Spinal Muscular Atrophy

Contents

Spinal muscular atrophy (SMA) is a disorder characterized by degeneration of lower motor neurons and occasionally bulbar motor neurons, leading to progressive limb and trunk paralysis as well as muscular atrophy. It is a clinically and genetically heterogeneous group of neuromuscular diseases. It is the second most common lethal autosomal recessive disorder after cystic fibrosis in Caucasian populations with an overall incidence of 1 in 10,000 live births and a carrier frequency of approximately 1 in 50 (Biros and Forrest 1999).

Synonyms and Related Disorders

Adult SMA; Arthrogryposis multiplex congenita-SMA; Congenital axonal neuropathy; Dubowitz disease; Kugelberg-Welander disease; Werdnig-Hoffman disease

Genetics/Basic Defects

1. Inheritance
    1. Autosomal recessive in most cases (SMA1, SMA2, SMA3) (Crawford and Pardo 1996)
    2. Autosomal dominant in both juvenile and adult form, representing 2% of infantile and about 30% of adult SMA (Pearn 1978)
    3. X-linked infantile spinal muscular atrophy (Xp11.3-q11.2) (Dressman et al. 2007)
2. Caused by mutation or deletion of *survival motor neuron-1* (*SMN1*) (Lefebvre et al. 1995)
3. Mutation in all three forms (SMA1, SMA2, and SMA3) mapped to chromosome 5q13 (SMA critical region) (Roy et al. 1995; Brahe and Bertini 1996)
4. SMN deletions
    1. High frequency of *SMN* deletions in SMA patients (92.8%) provides a direct and accurate genetic test for:
        1. Diagnostic confirmation of SMA
        2. Prenatal prediction of SMA
    2. Homozygous deletion of *SMN* observed in:
        1. Atypical forms of SMA associated with congenital heart defects
        2. Arthrogryposis
        3. Some cases of congenital axonal neuropathy
        4. Some patients affected with adult form of SMA
    3. Rare cases of homozygous *SMN* exon 7 deletion or conversion reported in

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asymptomatic relatives of haploidentical type II or III SMA patients
4. Absence of deletion of the *SMN* gene or linkage to chromosome 5q in (Zerres et al. 1997):
    1. SMA associated with diaphragmatic involvement
    2. SMA with olivopontocerebellar atrophy
    3. Autosomal dominant form of SMA
    4. Amyotrophic lateral sclerosis
    5. Post-polio syndrome
5. Molecular-phenotype correlation (Lorson et al. 2010; MacKenzie 2010)
    1. Phenotype of SMA associated with disease-causing mutations of the *SMN* gene spans a continuum without a clear delineation of subtypes.
    2. The severity of the SMA phenotype inversely correlated with:
        1. *SMN2* copy number: The greater the *SMN2* copy number (both in infants and children with spinal muscular atrophy and in mouse models), the milder the disease.
        2. The level of full-length SMN protein produced by *SMN2* (~10–15% compared with *SMN1*).

Clinical Features

1. Variability of clinical features and severity (Arnold et al. 2015):
    1. The predominant clinical features of SMA: muscle weakness and atrophy attributed to motor neuron dysfunction and loss.
    2. Weakness: usually symmetric and proximally predominant.
    3. The spectrum of severity: ranges from mild proximal limb weakness noticed in adulthood to severe generalized weakness with respiratory failure in the neonatal period.
    4. Lower limbs: more involved than upper limbs, and bulbar and respiratory weakness usually occurs in patients with more severe limb weakness.
    5. Onset and progression of weakness: distinct from many other motor neuron disorders in that there is usually a presymptomatic period in all but the most severe cases (type 0), followed by rapidly progressive functional loss and a later relatively static phase with slow progression.
2. Existing classification system based on age of onset of symptoms, useful for prognosis and management (Tsao 2013):
    1. Congenital axonal neuropathy (Korinthenberg et al. 1997)
        1. Prenatal onset of SMA
        2. Decreased fetal movement
        3. Maternal polyhydramnios
        4. Severe muscle weakness (hypotonia)
        5. Absence of movement
        6. Joint contractures
        7. Facial diplegia
        8. Ophthalmoplegia
        9. Respiratory failure requiring immediate endotracheal intubation and ventilation
        10. Death from respiratory failure within days
    2. Arthrogryposis multiplex congenita-SMA (Burglen et al. 1996)
        1. Prenatal onset of SMA
        2. Decreased fetal movement
        3. Maternal polyhydramnios
        4. Breech presentation
        5. Severe muscular weakness (hypotonia)
        6. Arthrogryposis multiplex congenita
        7. Absence of movement except for extraocular and facial movement
        8. Death from respiratory failure before 1 month of age
    3. SMA1 (acute spinal muscular atrophy, Werdnig-Hoffman disease) (Byers and Banker 1961; Thomas and Dubowitz 1994)
        1. Represents about 30% of all SMA cases
        2. Onset before 6 months of age
        3. The most severe form with fatal outcome
        4. Severe generalized muscular weakness (hypotonia)
        5. Lack of motor development

