation in SMA, but point mutations also occur. Thus, sequencing of *SMN1* to look for a point mutation should be pursued if the clinical manifestations are typical of SMA and only a single deletion is identified.

The absence of a pathogenic mutation in *SMN1* casts serious doubt on the diagnosis. In this situation, it is imperative to consider other conditions in the differential diagnosis (eg, spinal muscular atrophy with respiratory distress type 1). (See 'Differential diagnosis' below.)

Electromyography and muscle biopsy were once a standard part of the diagnostic evaluation for SMA but are seldom needed now that molecular genetic testing is widely available. Electromyography in SMA shows abnormal spontaneous activity with fibrillations and positive sharp waves [54,55]. The mean duration and amplitude of motor unit action potentials are increased, and many are polyphasic. Muscle biopsy reveals large groups of circular atrophic type 1 and 2 muscle fibers interspersed among fascicles of hypertrophied type 1 fibers [54]. The enlarged fibers have been reinnervated by the sprouting of surviving nerves and are three to four times larger than normal. Histologic diagnosis may be more challenging to make in the newborn infant because only widespread atrophy of muscle fibers may be seen, but a later repeat biopsy usually demonstrates the mixture of hypertrophied and atrophic fibers seen after reinnervation occurs.

SMA was added to the Recommended Uniform Screening Panel (RUSP) for newborns in the United States (US) in 2018, and most states in the US now have active newborn screening for SMA. National or pilot newborn screening programs for SMA are also operational in most Canadian provinces, several European countries, Taiwan, and Australia [56-60]. The feasibility and utility of newborn screening for SMA using different high-throughput molecular techniques is supported by results from several prospective pilot studies [61,62]. Newborn screening programs identify approximately 95 percent of newborns with SMA through detection of the exon 7 deletion in *SMN1* using quantitative PCR (qPCR) [56,63]. Newborns with point mutations in *SMN1* will not be detected [61].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SMA varies according to the age of onset.

Onset from prenatal to six months of age — The differential diagnosis for prenatal and neonatal SMA (types 0 and 1) includes other causes of floppy (hypotonic) infants [1]. Many neuromuscular conditions can present in newborns (table 3).

X-linked infantile spinal muscular atrophy — X-linked infantile spinal muscular atrophy (XL-SMA or SMAX2) is a rare disorder characterized by congenital hypotonia, areflexia, congenital contractures and/or fractures, and loss of anterior horn cells [64,65]. The disease course in XL-SMA is similar to the severe forms of classic neonatal SMA (SMA types 0 and 1) [65]. The disorder is associated with mutations in the gene for ubiquitin activating enzyme 1 (called *UBA1* or *UBE1*) [66].

Spinal muscular atrophy with respiratory distress type 1 — Spinal muscular atrophy with respiratory distress type 1 (SMARD1), also known as autosomal recessive distal spinal muscular atrophy 1 (DSMA1), is characterized by diaphragmatic paralysis and respiratory failure that presents early in life, generally from one to six months of age [67,68]. There is a high frequency of intrauterine growth retardation and premature birth. Eventration of the diaphragm may be seen on chest radiographs. Clinical deterioration continues for the first two years of life, followed by stabilization or less often by some clinical improvement [68]. While all affected children remain dependent on mechanical ventilation and require full time care, some can participate in daily life activities and schooling. The disorder is caused by biallelic mutations in the immunoglobulin mu binding protein 2 gene (*IGHMBP2*).

Other neuromuscular disorders — Congenital myasthenic syndromes, congenital myopathies, and myelopathies can present with muscle weakness and hypotonia in infancy.

- **Congenital myasthenic syndromes** – Newborns with congenital myasthenia frequently have ptosis, in contrast to patients with the transient disorder. In addition, they typically demonstrate ophthalmoplegia and bulbar and respiratory muscle weakness. Affected infants may have fluctuating generalized hypotonia, weakness, and life-threatening episodes of apnea. Arthrogryposis can be present at birth. (See "Neuromuscular junction disorders in newborns and infants", section on 'Congenital myasthenic syndromes'.)
- **Congenital myopathies** – Congenital myopathies (eg, nemaline myopathy, central core disease, myotubular myopathy, and congenital fiber type disproportion) present with hypotonia and weakness that is greater proximally than distally. Tendon reflexes are decreased in proportion to the weakness. (See "Congenital myopathies".)
- **Congenital myotonic dystrophy** – The congenital form of myotonic dystrophy (DM1) is characterized by profound hypotonia, facial diplegia, poor feeding, arthrogryposis (especially of the legs), and respiratory failure. Affected infants have a characteristic "V" shape of the upper lip that results from facial diplegia. In some cases, DM1 may present before birth as polyhydramnios, talipes equinovarus (clubfoot), and reduced fetal movement. Myotonia is not usually present in the first year of life. Respiratory involvement is common and is the leading cause of death in the neonatal period. (See "Myotonic dystrophy: Etiology, clinical features, and diagnosis", section on 'Congenital DM1'.)
- **Hypoxic-ischemic myelopathy** – Severe hypoxic-ischemic injury can sometimes result in hypotonia or flaccid paralysis with diminished or absent reflexes caused by the death of spinal motor neurons [69]. In these cases, infants typically have encephalopathy and may have seizures or signs of other end-organ damage. (See "Neonatal encephalopathy: Clinical features and diagnosis".)
- **Traumatic myelopathy** – Myelopathy caused by trauma to the high cervical spinal cord is a rare cause of hypotonia in infants. This condition results in flaccid paralysis, which may be asymmetric, and absent reflexes. Physical examination may reveal evidence of trauma, such as bruising or fractures. If no accompanying brain injury is present, the infant will be alert with no cranial nerve abnormalities. A pinprick on the face will elicit a facial grimace but no response below the neck. A useful sign is withdrawal to a noxious stimulus of a limb with no spontaneous activity. Bladder distension, priapism, and absence of sweating below the level of the spinal lesion typically will appear as the myelopathy evolves over several days.

