Spinal Muscle Atrophy

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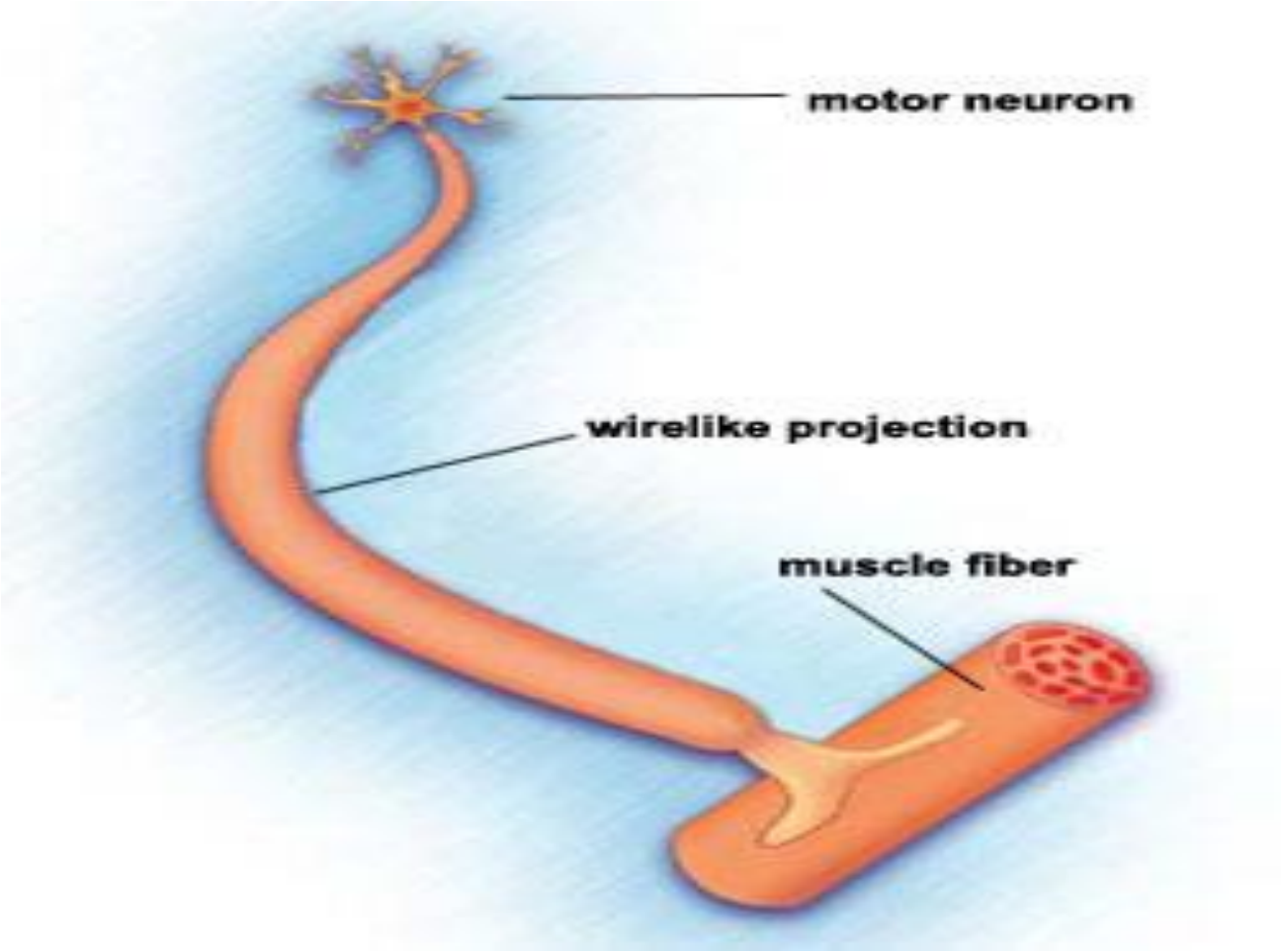
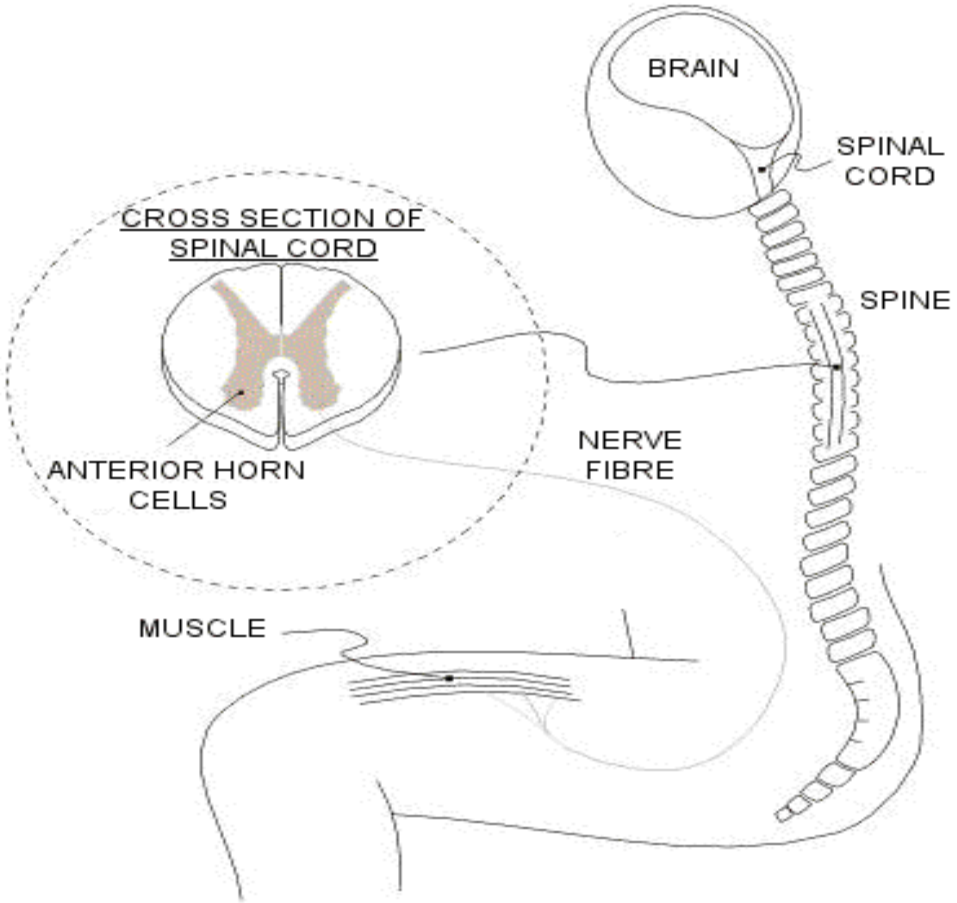
History