6. Mild joint contractures at the knees and rarely at the elbows
7. Most severely affected neonates:
    1. Difficulty in sucking and swallowing
    2. Abdominal breathing
8. Facial muscles spared completely with a bright, normal expression
9. Ocular muscles and the diaphragm not involved until late in the course of the disease
10. Fasciculation of the tongue seen in most but not all cases
11. Intercostal paralysis with severe collapse of the chest: the rule
12. Affected children unable to sit without support
13. Absence of tendon reflexes (areflexia)
14. Normal intelligence
15. Usually die within 2 years due to the following:
    1. Feeding difficulty
    2. Breathing difficulty

4. SMA2 (chronic infantile spinal muscular atrophy, Dubowitz disease)
    1. Represent about 45% of SMA cases
    2. Onset between 6 and 12 months
    3. The intermediate form (a more slowly progressive generalized disease with a variable prognosis)
    4. Poor muscle tone at birth or within first 2 months of life
    5. Slow attainment of motor milestones
        1. Not sitting independently by age 9–12 months
        2. Not standing by 1 year of age
    6. Frequent tongue fasciculation and atrophy
    7. Common finger trembling and general flaccidity
    8. Diminished or absent deep tendon reflexes
    9. Intact sensation
    10. Loss of the ability to sit independently by the mid-teens
    11. Slow or arrest of clinical progression
    12. Severe scoliosis if untreated
    13. Defect in respiratory ventilation
    14. Highly variable life expectancy, ranging up to adult life in some cases
5. SMA3 (juvenile spinal muscular atrophy, Kugelberg-Welander disease) (Kugelberg and Welander 1956)
    1. Represents about 8% of all SMA cases
    2. Childhood onset after 12 months (usually after 18 months to 30 years of life)
    3. The mild chronic form
    4. Motor milestones
        1. Ability to walk but frequent fall on walking
        2. Trouble walking upstairs and downstairs at age 2–3 years
    5. Muscle weakness
        1. Proximal muscle weakness associated with muscle atrophy
        2. Legs more severely affected than the arms
    6. Normal sensation
    7. No evidence of upper motor neuron involvement
    8. Hypertrophy of the calves in about 25% of cases
    9. Prognosis generally correlates with the maximum motor function attained.
    6. SMA4 (adult SMA)
        1. Adult onset (after 20 or 30 years of age)
        2. Muscle weakness (after 30 years of age)
        3. Clinical features similar to those described for SMA3 with evidence of lower motor neuron involvement
            1. Tongue fasciculations
            2. Muscle atrophy
            3. Depressed deep tendon reflexes
            4. Normal sensation

3. Dubowitz classification of childhood SMA (Dubowitz 1995):
    1. Type 1: severe (variable)
    2. Type 2: intermediate (variable)
    3. Type 3: mild (variable)
    4. Type 4.0: normal
4. Subtypes of childhood SMA (Munsat 1991; Nicole et al. 2002; Carre and Empey 2015):
    1. Type 0
        1. Age of onset: prenatal

2. Clinical presentations
    1. Most severe
    2. Lack of fetal movement
    3. Arthrogryposis
    4. Joint contractures
    5. Fatal at birth unless respiratory/medical support is available.
2. Type I
    1. Age of onset: birth to 6 months
    2. Clinical presentations
        1. Severe generalized muscle weakness and hypotonia at birth
        2. Motor milestones: never sit alone
        3. Death from respiratory failure in less than 2 years
3. Type II
    1. Age of onset: 6–12 months
    2. Clinical presentations
        1. Motor milestones: able to sit, unable to walk or stand without aid
        2. Death: >2 years
4. Type III
    1. Age of onset: after 18 months
    2. Clinical presentations
        1. Milder form
        2. Motor milestones: can stand and walk unaided but lose ambulation as disease progresses
        3. Death: adult
5. Type IV
    1. Age of onset: adolescence to adulthood
    2. Clinical presentations: like type III, but rarely diagnosed

5. Consider diagnosis of SMA in infants presenting with the following clinical features:
    1. During neonatal period
        1. Severe hypotonia
        2. Absent movement
        3. Contractures, usually of a mild degree
        4. Evidence of anterior horn cell (i.e., lower motor neuron) involvement
            1. Tongue fasciculations
            2. Absence of deep tendon reflexes
        5. Respiratory failure
        6. Variable cranial nerve involvement usually apparent late in the course
            1. Ophthalmoplegia
            2. Facial diplegia
    2. After neonatal period
        1. Poor muscle tone
        2. Symmetric muscle weakness
            1. Sparing the ocular muscles
            2. Involving the facial muscles and diaphragm late in the course of the disease
        3. Delayed acquisition of motor skills
        4. Evidence of anterior horn (i.e., lower motor neuron) involvement
            1. Tongue fasciculations (seen in only 65% of patients)
            2. Absence of deep tendon reflexes
        5. Normal reaction to sensory stimuli
        6. Normal intelligence
6. Natural history (Lorson et al. 2010; MacKenzie 2010):
    1. Clinical features of the disease are caused by specific degeneration of α-motor neurons in the spinal cord, leading to muscle weakness, atrophy, and, in the majority of cases, premature death.
    2. Most afflicted infants and children, while largely neurologically and completely cognitively intact, grow progressively weaker over time, with many ultimately succumbing to respiratory failure at a young age.
    3. The natural history of SMA has been altered over the past several decades, primarily through supportive care measures, but an effective treatment does not presently exist.
7. Spinal muscular atrophy not linked to *SMN* gene (Wang et al. 2007; Savas et al. 2014):
    1. Scapuloperoneal spinal muscular atrophy
        1. Inheritance (gene locus): autosomal dominant (gene mapped on 12q24.1–q24.31)
        2. Clinical presentations
            1. Congenital absence of muscles
            2. Progressive weakness of scapuloperoneal and laryngeal muscles
    2. Pontocerebellar hypoplasia with spinal muscular atrophy (Barth 1993)
        1. Inheritance (gene locus): autosomal recessive (*VRK1*)
        2. Clinical presentations
            1. Onset at 0–6 months
            2. Cerebellar and brainstem hypoplasia