Multisystem disorders — Several multisystem disorders may be associated with muscle weakness and hypotonia in infancy.

- **Glycogen storage disease II** – The classic infantile form of glycogen storage disease II (Pompe disease) is characterized by hypertrophic cardiomyopathy and severe generalized muscular hypotonia that presents during the first few months of life. The tongue may be enlarged. Hepatomegaly also may be present and is usually due to heart failure. (See "Lysosomal acid alpha-glucosidase deficiency (Pompe disease, glycogen storage disease II, acid maltase deficiency)".)
- **Prader-Willi syndrome** – Neonatal hypotonia is one of the hallmark features of Prader-Willi syndrome. The profound hypotonia can lead to asphyxia. Affected infants often have feeding difficulties, including a poor suck, which may lead to failure to thrive. Other common features include a weak cry and genital hypoplasia. The hypotonia associated with Prader-Willi syndrome improves gradually during infancy, unlike SMA type 1 in which progressive deterioration occurs. (See "Prader-Willi syndrome: Management".)
- **Zellweger syndrome** – Newborns with Zellweger syndrome present with a characteristic craniofacial dysmorphism. Neurologic abnormalities include hypotonia and weakness with absent reflexes, severe impairment of hearing and vision, neonatal seizures, and developmental delay. Hepatomegaly is common. (See "Peroxisomal disorders", section on 'Zellweger spectrum disorders'.)

Arthrogryposis multiplex congenita — Arthrogryposis multiplex congenita is a syndrome characterized by contractures of multiple joints [70,71]. It is associated with a heterogeneous group of disorders. Most cases are neurogenic; the remaining cases have connective tissue or mixed mechanisms [72,73]. Neurogenic arthrogryposis can result from neuromuscular disorders, central nervous system disorders, genetic syndromes, and chromosomal aberrations. The severity is variable. Bulbar and respiratory muscle functions are severely affected in some cases, which have a poor prognosis [74]. In others, muscle strength does not deteriorate and may improve. The disorders that result in neurogenic arthrogryposis are genetically heterogeneous. Some patients (6 of 12 in one series) have deletions of *SMN1*, the gene that is associated with SMA [75,76].

Onset six months to childhood — The differential diagnosis for intermediate forms of SMA (ie, SMA type 2 and SMA type 3) involves a number of neuromuscular conditions including myopathies, neuromuscular junction disorders, inflammatory neuropathies, and other motor neuron disorders [25]. Examples include the following:

- **Duchenne and Becker muscular dystrophy** – The clinical onset of weakness with Duchenne muscular dystrophy usually occurs between two and three years of age. Affected children usually present with delayed walking (beyond age 18 months) and frequently have varying degrees of mild cognitive impairment. Muscle weakness affects the proximal before the distal limb muscles. Additional features include cardiomyopathy and conduction abnormalities, bone fractures, and scoliosis. Physical examination reveals pseudohypertrophy of the calf and (occasionally) quadriceps muscles, lumbar lordosis, a waddling gait, shortening of the Achilles tendons, and hyporeflexia or areflexia. The serum creatine kinase level is typically very high (eg, several thousand). Becker muscular dystrophy has a similar presentation to Duchenne, but typically has a later onset and a milder clinical course. (See "Duchenne and Becker muscular dystrophy: Clinical features and diagnosis".)
- **Limb-girdle muscular dystrophy** – Limb-girdle muscular dystrophy (LGMD) includes a number of disorders with heterogeneous etiologies. It is used as a generic term to describe those patients with muscular dystrophy of girdle distribution, having a predominantly proximal distribution of weakness that, early in the course of the disease, spares distal muscles as well as facial and extraocular muscles. Weakness in LGMD may affect the shoulder girdle, the pelvic girdle, or both. Facial weakness is usually mild and, in some cases, totally absent. Intellect is usually normal. (See "Limb-girdle muscular dystrophy".)
- **Myasthenia gravis** – In generalized myasthenia gravis, the weakness may also commonly affect ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles. More than 50 percent of patients present with ocular symptoms of ptosis and/or diplopia. Approximately 15 percent of patients present with bulbar symptoms. Less than 5 percent present with proximal limb weakness alone. Age of onset is characterized by an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance). (See "Clinical manifestations of myasthenia gravis" and "Diagnosis of myasthenia gravis".)
- **Guillain-Barré syndrome** – Guillain-Barré syndrome (GBS) is often triggered by an antecedent infection that evokes an immune response directed towards the myelin or the axon of peripheral nerve. The end result is an acute polyneuropathy. GBS is the most common cause of acute flaccid paralysis in healthy infants and children. GBS has several variant forms. The classic presentation of GBS is one of ascending paralysis with progressive, mostly symmetric muscle weakness and absent or depressed deep tendon reflexes. Atypical variants present with local or regional involvement of particular muscle groups or nerves. (See "Guillain-Barré syndrome in children: Epidemiology, clinical features, and diagnosis".)
- **Non-5q forms of spinal muscular atrophy** – There are a number of rare non-5q spinal muscular atrophies. The non-5q SMAs are genetically and clinically heterogeneous (table 1).
- **Late-onset hexosaminidase A deficiency** – Hexosaminidase A deficiency causes a number of related neurodegenerative disorders characterized by intralysosomal storage of GM2 ganglioside [77]. The acute infantile variant is known as Tay-Sachs disease. Juvenile (subacute), chronic, and adult-onset variants are notable for slower disease progression and variable neurologic phenotypes, which include dystonia, cerebellar degeneration, motor neuron disease, and/or psychosis.

Adult onset — For patients with adult-onset disease, the differential is similar to that of intermediate forms of SMA with onset in childhood (see 'Onset six months to childhood' above) [25]. Additional considerations for adults include later-onset neuromuscular disorders, particularly amyotrophic lateral sclerosis and spinobulbar muscular atrophy.

- **Amyotrophic lateral sclerosis** – The clinical hallmark of amyotrophic lateral sclerosis (ALS) is the combination of upper motor neuron and lower motor neuron signs and symptoms. Upper motor neuron findings of weakness, hyperreflexia, and spasticity result from degeneration of frontal motor neurons. The lower motor neuron findings of weakness, atrophy or amyotrophy, and fasciculations are a direct consequence of degeneration of lower motor neurons in the brainstem and spinal cord. Asymmetric limb weakness is the most common presentation of ALS (80 percent). Bulbar onset, usually manifested as dysarthria or dysphagia, is the next most common pattern (20 percent). However, differences in site and segment (cranial, cervical, thoracic, or lumbosacral) of onset, pattern and speed of spread, and the degree of upper and lower motor neuron dysfunction produce a disorder that is remarkably variable between individuals. Some affected individuals develop cognitive impairment, typically related to frontotemporal executive dysfunction. (See "Clinical features of amyotrophic lateral sclerosis and other forms of motor neuron disease" and "Diagnosis of amyotrophic lateral sclerosis and other forms of motor neuron disease".)
- **Spinobulbar muscular atrophy** – Spinobulbar muscular atrophy (Kennedy disease) is an X-linked disorder characterized with onset from ages 20 to 60 years of slowly progressive weakness and atrophy affecting facial, bulbar and limb muscles that may be predominantly asymmetric, symmetric, proximal, or distal. Associated endocrine disturbances include late-onset gynecomastia, defective spermatogenesis, and a hormonal profile consistent with androgen resistance. (See "Diagnosis of amyotrophic lateral sclerosis and other forms of motor neuron disease", section on 'Spinobulbar muscular atrophy'.)

SUPPORTIVE THERAPY —

Supportive therapy is directed at providing nutrition and respiratory assistance as needed and treating or preventing complications of weakness [23,25,78,79]. Recommended evaluations at baseline include assessments of nutritional and feeding requirements, respiratory function, sleep, activities of daily living, and orthopedic status. Individuals with SMA should be evaluated at least every six months, and those with more severe weakness should be evaluated more frequently.

Pulmonary — Respiratory muscle weakness often results in difficulty clearing lower respiratory secretions and hypoventilation during sleep [80]. Important interventions include methods for mobilization and clearance of airway secretions, and respiratory support.

- Secretion mobilization and clearance techniques involve manual or mechanical chest physiotherapy with postural drainage, and manual cough assistance and/or use of a mechanical insufflation/exsufflation device [80].
- Noninvasive nasal ventilation is an alternative to tracheostomy and conventional ventilator support in some children with respiratory failure [26,81,82]. Early intervention with noninvasive respiratory support can improve quality of life for infants with SMA type 1 [43,80]. When noninvasive ventilation becomes insufficient, decisions about initiating ventilator support should be individualized, taking into account the medical facts and the values of the family or guardians, in consultation with a palliative care team [80].