- 1890- G. Werdnig described for the first time the classic infantile form of SMA.
  - Werdnig, and Hoffman, in 1891, reported cases of muscular dystrophy occurring in infants that were otherwise similar to cases of muscular dystrophy found in older children and adults (eg, Duchenne muscular dystrophy)
- 1956- Kugelberg and Welander described the less severe form of SMA.

Background

- Autosomal recessive hereditary disease characterized by progressive hypotonia and muscular weakness (except SBMA, which is X-linked recessive)
- Disease of the anterior horn cells, affecting the voluntary muscles for activities such as crawling, walking, head and neck control and swallowing
- Most common diagnosis in girls with progressive weakness
- Occurs due to a progressive degeneration of the *alpha* motor neuron from anterior horn cells in the spinal cord


motor neuron
wirelike projection
muscle fiber



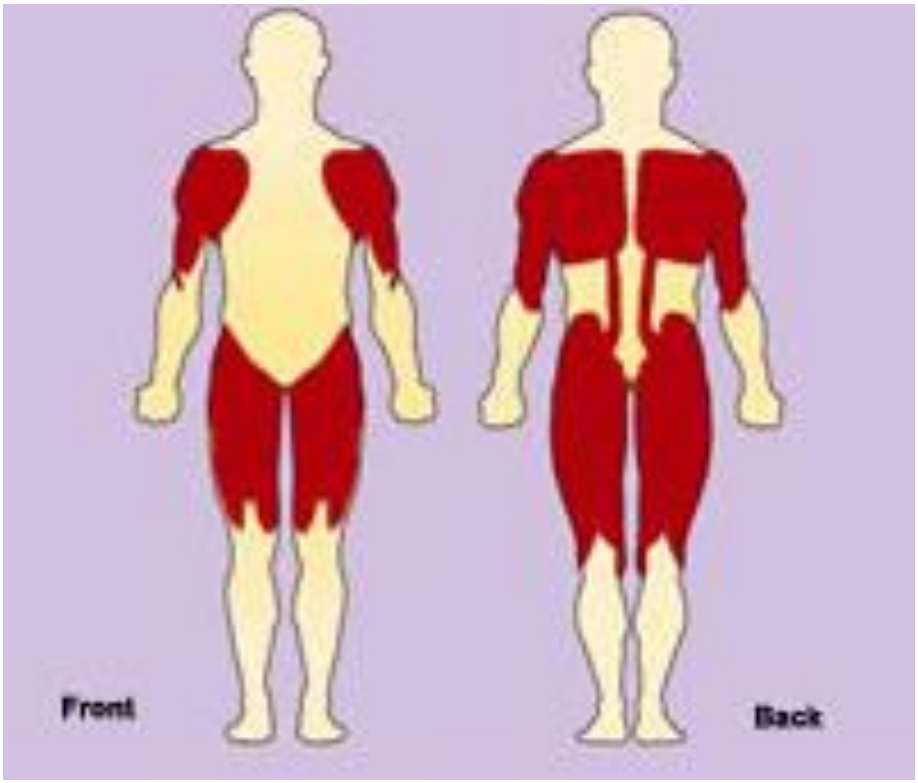
MOTOR UNIT = Anterior Horn Cell + Nerve Fibre + Muscle Fibre

In SMA some of the Anterior Horn Cells are affected and fail to provide the link between the Brain and the Nerve Fibres

Background

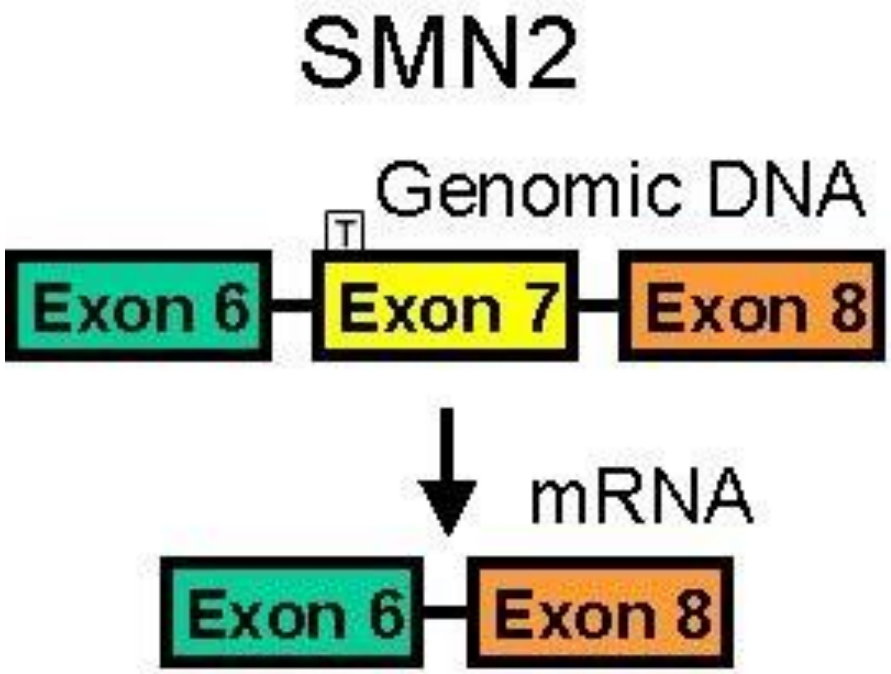
- Motor neurons of cranial nerves (especially the CNV-CNXII) can also be involved
- Sensation, which originates from the posterior horn cells of the spinal cord, is spared, as is intelligence
- Several muscles are spared, including the diaphragm, the involuntary muscles of the gastrointestinal system, the heart, and the sphincters
- More severe in the proximal musculature than in the distal segments

Muscles Affected



Pathophysiology

- SMA is caused by a mutation in the survival motor neuron gene (SMN). This gene becomes active in the healthy mature fetus to stabilize the neuronal population. In its absence, programmed cell death persists. The mechanism and timing of abnormal motor neuron death remain unknown
- This deletion has been demonstrated in up to 98% of patients with SMA.