3. Absent dentate nucleus
4. Neuronal loss in basal ganglia
5. Cortical atrophy

3. X-linked infantile spinal muscular atrophy with arthrogryposis
   1. Inheritance (gene locus): X-linked (gene mapped on Xp11.3–q11.2)
   2. Clinical presentations
      1. Onset at birth or infancy
      2. Contractures
      3. Death before 2 years of age
4. Spinal muscular atrophy with respiratory distress type 1 (Grohmann et al. 2003)
   1. Inheritance (gene locus): autosomal recessive (gene mapped on 11q13.2–q13.4)
   2. Clinical presentations
      1. Onset within the first 3 months of age
      2. Eventuation of the right or both hemidiaphragms
      3. Finger contractures
      4. Pes equinus foot deformities
5. Congenital SMA with predominant lower limb involvement (Fleury and Hageman 1985)
   1. Inheritance (gene locus): autosomal dominant or sporadic (*DYNC1H1*)
   2. Clinical presentations
      1. Arthrogryposis
      2. Weakness, especially distal lower limbs early
      3. Nonprogressive but severe disability
6. Congenital SMA with predominant upper limb involvement (Darwish et al. 1981; Hageman et al. 1993)
   1. Inheritance (gene locus): unknown
   2. Clinical presentations
      1. Arthrogryposis
      2. Weakness, especially distal upper limbs early
      3. Nonprogressive

Diagnostic Investigations

1. Increased serum creatine phosphokinase (CK) activity in about half of the patients with type III SMA
2. Electromyography (EMG)
   1. During voluntary effort
      1. Spontaneous discharge activity in resting muscle
      2. Increased amplitude
      3. Prolonged duration of motor unit potentials
   2. Severe denervation commonly found in older patients
   3. Nerve conduction velocity
      1. Generally considered normal (Emery 1971)
      2. Some decrease in velocity in severe case
3. Muscle histology (Emery 1971)
   1. Denervation changes with small groups of atrophic muscle fibers associated with markedly hypertrophied fibers.
   2. Small angular fibers randomly intermixed with normal-sized fibers.
   3. Atrophic fibers arranged in groups
      1. Usually of uniform fiber type based on the myosin ATPase reaction
      2. Considered as an extensive collateral reinnervation of previously denervated muscle fibers by sprouts from surviving motor neurons
   4. In SMA type III, but not in infantile SMA (type I or II)
      1. Markedly hypertrophic fibers
      2. Excessive variation in fiber size
      3. Internal nuclei
      4. Observation of degenerative changes with necrosis and regenerative fibers associated with proliferative interstitial connective tissue
         1. Interpreted as “pseudomyopathic” changes.
         2. Usually found in patients with high serum levels of CK activity suggesting the presence of a myopathic process secondary to neurogenic process.
         3. These pseudomyopathic changes not observed in other human neurogenic diseases suggest that they can be specific to the molecular mechanism resulting in or associated with juvenile SMA.