Nutrition and gastrointestinal — Bulbar dysfunction with impaired feeding and risk of aspiration and failure to thrive is universal in SMA type 1 [1]. Bulbar dysfunction can develop over time into a serious concern in SMA type 2. Additional common problems in SMA, particularly for those who cannot sit or stand, include gastrointestinal reflux, delayed gastric emptying, and constipation. Ambulatory patients are less prone to nutritional and gastrointestinal complications.

Management includes changing food consistency to improve food intake and protect against aspiration. Early gastrostomy in infants with SMA type 1 can help to maintain proper nutrition and reduce the risk of aspiration.

Orthopedic and musculoskeletal — Physical therapy may be helpful. Spinal bracing can be used to delay the development of progressive scoliosis that is caused by muscle weakness. However, spinal bracing applied to patients with SMA types 1 or 2 while in the sitting position significantly reduces expiratory tidal volume, and thus it should be used cautiously [83]. Surgical repair of scoliosis may be an option but there is no consensus about efficacy [16].

DISEASE-MODIFYING THERAPY —

Treatment for SMA has been mainly supportive, but disease-modifying therapy (DMT) with nusinersen, onasemnogene abeparvovec, and risdiplam is now available.

Approach to choosing DMT — For infants and very young children (age <2 years) with SMA who are not ventilator-dependent, we recommend offering treatment with DMT using either nusinersen, onasemnogene abeparvovec, or risdiplam where these are available. The efficacy of onasemnogene abeparvovec for children two years of age and older is unknown. For older children (age ≥2 years) and adults with moderate symptoms of SMA, we suggest treatment with nusinersen or risdiplam. The choice among these treatments should be individualized according to drug cost, availability, adverse effect profile, burden of administration, and patient values and preferences, using a process of shared decision-making. (See 'Nusinersen' below and 'Onasemnogene abeparvovec' below and 'Risdiplam' below.)

Short-term trials have shown modest efficacy for these treatments in a disease that, left untreated, leads to profound disability and death. However, these therapies are extraordinarily expensive. Direct comparisons between these drugs are lacking.

Children or adults who are ventilator-dependent, need enteral feeds, or have severe contractures or scoliosis may be too debilitated to derive benefit from these disease-modifying therapies. Given the uncertain benefit and unknown long-term risks for individuals with very advanced SMA (eg, those on chronic assisted ventilation) and older children and adults with mild SMA, we advise individualized treatment decisions for these patients. As an example, a patient with impending loss of ambulation

may place a higher value on potential benefits and a lower value on the burden and harms of treatment, while an adult with mild symptoms may place a higher value on avoidance of burdens and harms of treatment until more is known about disease-modifying drugs in this setting.

Administration differs:

- Nusinersen is given by intrathecal injection with maintenance dosing every four months after the initial four loading doses, which are given over eight weeks.
- Onasemnogene abeparvovec is given as a one-time intravenous infusion.
- Risdiplam is given daily by mouth using a syringe.

Preliminary studies suggest that combination therapy using agents with different mechanisms of action (eg, onasemnogene and nusinersen) may be beneficial for SMA, but larger and longer-term studies are needed to determine the feasibility of this approach [84-86].

Nusinersen — Nusinersen is an antisense oligonucleotide that modifies splicing of the *SMN2* gene to increase production of normal, full-length survival motor neuron protein, which is deficient in SMA. (See 'Genetics' above.)

Nusinersen is approved for marketing in several countries and regions including the United States, Canada, Brazil, Europe, Australia, and Japan.

- **Effectiveness** – The multicenter, double-blind, ENDEAR trial enrolled infants with SMA who were seven months of age or younger at screening, excluding those with peripheral oxygen desaturation (ie, oxygen saturation below 96 percent without ventilation support). Infants were randomly assigned to intrathecal nusinersen treatment or sham procedure (control) in a 2 to 1 ratio. In the final analysis, improvement in motor milestones was noted in 37 of 73 (51 percent) infants treated with nusinersen, versus 0 of 37 (0 percent) infants who received the sham procedure [87]. In the nusinersen treatment group, motor milestones achieved included head control (22 percent), rolling over (10 percent), sitting independently (8 percent), and standing (1 percent). In the sham procedure group, no infants achieved motor milestones. The proportion of infants who died or received permanent assisted ventilation was lower in the nusinersen group compared with the sham group (39 versus 68 percent, hazard ratio 0.53, 95% CI 0.32-0.89).