SMN2
Genomic DNA
T
Exon 6
Exon 7
Exon 8
mRNA
Exon 6
Exon 8

Frequency

- Occurs in approx 1 case in 15,000-20,000 (5-7 per 100,000) live births. The prevalence of persons with the carrier state is 1 in 80.

-Most common degenerative disease of the nervous system in children.

-2nd most common disease inherited in an autosomal recessive pattern, (CF), to affect children.

-leading heritable cause of infant mortality

More statistics

- Death occurs due to respiratory compromise.
- The younger the patient is at onset, the worse the prognosis
- Male:female= (2:1 ratio) clinical course in males is more severe
- As the age at onset increases, incidence in females decreases

SMA Type I- Werdnig Hoffman

- General Notes
  - Most mothers report decreased activity of the fetus in the latter stages of pregnancy
  - Newborns are floppy and inactive
  - Child unable to roll over or sit.
  - Usually identified by 6 months of age
  - Swallowing and feeding may be difficult and the child may show some difficulties with their own secretions
  - Progressive clinical deterioration occurs.
  - Death usually occurs from respiratory failure and its complications in patients by age 2 years.
    - The majority of babies (approximately 80%) die in the first year of life.

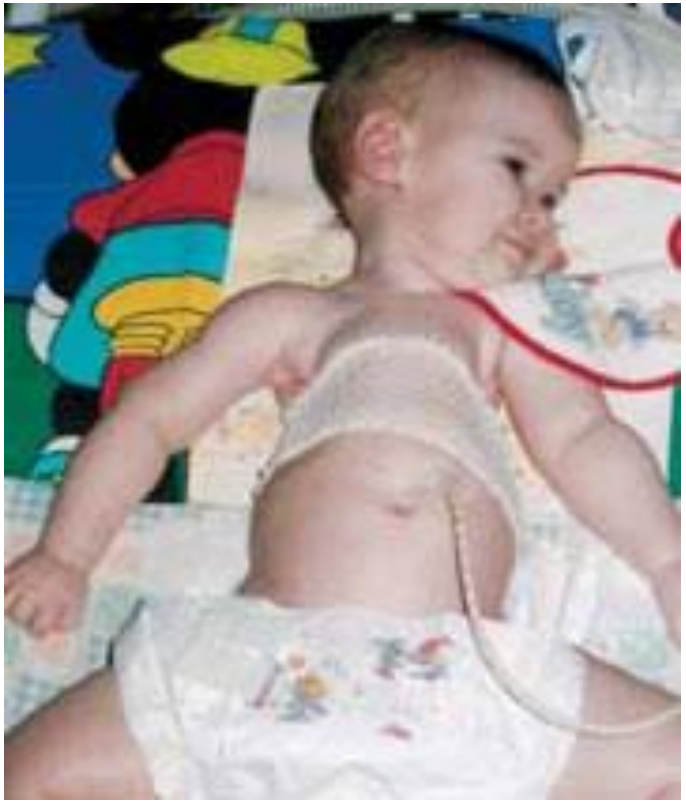
SMA-1

- At birth, they move the extremities little, if at all.
- The hips are flexed, abducted, and externally rotated. The knees are flexed.
- Because the distal musculature is usually spared, the fingers and toes move.
- Infants cannot control or lift the head. Areflexia is universal
- chest may appear concave (sunken in) due to the diaphragmatic (tummy) breathing

SMA-1 cont…

- They may do well for several months before, but they usually begin to have problems feeding or moving. They will no longer be able to hold their heads up, or they may no longer be able to turn their heads. The following symptoms are also likely to be present:
  1. Weak muscles
  2. Decreased muscle tone (hypotonia)
  3. Decreased muscle size (atrophy)
  4. Decreased reflexes
  5. Decreased joint movements (contractures)
  6. Irregular breathing patterns that show the chest collapsing when an infant breathes in
  7. Bell-shaped chest
  8. Decreased movement of fingers and toes
  9. tongue fasciculations

Respiratory muscle weakness in this baby with type 1 SMA requires assisted ventilation through a mask much of the time.