4. Neuropathologic features found at autopsy of SMA patients
    1. Loss of the large anterior horn cells of the spinal cord (most striking feature)
    2. Severe degree of central chromatolysis in the remaining surviving motor neurons, appearing as large ballooned cells without stored substances
    3. Other anterior horn cells
        1. Pyknotic
        2. Presence of occasional figures of neuronophagia associated with astrogliosis
        3. Small anterior roots
5. Algorithm of diagnostic tests for a patient suspected to have SMA (D'Amico et al. 2011)
    1. Homozygous SMN1 deletion detected: confirm 5q SMA diagnosis
    2. Homozygous SMN1 deletion not detected
        1. Creatine kinases dosage and electrophysiological tests such as electromyography (EMG), and nerve conduction study, should be performed. If EMG suggests a motor neuron disease, then further testing for SMN mutations should be pursued.
        2. SMN1 gene copy number testing using multiplex ligation-dependent probe amplification (MLPA) or real-time PCR.
        3. If the patient has a single *SMN1* copy, it is mandatory to sequence the coding region of the undeleted allele to identify the second causative mutation, generally subtle sequence variations, including point mutations, insertions, and deletions.
        4. However, in about one third of patients with a typical clinical picture and a single SMN1 copy, the second mutation is not found in *SMN1*/*SMN2* coding region. This finding is more common in type III SMA and might be due to the presence of deep intronic mutations, unidentified so far. Finally, sequence analysis of SMN1 gene is suggested also in those patients who have a typical clinical picture, two *SMN1* copies, and are born to consanguineous parents or originate from genetic isolates. Indeed, rare patients homozygous for *SMN1* subtle mutations have been occasionally reported.
        5. Conversely, in a patient with two *SMN1* copies, SMA diagnosis, related to SMN1 mutations, is virtually excluded, and other motor neuron disorders such as spinal muscular atrophy with respiratory distress (SMARD1), X-linked spinal muscular atrophy, distal SMA, and juvenile amyotrophic lateral sclerosis should be considered.
        6. If the electrophysiological examination excludes a motor neuron disease, the child should be reexamined and must receive additional diagnostic testing considering other disorders.
6. Molecular diagnosis of SMA (Prior and Russman 2011)
    1. Molecular testing for homozygous deletion or mutation of the *SMN1* gene allows efficient and specific diagnosis. In combination with loss of *SMN1*, patients retain variable numbers of copies of a second similar gene, *SMN2*, which produces reduced levels of the survival motor neuron (SMN) protein that are insufficient for normal motor neuron function (Arnold et al. 2015).
    2. The following relatively simple DNA tests enable confirmation of a suspected clinical diagnosis of SMA or prediction of the outcome of a pregnancy in families with a history of SMA (Biros and Forrest 1999).
        1. SSCP analysis
        2. PCR followed by restriction enzyme digestion
    3. Mutation analysis of *SMN1* available on clinical basis.
        1. Used to detect deletion of exons 7 and 8 of *SMN1*
        2. Homologous deletions of exon 7 of *SMN1* in 95% of cases with clinical diagnosis of SMA (Ogino et al. 2002)
        3. Compound heterozygotes for deletion of *SMN1* exon 7 and an intragenic mutation of *SMN1* in 2–5% of patients with a clinical diagnosis of SMA
    4. Sequence analysis of all *SMN1* exons and intron/exon borders available on clinical basis.

1. Used to identify the intragenic *SMN1* mutations present in the 2–5% of patients who are compound heterozygotes
2. Limitations
    1. Cannot determine whether the point mutation is in the SMN1 gene or the SMN2 gene, unless one of these genes is absent
    2. Does not detect exonic duplications
    3. Cannot detect deletions of whole exons if more than one SMN gene copy is present

5. Duplication analysis to determine *SMN2* copy number.
    1. *SMN2* copy number ranges from 0 to 5
    2. Quantitative PCR: currently used for accurate determination of *SMN2* copy number
6. SMA carrier testing (gene dosage analysis) available clinically.
    1. Mutation analysis not reliable for carrier detection since it does not quantitate the number of *SMN1* gene copies.
    2. A PCR-based dosage assay (called SMA carrier testing or *SMN* gene dosage analysis) allows for the determination of the number of *SMN1* gene copies, thus permitting highly accurate carrier detection.
    3. Dosage analysis to differentiate carriers from non-carriers (Zeesman et al. 2002).
7. Linkage analysis available on clinical basis.
    1. Available to families in which direct DNA testing is not informative
    2. May be used for confirmation of carrier testing results and prenatal testing results
8. UBA1 sequence analysis for X-linked infantile spinal muscular atrophy (Baumbach-Reardon et al. 2012)

7. Newborn screening: An effective technology exists for newborn screening of SMA (Prior et al. 2010).

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Autosomal recessive inheritance: 25%
        2. Autosomal dominant inheritance: not increased unless a parent is affected
        3. X-linked recessive inheritance (Baumbach-Reardon et al. 2012): If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
    2. Patient's offspring: only milder forms of SMA likely to reproduce
        1. Autosomal recessive inheritance
            1. All offspring: carriers
            2. Recurrence risk not increased unless the spouse is affected or a carrier (Carre and Empey 2015)
        2. Autosomal dominant inheritance: 50%
        3. X-linked recessive inheritance (Baumbach-Reardon et al. 2012): Males with a severe phenotype do not generally survive; males with milder phenotypes will pass the disease-causing mutation to all of their daughters and none of their sons.
2. Prenatal diagnosis (Matthijs et al. 1998; Stewart et al. 1998; Baumbach-Reardon et al. 2012; Carre and Empey 2015)
    1. Possible to detect fetuses at 25% risk when the disease-causing *SMN* mutations in both parents are known
    2. Mutation analysis on fetal DNA obtained from CVS or amniocentesis
    3. Prenatal diagnosis cannot predict the clinical outcome in terms of severity, because the number of copies of *SMN2* is not specific to each SMA subtype: two copies of *SMN2* can be present in either SMA type 1 or type 2 (Feldkötter et al. 2002)
    4. Linkage analysis
        1. Many diagnostic laboratories still perform linkage analysis in addition to direct SMN^T mutation analysis in families where the previously affected child lacks both copies of SMN^T, since there are people in the normal population who lack both copies of SMN^T but not clinically affected.