  The evidence of benefit for older children with SMA is based upon a positive interim analysis of 126 patients (84 patients assigned to nusinersen treatment and 42 assigned to sham control) in the double-blind CHERISH trial, which enrolled children 2 to 12 years of age with SMA [88]. Eligible children had the onset of symptoms at greater than six months of age, were able to sit independently but never walked independently, and had an estimated life expectancy of more than two years (table 4). Exclusion criteria included respiratory insufficiency (ie, need for invasive or noninvasive ventilation for more than 6 hours per 24-hour period), need for a gastric feeding tube for majority of feeds, severe contractures or severe scoliosis, or medical disability (eg, wasting or cachexia). The trial was stopped early for benefit after a prespecified interim analysis. In the final analysis, patients who received nusinersen had a mean improvement on the Hammersmith Functional Motor Scale Expanded (HFMSE) of 3.9 points at month 15 of treatment, versus a decline of 1.0 points for those in the control group, for a mean difference of 4.9 points (95% CI 3.1-6.7), where a difference of ≥3 points was considered clinically meaningful [88].

  Treatment benefit appears to be greater for children younger than two years of age at the start of nusinersen treatment, as shown in a study of 143 patients from the SMArtCARE registry with early-onset SMA who were unable to sit independently prior to treatment [89]. During the follow-up period of up to 38 months of treatment, major improvements in motor function were reported, mainly in children <2 years of age at the start of treatment. The ability to sit independently was achieved by 25 percent of children overall (33 percent in children younger than two years and 11 percent in the older cohort). Bulbar and respiratory function did not show similar improvement, and the need for tube feeding and intermittent ventilator support increased over time.

  Evidence of benefit for adults with SMA comes from a prospective observational cohort study patients, ages 16 to 65 years, who received nusinersen and had complete data available at six months (n = 124), 10 months (n = 92), and 14 months (n = 57) [90]. A clinically meaningful improvement, defined as an increase of 3 points or more in the HFMSE score compared with baseline, was observed with nusinersen treatment at six months in 28 percent, at 10 months in 35 percent, and at 14 months in 40 percent of patients.

- **Adverse effects** – The most common adverse events associated with intrathecal nusinersen treatment were respiratory tract infections and constipation [91]. The prescribing label notes an increased risk for thrombocytopenia, coagulation abnormalities, and renal toxicity [92]. Thus, laboratory testing for platelet count, prothrombin time, activated partial thromboplastin time, and quantitative spot urine protein is recommended at baseline and prior to each dose.
- **Administration** – Nusinersen is administered by intrathecal injection; each dose is 12 mg per 5 mL supplied in a single vial [92]. Treatment is initiated with four loading doses; the first three loading doses are given at 14-day intervals, while the fourth loading dose is given 30 days after the third. Thereafter, a maintenance dose is given once every four months. The cost of each dose is listed as $125,000.

Onasemnogene abeparvovec — Another approach to treating SMA involves gene replacement of mutated *SMN1* with normal *SMN1*. Onasemnogene abeparvovec is a recombinant adeno-associated viral vector containing complementary DNA encoding the normal human survival motor neuron protein (SMN1).

Onasemnogene abeparvovec was approved by the FDA in 2019 for the treatment of children less than two years of age with SMA who have bi-allelic mutations in *SMN1* [93].

- **Efficacy** – Onasemnogene abeparvovec (formerly called AVXS-101) was tested in an open-label study of 15 infants (age range 1 to 8 months) with SMA who had homozygous *SMN1* deletions of exon 7 [94]. The patients were assigned to high-dose (n = 12) or low-dose (n = 3) one-time intravenous administration of onasemnogene abeparvovec. At 20 months of age, all 15 patients were alive and did not require permanent mechanical ventilation, whereas the rate of survival without permanent ventilation in a historical control group was only 8 percent. Patients in the high-dose cohort exhibited an increase from baseline in motor function compared with a decrease in the historical controls. Unlike historical controls, a number of treated infants achieved motor milestones including sitting unassisted (n = 11), feeding orally (n = 11), rolling over (n = 9), and walking independently (n = 2). In an extension study of 13 patients, with approximately five years of follow-up since dosing, all 10 patients in the high-dose group maintained previously acquired milestones without need for permanent ventilation, while two patients reached a new milestone of standing with assistance [95].

  Additional evidence of efficacy comes from results of the open-label STR1VE-US and STR1VE-EU studies [96,97]. STR1VE-US treated 22 patients with infantile-onset SMA (mean age at enrollment 3.7 months) who were able to feed by mouth exclusively and who did not require noninvasive ventilatory support at enrollment [96]; STR1VE-EU included 32 patients with infantile-onset SMA (mean age at enrollment 4.1 months); patients needing feeding support or noninvasive ventilatory support for less than 12 hours daily were eligible, allowing for inclusion of patients with more severe disease than STR1VE-US [97]. At age 14 months, survival without need for permanent ventilation was achieved by 20 patients (91 percent, 95% CI 79-100) in STR1VE-US and 31 patients (97.5 percent, 95% CI 91-100) in STR1VE-EU, compared with 6 of 23 (26 percent, 95% CI 8-44) in untreated historical controls. At the 18 month-of-age study visit, the ability to sit without support was achieved by 13 patients (59 percent, 97.5% CI 36-100) in STR1VE-US and 14 patients (44 percent, 97.5% CI 26-100) in STR1VE-EU, compared with 0 of 23 untreated historical controls.