Because SMA affects the swallowing muscles, this baby is fed through a gastrostomy tube. Note Bell-shaped chest

SMA Type II (Chronic)

- Patients have normal development for the first 4-6 months of life.
- Able to sit independently, but they are never able to walk.
- Feeding and swallowing problems are not usually characteristic
- May be able to stand. This is most often accomplished with the aid of bracing and/or parapodium/standing frame
- Require a wheelchair for locomotion.
- They have a longer life span than pts with type I SMA that is variable, but some may live into the 5th decade of life
- Diagnosed in infants approx. aged 6-12 months

SMA Type II- cont…

- Have head control
- 75% of these patients can sit independently
- Muscular weakness is greater in the lower extremities than the upper extremities.
- Patellar reflex is absent, but may have bicipital and triceps tendon reflexes.
- Tongue fasciculations are present, as are upper extremity tremors, but less than in Type I
- Scoliosis is universal
- Most patients develop hip dislocation, either unilateral or bilateral, when <10 yo
- Hands may get weak eventually, but they usually stay strongest the longest, and, even if they do weaken, they usually remain strong enough for typing on a computer keyboard and other basic functions of modern life

This girl with SMA type 2 used a back brace as a toddler. At 9, she underwent surgery to correct a spinal curvature, and wore a temporary brace while recovering from surgery.

SMA Type III- (Kugelberg-Welander disease)

- A.k.a. Juvenile Spinal Muscular Atrophy
- Presenting complaint is difficulty climbing stairs or getting up from the floor (due to hip extensor weakness).
- fine tremor can be seen in the outstretched fingers but tongue fasciculations are seldom seen.
- Life span is nearly normal
- These patients walk early in life and maintain their ambulatory capacity into adolescence.
- Weakness may cause foot drop, and patients have limited endurance.
- 1/3 of the patients become wheelchair bound as adults (mean age 40 years).
- diagnosed in children aged 2-15 years

People with
SMA type 3
often retain some
ability to walk
well into
adulthood.

SMA Type IV- Adult Onset

- Sx's usually start after age of 35
  - Very rare for Spinal Muscular Atrophy to begin between the ages of 18 and 30
- Insidious onset and very slow progression
- The bulbar muscles, those muscles used for swallowing and respiratory function, are rarely affected

Adult-Onset X-linked SMA

- A.k.a. Kennedy's Syndrome (after William Kennedy) or Spino-Bulbar Muscular Atrophy
  - Occurs only in males between ages 30-50, although 50% of female offspring are carriers
  - associated with a mutation in the gene that codes for part of the androgen receptor and therefore these male patients often have breast enlargement known as gynecomastia
  - Slowly or non-progressive.

Adult-Onset X-linked SMA

- SBMA also involves weakness and atrophy of the arm and leg muscles, particularly those nearest the center of the body. Twitching or cramping of muscles can also occur
- Bulbar muscle involvement can be significant, affecting speech, chewing and swallowing
- The swallowing muscle weakness can lead to choking on food or liquids or inhaling them into the lungs. This kind of inhalation can lead to obstruction of airways or infection

Adult-Onset X-linked SMA

- Weakness in the throat muscles can also make breathing during sleep difficult. Ventilation aids, which push air in under pressure, can help with this
- Facial muscle weakness can occur, making it hard to smile or convey emotion through facial expressions
- This weakness is often first noticed as trouble with stairs or difficulty walking long distances, such as through malls or parking lots

SBMA usually affects men between ages 30 and 50.

Other general SMA points…

- A long C-shaped thoracolumbar scoliotic curve is present in patients with type II SMA and in half of patients with type III SMA. The curve progresses to a severe and incapacitating deformity if not treated. Thirty percent of patients have kyphotic deformities as well.
- Pseudohypertrophy of the calf is present, which may confound the diagnosis (ie, with Duchenne muscular dystrophy and Becker muscular dystrophy).
- Tongue fasciculations are pathognomonic of SMA (all types), as opposed to all other neuromuscular diseases of infancy. Presence of tongue fasciculations can aid in the diagnosis, as 56% of patients exhibit this symptom.
- BRAIN IS TOTALLY UNAFFECTED!!!