2. The only option available to the families where no deletion has been observed but the clinical findings are consistent with 5q SMA.
5. Preimplantation genetic diagnosis: available clinically for families in which the disease-causing mutations have been identified in an affected family member

3. Management (Iannaccone 2007; Sendtner 2010)
   1. Treat and prevent complications of weakness and maintain quality of life.
   2. Several organ systems affected by weakness.
      1. Respiratory (restrictive lung disease)
         1. Noninvasive ventilation support using new technology for patients with sufficient orofacial muscle strength. Long-term ventilatory support is not usually considered.
         2. A new awareness of the importance of identifying sleep-disordered breathing.
         3. A new multidisciplinary approach to standard of care.
      2. Gastrointestinal (dysphagia): feeding gastrostomy for children with difficulty in sucking and swallowing
      3. Orthopedic (progressive deformities)
         1. Orthosis to allow to sit upright rather than be bedridden
         2. Option of surgical repair for the severe scoliosis
   3. Therapy development.
      1. Previous therapy approaches have focused on upregulation of SMN expression from a second SMN (*SMN2*) gene that gives rise to low amounts of functional SMN protein.
      2. Drug development to target disease-specific mechanisms at cellular and physiological levels is in its early stages, as the pathophysiological processes that underlie the main disease symptoms are still not fully understood.
      3. Human-induced pluripotent stem cell technology for generation of large numbers of human motor neurons could help to fill this gap and advance the power of drug screening.
      4. In parallel, advances in oligonucleotide technologies for engineering *SMN2* pre-mRNA splicing are approaching their first clinical trials, whose success depends on improved technologies for drug delivery to motor neurons.
      5. If this obstacle can be overcome, this could boost therapy development, not only for SMA but also for other neurodegenerative disorders.
   4. Future treatment approaches (Tisdale and Pellizzoni 2015).
      1. Results from ongoing clinical trials are eagerly awaited, and evidence of therapeutic benefit would favor the implementation of universal newborn screening, in turn allowing both earlier diagnosis and therapeutic intervention and possibly improved clinical outcome.
      2. It is anticipated that continuing progress in SMA research will strongly affect not only this devastating disease of childhood, but also other neurodegenerative conditions of the motor system.

References

Arnold, W. D., Kassar, D., & Kissel, J. T. (2015). Spinal muscular atrophy: Diagnosis and management in a new therapeutic era. *Muscle and Nerve, 51*, 157–167.

Barth, P. G. (1993). Pontocerebellar hypoplasias: An overview of a group of inherited neurodegenerative disorders with fetal onset. *Brain Development, 15*, 411–422.

Baumbach-Reardon, L., Sacharow, S., & Ahearn, M. E. (2012). Spinal muscular atrophy, X-linked infantile. GeneReviews. Updated September 13, 2012. Available at http://www.ncbi.nlm.nih.gov/books/NBK2594/

Biros, I., & Forrest, S. (1999). Spinal muscular atrophy: Untangling the knot? *Journal of Medical Genetics, 36*, 1–8.

Brahe, C., & Bertini, E. (1996). Spinal muscular atrophies: Recent insights and impact on molecular diagnosis. *Journal of Molecular Medicine, 74*, 555–562.

Burglen, L., Amiel, J., Viollet, L., et al. (1996). Survival motor neuron gene deletion in the arthrogryposis multiplex congenita-spinal muscular atrophy association. *The Journal of Clinical Investigation, 98*, 1130–1132.

Byers, R. K., & Banker, B. Q. (1961). Infantile muscular atrophy. *Archives of Neurology, 5*, 140–164.

Carre, A., & Empey, C. (2015). Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. *Journal of Genetic counseling*, Published online, Aug 8, 2015.

Crawford, T. O., & Pardo, C. A. (1996). The neurobiology of childhood spinal muscular atrophy. *Neurobiology of Disease, 3*, 97–110.

D'Amico, A., Mercuri, E., Tiziano, F. D., et al. (2011). Spinal muscular atrophy. *Orphanet Journal of Rare Diseases, 6*, 71–80.

Darwish, H., Sarnat, H., Archer, C., et al. (1981). Congenital cervical spinal atrophy. *Muscle and Nerve, 4*, 106–110.

Dressman, D., Ahearn, M. E., Yariz, K. O., et al. (2007). X-linked infantile spinal muscular atrophy: Clinical definition and molecular mapping. *Genetics in Medicine, 9*, 52–60.

Dubowitz, V. (1995). Chaos in the classification of SMA: A possible resolution. *Neuromuscular Disorders, 5*, 3–5.

Emery, A. E. H. (1971). The nosology of the spinal muscular atrophies. *Journal of Medical Genetics, 8*, 481–495.

Feldkötter, M., Schwarzer, V., Wirth, R., et al. (2002). Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: Fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *American Journal of Human Genetics, 70*, 358–368.

Fleury, P., & Hageman, G. (1985). A dominantly inherited lower motor neuron disorder presenting at birth with associated arthrogryposis. *Journal of Neurology, Neurosurgery and Psychiatry, 48*, 1037–1048.

Grohmann, K., Varon, R., Stolz, P., et al. (2003). Infantile spinal muscular atrophy with respiratory distress type 1 (SMARD1). *Annals of Neurology, 54*, 719–724.

Hageman, G., Ramaekers, V. T., Hilhorst, B. G., et al. (1993). Congenital cervical spinal muscular atrophy: A non-familial, non-progressive condition of the upper limbs. *Journal of Neurology, Neurosurgery and Psychiatry, 56*, 365–368.

Iannaccone, S. T. (2007). Modern management of spinal muscular atrophy. *Journal of Child Neurology, 22*, 974–978.

Korinthenberg, R., Sauer, M., Ketelsen, U. P., et al. (1997). Congenital axonal neuropathy caused by deletions in the spinal muscular atrophy region. *Annals of Neurology, 42*, 364–368.