  Larger and longer-term studies are needed to define the benefits and risks of this therapy.

- **Adverse effects** – The most common adverse effects with onasemnogene abeparvovec are elevated aminotransferases (approximately 27 percent) and vomiting (approximately 7 percent). The label includes a boxed warning about the potential for serious liver injury; rare cases of fatal acute liver failure have been reported [98,99]. Transient decreases in platelet counts, sometimes meeting criteria for thrombocytopenia, and increased serum troponin have also been observed. Several cases of severe thrombocytopenia and microangiopathic hemolysis, including one fatality, have also been reported [100,101]. (See 'Drug-induced thrombotic microangiopathy (DITMA)', section on 'Gene therapy (mechanism unclear)'.)

  Increases in cardiac troponin I levels, up to 0.176 microg/L, have been observed in clinical trials, although the clinical relevance of this is unknown [99].

  In an extension study of 13 children with approximately five years of follow-up, serious adverse events were primarily related to SMA disease, including acute respiratory failure and pneumonia [95].

- **Administration** – Onasemnogene abeparvovec is given as a one-time single dose of 1.1×10^{14} vector genomes/kg by intravenous infusion over 60 minutes to patients with clinically stable baseline health status including hydration, nutrition, and absence of infection [99]. Administration should be postponed in patients with concurrent infection. Systemic glucocorticoids equivalent to oral prednisolone 1 mg/kg per day for 30 days should be started one day prior to onasemnogene infusion [99].

  There are comprehensive instructions regarding onasemnogene abeparvovec administration, laboratory testing, and monitoring to assess safety. These include baseline platelet count, serum troponin-I level, and anti-adeno-associated virus (AAV) antibody testing, along with baseline levels and monitoring after onasemnogene infusion for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Detailed information regarding treatment indication, dosing, and monitoring for onasemnogene abeparvovec can be found at https://www.fda.gov/vaccines-blood-biologics/zolgensma.

  The estimated cost of one dose of onasemnogene abeparvovec is US $2,125,000 [102].

Risdiplam — Risdiplam is a small molecule *SMN2* splicing modifier that binds two sites in *SMN2* pre-messenger RNA, thereby correcting the splicing deficit of *SMN2*, leading to increased levels of full-length SMN protein. Risdiplam is approved by the FDA for the treatment of SMA in pediatric and adult patients [103].

- **Efficacy** – An open-label study (FIREFISH) of risdiplam included 21 symptomatic infants with SMA type 1 who were one to seven months of age at enrollment [104]. After 12 months of treatment at the higher dose (0.2 mg/kg per day), the number able to sit without support for at least five seconds was 7 of 17 patients (41 percent), and the number alive without permanent ventilation for both high and low dose groups was 19 of 21 patients (90 percent). At 12 months of follow-up, three infants had died, and a fourth infant died during safety follow-up at 23.8 months. These outcomes were better than those expected from the natural history of SMA disease progression. A subsequent open-label study (FIREFISH part 2) from the same investigators treated 41 infants with SMA type 1 using the higher dose of risdiplam (0.2 mg/kg per day) [105]. After 12 months of treatment, the proportion of patients able to sit without support for at least five seconds was 29 percent, compared with none expected based upon the natural history of SMA; the proportion who survived without permanent ventilation was 85 percent, compared with a natural history performance criterion of 42 percent, which was the upper limit of the 90 percent confidence interval for this outcome among 40 historical controls. Secondary analysis at 24 months, with 38 infants ongoing in the study, suggested continued improvement in motor function and achievement of motor milestones [106]. As an example, the proportion of patients able to sit without support for at least 30 seconds was 44 percent, though none could stand or walk alone.

  A controlled trial (SUNFISH) randomly assigned 180 patients ages 2 to 25 years with SMA type 2 or nonambulatory SMA type 3 to treatment with risdiplam or placebo in a 2:1 ratio [107]. Outcome (motor function) was assessed by the 32-item Motor Function Measure score (MFM36). At one year, risdiplam treatment led to clinically meaningful improvement, with an average increase in MFM36 score of 1.36, compared with an average 0.19 decrease in MFM36 score for the placebo group (treatment difference 1.55, 95% CI 0.30-2.81).