Differential Diagnosis

Cerebral palsy (hypotonic diplegia)
Congenital muscular dystrophy
Transverse myelitis
Juvenile myasthenia gravis
Polymyositis
Benign congenital hypotonia
Multifocal motor neuropathy
Chronic inflammatory demyelinated polyneuropathy
Inflammatory myopathy
Progressive muscular dystrophy

Diagnosis

- PHYSICAL EXAM IS MOST IMPORTANT ASPECT!!!

A physical exam is a key part of diagnosing SMA.

Diagnosis

2) SMN gene test very useful for the diagnosis of SMA.

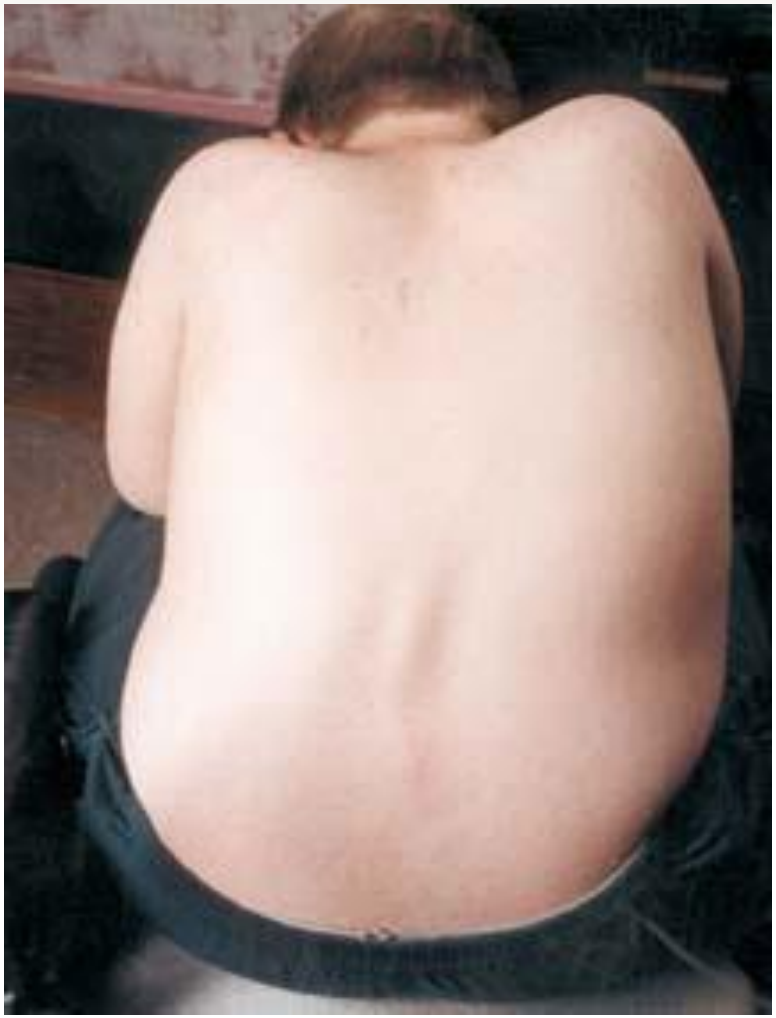
It cannot be used to indicate the severity of the disease, although it is believed that a blood test to screen for SMN deletion is all that is necessary to make the diagnosis (No EMG really needed)

Once the deletion has been shown in an affected child, pre-natal diagnosis is now possible on a chorionic villi sample in any future pregnancy by direct assessment as to whether the fetus is carrying the deletion, and is therefore affected or not

- The absence or dysfunction of SMN is reflected by an enhanced neuronal death. A heterozygous deletion leads to an asymptomatic carrier state.
- A significant increase in nuclear DNA vulnerability was detected in fetuses with SMA at 12-15 weeks' gestational age. It reflected a decrease in the number of anterior horn neurons.