Kugelberg, E., & Welander, L. (1956). Heredofamilial juvenile muscular atrophy simulating muscular dystrophy. *Acta Neurologica et Psychiatrica, 75*, 500.

Lefebvre, S., Burglen, L., Reboullet, S., et al. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell, 80*, 155–165.

Lorson, C. L., Rindt, H., & Shababi, M. (2010). Spinal muscular atrophy: Mechanisms and therapeutic strategies. *Human Molecular Genetics, 19*, R111–R118.

MacKenzie, A. (2010). Genetic therapy for spinal muscular atrophy. *Nature Biotechnology, 28*, 235–237.

Matthijs, G., Devriendt, K., & Fryns, J.-P. (1998). The prenatal diagnosis of spinal muscular atrophy. *Prenatal Diagnosis, 18*, 607–610.

Munsat, T. L. (1991). Workshop report: International SMA Collaboration. *Neuromuscular Disorders, 1*, 81.

Nicole, S., Diaz, C. C., Frugier, T., et al. (2002). Spinal muscular atrophy: Recent advances and future prospects. *Muscle & Nerve, 26*, 4–13.

Ogino, S., Leonard, D. G., Rennert, H., et al. (2002). Genetic risk assessment in carrier testing for spinal muscular atrophy. *American Journal of Medical Genetics, 110*, 301–307.

Pearn, J. (1978). Autosomal dominant spinal muscular atrophy. A clinical and genetic study. *Journal of the Neurological Sciences, 38*, 263–275.

Prior, T.W., & Russman, B. (2011). Spinal muscular atrophy. *GeneReviews*. Retrieved 27 Jan 2011. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1352/

Prior, T. W., Snyder, P. J., Rink, B. D., et al. (2010). Newborn and carrier screening for spinal muscular atrophy. *American Journal of Medical Genetics Part A, 152A*, 1608–1616.

Roy, N., McLean, M. D., Besner-Johnston, A., et al. (1995). Refined physical map of the spinal muscular atrophy gene (SMA) region at 5q13 based on YAC and cosmid contiguous arrays. *Genomics, 26*, 451–460.

Savas, T., Erol, I., Ozkale, Y., et al. (2014). Congenital segmental spinal muscular atrophy: A case report. *Journal of Child Neurology, 30*, 509–512.

Sendtner, M. (2010). Therapy development in spinal muscular atrophy. *Nature Neuroscience, 13*, 795–799.

Stewart, H., Wallace, A., McGaughran, J., et al. (1998). Molecular diagnosis of spinal muscular atrophy. *Archives of Disease in Childhood, 78*, 531–535.

Thomas, N. H., & Dubowitz, V. (1994). The natural history of type I (severe) spinal muscular atrophy. *Neuromuscular Disorders, 4*, 497–502.

Tisdale, S., & Pellizzoni, L. (2015). Disease mechanisms and therapeutic approaches in spinal muscular atrophy. *The Journal of Neuroscience, 35*, 8691–8700.

Tsao, B. (2013). Spinal muscular atrophy. *eMedicien from WebMD*. Updated 8 May 2013. Available at: http://emedicine.medscape.com/article/1181436-overview

Wang, C. H., Finkel, R. S., Bertini, E. S., et al. (2007). Consensus statement for standard of care in spinal muscular atrophy. *Journal of Child Neurology, 22*, 1027–1049.

Zeesman, S., Whelan, D. T., Carson, N., et al. (2002). Parents of children with spinal muscular atrophy are not obligate carriers: Carrier testing is important for reproductive decision-making. *American Journal of Medical Genetics, 107*, 247–249.

Zerres, K., Wirth, B., & Rudnik-Schoneborn, S. (1997). Spinal muscular atrophy-clinical and genetic correlations. *Neuromuscular Disorders, 7*, 202–207.

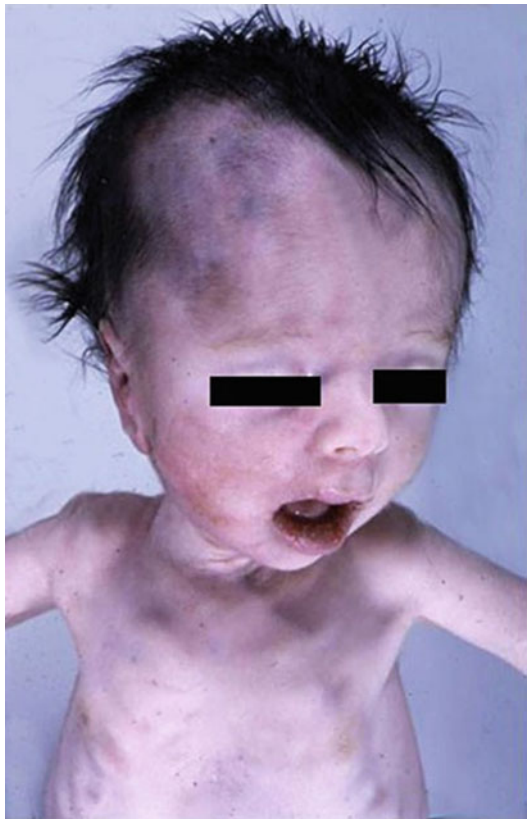

Fig. 1 A 2 1/2-week-old white male died of respiratory failure associated with congenital spinal muscular atrophy (Werdnig-Hoffman disease). There was generalized muscle atrophy including respiratory muscle