- **Adverse effects** – In patients with later-onset SMA, the most common adverse effects were fever, diarrhea, and rash [108]. In patients with infantile-onset SMA, similar adverse effects were seen, along with upper respiratory tract infection, pneumonia, constipation, and vomiting.
- **Administration** – Risdiplam is available as an oral solution and a tablet. The oral solution is given by mouth once a day using an oral syringe. The recommended daily dose is determined by age and body weight [108]:
  - For patients less than two months of age, the dose is 0.15 mg/kg daily.
  - For patients two months to less than two years of age, the dose is 0.2 mg/kg daily.
  - For patients two years of age and older weighing less than 20 kg, the dose is 0.25 mg/kg daily.
  - For patients two years of age and older weighing 20 kg or more, the dose is 5 mg daily.

  Risdiplam 5 mg tablet is intended only for patients prescribed the 5 mg dose. The tablet can be swallowed whole with water or dispersed in non-chlorinated drinking water.

GENETIC COUNSELING —

Affected individuals with SMA and their parents should be referred for genetic counseling, which may be challenging. Occasionally, carriers have normal dosage studies for the *SMN1* deletion because they have a deletion on one homologue and a *SMN1* gene duplication on the other. Studies in the extended family are usually required to clarify these situations. There is also a significant de novo mutation rate (1.7 percent).

The American College of Medical Genetics recommends offering carrier testing to all couples regardless of race or ethnicity [109,110]. The American College of Obstetricians and Gynecologists (ACOG) recommends that screening for SMA should be offered to all women who are considering pregnancy or are currently pregnant [111].

PREGNANCY —

As noted earlier, all SMA types are associated with a restrictive, progressive respiratory insufficiency. Thus, pregnancy in women with SMA is associated with increased risk because of impaired respiratory function, which is further limited in many cases by kyphoscoliosis and wheel chair dependency [112]. In addition, limited retrospective data suggest that pregnancy in women with SMA is often complicated by preterm labor [113] and an increased frequency of urinary tract infections [114].

Despite these issues, no deleterious effects have been detected with respect to fetal outcome [112,113]. Successful pregnancies have been reported in women with SMA who have forced vital capacities of 50 to 70 percent of predicted values [115-117].

Ideally, such pregnancies should be managed by obstetricians and anesthesiologists familiar with neuromuscular disorders [112]. There are no guidelines regarding mode of delivery. Successful outcomes have been reported with both cesarean section and vaginal delivery [113,114]. Spinal and epidural anesthesia may be difficult because of severe spine deformity [114]. However, there is no evidence of an increased risk of malignant hyperthermia in SMA [112].

Women with SMA may experience worsening of muscle weakness after the second trimester and/or delayed postpartum recovery [113,116]. In one report, an uneventful pregnancy and cesarean section was followed by extreme muscle weakness with dyspnea and bulbar involvement lasting one to two weeks [116]. Motor function then improved to baseline.

PROGNOSIS —

SMA encompasses a spectrum of phenotypes ranging from severe forms with early onset to milder forms with later onset (table 2). The natural history of SMA according to phenotype is summarized as follows (see 'Clinical features' above):

- SMA type 0, with prenatal onset, is associated with early death from respiratory failure, usually within weeks after birth.
- SMA type 1, with onset between birth and age six months, leads to death from respiratory failure before the age of two years.
- SMA type 2, with onset between 3 and 15 months of age, is notable for inability to achieve independent walking or standing but is compatible with survival into adulthood. Most affected individuals live to age 25 years.
- SMA type 3, with onset between age 18 months and adulthood, is characterized by slowly progressive proximal weakness, which may lead to loss of independent ambulation, and a normal lifespan.
- SMA type 4, with adult onset, is otherwise similar to SMA type 3 and is associated with a normal lifespan.

The eventual impact of novel disease-modifying therapy (eg, nusinersen) for ameliorating the expected course of SMA is uncertain. (See 'Nusinersen' above.)

Limited data suggest that survival has increased in patients with SMA type 1 born from 1995 through 2006 compared with those born from 1980 to 1994 [43]. Ventilation for >16 hours a day, use of mechanical insufflation-exsufflation device, and gastrostomy tube feeding were significantly and independently associated with prolonged survival, while year of birth was not. Thus, longer survival in the later time period appears to be related to more aggressive care.

SOCIETY GUIDELINE LINKS —

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Spinal muscular atrophy".)