Diagnosis

- 3) Aldolase and serum CK- wnl (as opposed to findings in patients with Duchenne and Becker muscular dystrophy).
  - In Type I (Werdnig-Hoffmann) this enzyme tends to be normal, but moderate elevation may occur in the milder forms
- 4) Pelvis anteroposterior (AP) and lateral views: Most patients with type II SMA develop hip dislocations. The dislocations are only temporarily symptomatic and do not influence function in these patients because they are nonambulatory.
- 5) Complete spine and scoliosis series: All patients with type II SMA and most patients with type III SMA develop a long C-shaped scoliotic curve



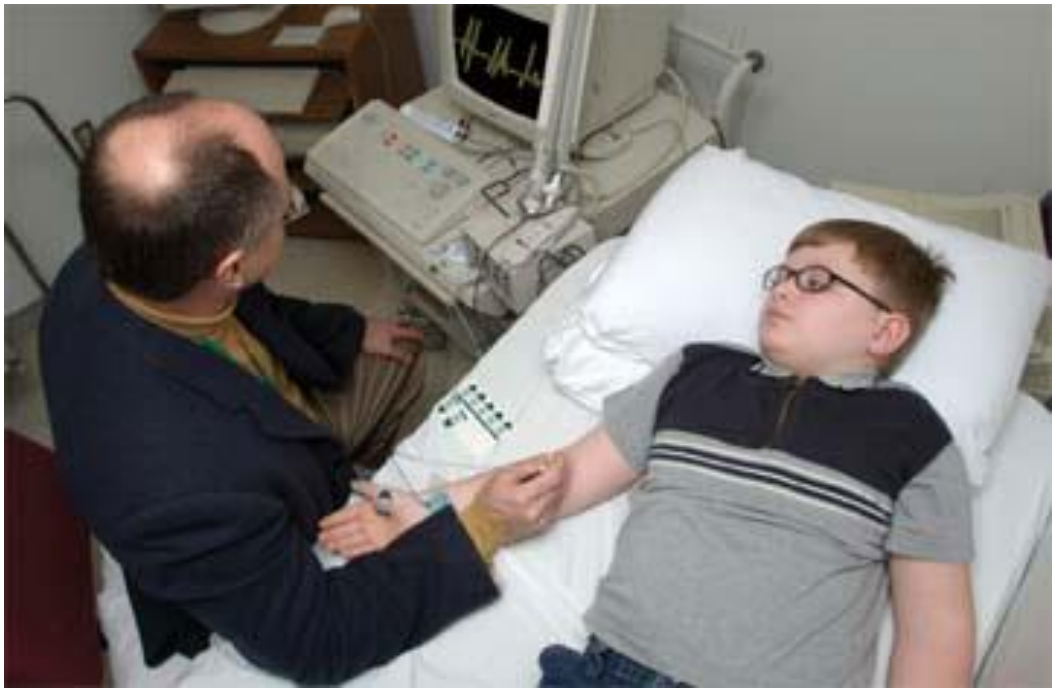
Scoliosis (spinal curvature) is a common problem in SMA and should be corrected

Diagnosis (other)

6) Electromyograms and nerve conduction studies: Electromyogram findings in patients with SMA are characteristic of a neuropathic disorder; they reveal fibrillation potentials, denervation, and increased amplitude. However, NCV results are normal

7) Incisional biopsy: Muscle biopsies reveal a uniform smaller diameter of all fibers. This contrasts biopsy findings for other muscular dystrophies, which consist of degenerating muscle with variable muscle fiber sizes.

Note: Biopsies in patients with hypotonic cerebral palsy reveal normal muscle fibers



A nerve conduction velocity test may be part of the diagnostic process in SMA.

Medical Care

- Patients with type I SMA require little, if any, involvement of an orthopedist due to their short life span.
- Suction machine to clear pharyngeal secretions
- Splinting is used for fractures.
- FEEDING TUBE may also be helpful when swallowing becomes difficult
- For patients with type II and type III SMA, PT may be employed for contractures.

Surgical Care

- Many children with SMA start to show a scoliotic curve early in life, which is often treated with a brace until the right time for surgery is reached.
- Surgeons generally wait until growth is complete or nearly so before surgically straightening and fusing the spine.
- They also take into account the child's pulmonary function and how fast the curve is likely to progress

Physical Therapy Goals

- Provide movements that babies are unable to make
- Clear chest to secretions to reduce incidence of infections
- Avoid stiffening of joints

Occuaptional Therapy

Occupational therapy can help people with SMA learn to write, use a computer and do other daily tasks.

Adaptions

Adults with SMA are often able to drive with specialized hand controls.