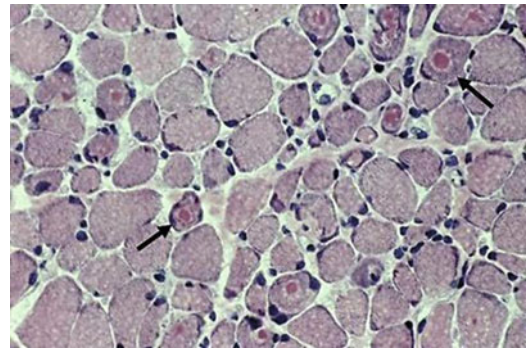

Fig. 3 Residual muscle seen in a 14-year-old female with spinal muscular atrophy showed chronic denervative change with presence of scattered target fibers (*arrows*) (H & E ×400)

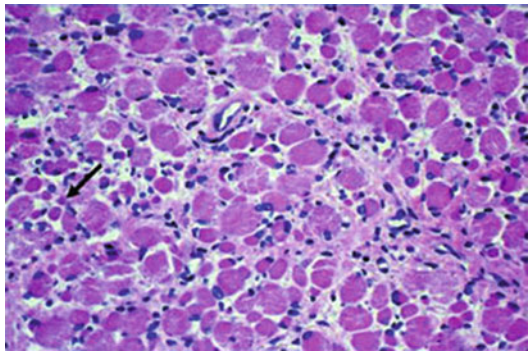

Fig. 2 Quadriceps muscle showed many exceedingly atrophic muscle fibers which tend to be in groups (*arrow*). No degenerative muscle fibers were present (H & E, ×100)

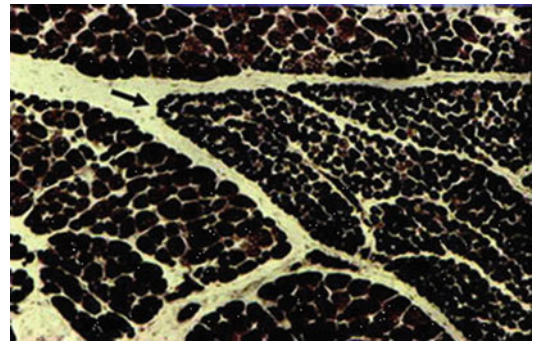

Fig. 4 Biopsy of quadriceps muscle from a 10-month-old girl with spinal muscular atrophy showed a group atrophy involving several entire fascicles (*arrow*). Both type I (*light-stained*) and type II (*dark-stained*) fibers were affected. This was accompanied by an enervative phenomenon (the large muscle fibers all stain pale) (Myosin ATPase, at 9.4, ×50)

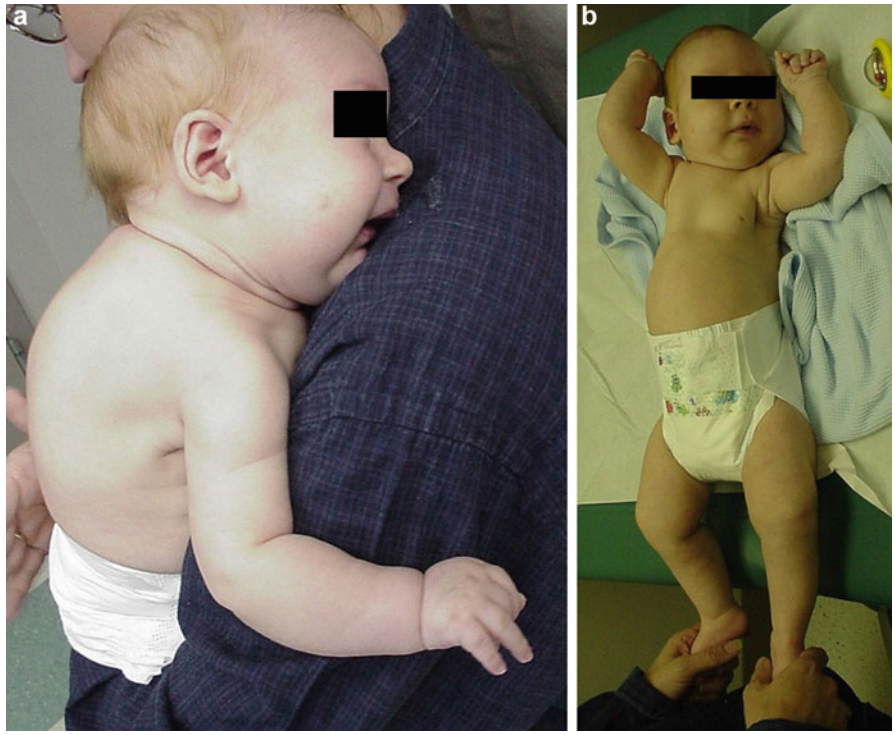

Fig. 5 A 3-month-old infant boy with Werdnig-Hoffman disease showing generalized hypotonia (**a**). He had a small chest with diaphragmatic breathing (**b**), fasciculation of the tongue, and absence of deep tendon reflexes. Molecular genetic analysis revealed homozygous exon 7 deletion and homozygous exon 8 deletion for the survival motor neuron genes (*SMN*)