SUMMARY AND RECOMMENDATIONS

- **Description and cause** – Spinal muscular atrophy (SMA) is characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy. The inheritance pattern of the common forms of SMA is autosomal recessive. These forms are caused by biallelic deletions or mutations in the *SMN1* gene on chromosome 5q13. The differences in SMN protein and phenotypic expression appear to be related in part to a modifying gene (*SMN2*) that lies close to the *SMN1* gene (figure 1). The rare non-5q spinal muscular atrophies, such as X-linked infantile spinal muscular atrophy, are genetically and clinically heterogeneous (table 1). (See 'Genetics' above.)
- **Phenotypes** – SMA phenotypes are classified as types 0 through 4 (table 2) depending upon the age of onset and clinical course. (See 'Clinical features' above.)
  - SMA type 0 designates prenatal onset of SMA, which presents at birth with severe weakness and hypotonia, and often with areflexia. No motor milestones are achieved. Death occurs from respiratory failure by age six months, and usually by one month. (See 'SMA type 0' above.)
  - SMA type 1 (infantile spinal muscular atrophy or Werdnig-Hoffmann disease) typically presents after birth but before age six months. Symptoms progress rapidly, and the majority of infants die before two years of age from respiratory failure. (See 'SMA type 1' above.)
  - SMA type 2 (intermediate form) and SMA type 3 (Kugelberg-Welander disease) have a less severe course. SMA type 2 presents between 3 and 15 months of age. SMA type 3 typically presents from 18 months of age until adulthood and progresses to a chronic course. (See 'SMA type 2' above and 'SMA type 3' above.)
  - SMA type 4 is notable for adult onset and is the mildest form. (See 'SMA type 4' above.)
- **Neurologic manifestations** – Patients with all forms of SMA have diffuse symmetric proximal muscle weakness that is greater in the lower than upper limbs and absent or markedly decreased deep tendon reflexes. Infants with SMA type 1 have a severe symmetric flaccid paralysis and are unable to sit unsupported. All SMA types, particularly SMA type 1, may be associated with restrictive lung disease. (See 'Clinical features' above.)
- **Genetic testing** – Molecular genetic testing can confirm the diagnosis in infants and children with suspected SMA by detection of homozygous deletions of exons 7 of the *SMN1* gene. (See 'Diagnosis' above.)
- **Differential diagnosis** – The differential diagnosis of SMA is broad and varies according to age of onset. (See 'Differential diagnosis' above.)
  - **Onset from prenatal to age six months** – The differential includes other neuromuscular conditions that can present in newborns (table 3). Of particular importance are the following conditions (see 'Onset from prenatal to six months of age' above):
    - X-linked infantile spinal muscular atrophy
    - Spinal muscular atrophy with respiratory distress type 1
    - Other neuromuscular disorders (eg, congenital myasthenic syndromes, congenital myopathies, hypoxic-ischemic myelopathy, traumatic myelopathy)
    - Multisystem disorders causing muscle weakness and hypotonia (eg, lysosomal acid maltase deficiency, Prader-Willi syndrome, Zellweger syndrome)
    - Arthrogryposis multiplex congenita
  - **Onset from six months through childhood** – For onset in this age group, the differential of SMA involves a number of neuromuscular conditions. Examples include Duchenne and Becker muscular dystrophy, limb-girdle muscular dystrophy, myasthenia gravis, Guillain-Barré syndrome, rare non-5q spinal muscular atrophies (table 1), and late onset hexosaminidase A deficiency. (See 'Onset six months to childhood' above.)
  - **Adult onset** – The differential includes later-onset neuromuscular disorders, particularly amyotrophic lateral sclerosis and X-linked spinobulbar muscular atrophy. (See 'Onset six months to childhood' above and 'Adult onset' above.)
- **Supportive therapy** – Treatment for SMA has been mainly supportive and directed at providing nutrition and respiratory assistance as needed and treating or preventing complications of weakness. (See 'Supportive therapy' above.)
- **Disease-modifying therapy (DMT)** – Nusinersen is approved in the United States and several other regions and countries around the world; onasemnogene abeparvovec and risdiplam are approved in the United States. Direct comparisons between nusinersen, onasemnogene abeparvovec, and risdiplam are lacking. Nusinersen is given by intrathecal injection with maintenance dosing every four months after the initial four loading doses, which are given over eight weeks. Onasemnogene abeparvovec is given as a one-time intravenous infusion. Risdiplam is given daily by mouth using a syringe. (See 'Nusinersen' above and 'Onasemnogene abeparvovec' above and 'Risdiplam' above.)
  - For infants and very young children with SMA who are not ventilator-dependent, we recommend treatment with DMT using either nusinersen, onasemnogene abeparvovec, or risdiplam where available (**Grade 1B**). For older children (age ≥2 years) and adults with moderate symptoms of SMA, we suggest treatment with nusinersen or risdiplam (**Grade 2C**). The efficacy of onasemnogene abeparvovec for children age ≥2 years is unknown. (See 'Approach to choosing DMT' above.)
  - The choice among these treatments should be individualized according to drug cost, availability, adverse effect profile, burden of administration, and patient values and preferences, using a process of shared decision-making. Short-term trials have shown modest efficacy for these treatments in a disease that, left untreated, leads to profound disability and death. However, these therapies are extraordinarily expensive. (See 'Approach to choosing DMT' above and 'Nusinersen' above and 'Onasemnogene abeparvovec' above and 'Risdiplam' above.)
- **Genetic counseling** – Affected individuals with SMA and their parents should be referred for genetic counseling. (See 'Genetic counseling' above.)

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Topic 6146 Version 63.0