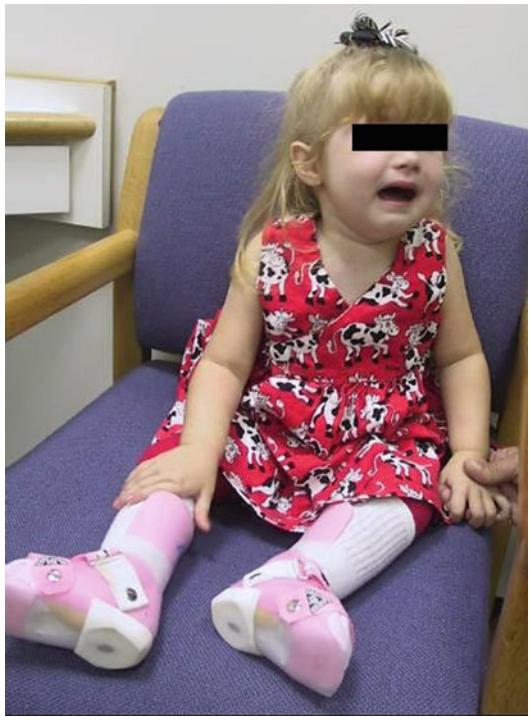

Fig. 6 A 27-month-old girl with SMA1. She could not stand holding or independently and had foot drops, absence of deep tendon reflexes, and muscle weakness. She was confined to a wheelchair. Molecular genetic analysis revealed homozygous exon 7 deletion and homozygous exon 8 deletion for the *SMN* gene

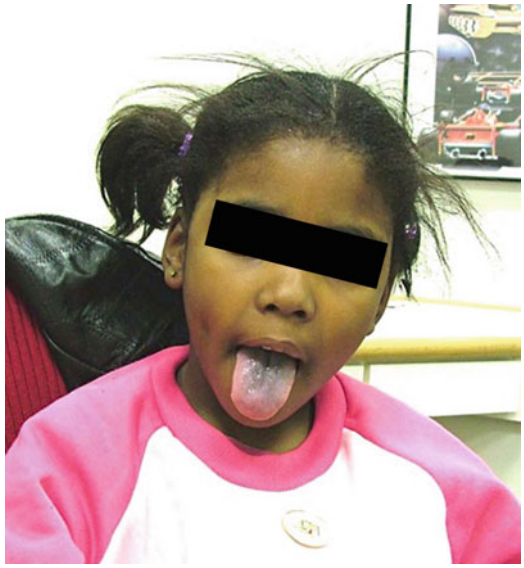

Fig. 7 A 5-year-old girl with SMA showing tongue fasciculation

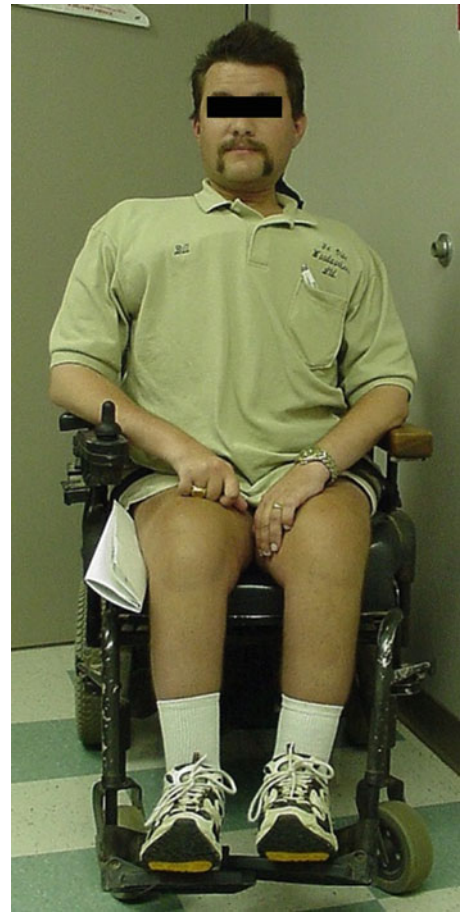

Fig. 8 A 30-year-old man with Kugelberg-Welander disease showing muscle weakness and had been confined to a wheelchair for some time. He had trouble standing and began to walk at 6 years of age. Molecular genetic diagnosis revealed homozygous exon 7 deletion and homozygous exon 8 deletion

Fig. 9 This 22-month-old boy was evaluated for spinal muscular atrophy. He never pulls himself up and stands alone. He used his hands to move his legs. Physical examination showed slightly atrophic lower leg muscles and absent knee jerks. Molecular genetic analysis (Athena Diagnostics) identified zero copy of the survival motor neuron gene 1 (*SMA1*), confirming the clinical diagnosis of spinal muscular atrophy in this patient, and three copies of *SMN2*. An increased number ($\geq$3 copies) of *SMN2* gene copies may be associated with a less severe phenotype of SMA. Conversely, fewer ($\leq$2) *SMN2* gene copies may be associated with a severe phenotype of SMA. *SMA2* genes are able to produce a protein identical to that of the *SMN1* gene but at a reduced (10–20 %) capacity