Spinal Muscular Atrophies (SMA)

Synonyms: ***Progressive Spinal Muscular Atrophy, Progressive Spinal Atrophy***

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**SMA** - progressive degeneration and loss of **LMN** (midbrain ÷ spinal cord).

* replacement of lost cells by gliosis (e.g. atrophic spinal cord at autopsy).
* UMN is not affected! (vs. in ALS)

| **Type** | **Inheritance** | **Age of Onset** | **Presenting Symptoms** | **Prognosis** |
| --- | --- | --- | --- | --- |
| **SMA type I** (infantile / acute / fatal SMA, Werdnig-Hoffman disease) | AR | In utero ÷ 6 months | Hypotonia and generalized weakness, problems with sucking, swallowing, and breathing; never able to sit | Average life expectancy - 8 months;  95% dead before age of 18 months |
| **SMA type II** (intermediate between type I and type III) | AR | 6 ÷ 15 months | < 25% learn to sit; never able to stand, facial muscles spared | Depends on respiratory complications |
| **SMA type III** (chronic SMA, Kugelberg-Welander disease) | AR, AD | 15 months ÷ teen years | Proximal leg weakness, delayed motor milestones |
| **Kennedy's disease** (bulbospinal muscular atrophy) | X-linked recessive | After age 40 yrs | Bulbar → distal limb weakness; endocrine dysfunction | Normal lifespan |
| **Fazio-Londe disease** (progressive bulbar palsy of childhood) |  | Late childhood ÷ adolescence | Bulbar weakness |  |
| **SMA type IV** (adult-onset SMA) | AD, AR, X- recessive (very rare) | median ≈ 37 years | Proximal weakness, variable within families, more severe in AD | Life expectancy not markedly reduced |
| **Distal SMA** (Charcot-Marie-Tooth type-SMA) | AR, AD | AR: birth ÷ infancy;  AD: adulthood | Distal weakness | Very slow clinical progression; does not alter lifespan |

Etiopathophysiology

Autosomal recessive **SMA types I, II, III** (allelic heterogeneity) have been linked to 5q11.3-13.1 - **gene for survival of motor neurons (SMN)**:

Defect in neuronal apoptosis!

* + contains multiple copies of genes and pseudogenes;
  + characterized by instability: deletions (98%), truncations, point mutations.
  + protein product has no known homolog, and its function is not yet known.
  + no correlation between genotype and phenotype! - but most affected siblings exhibit same phenotype - may be additional modifying factors, e.g. another gene tightly linked to pathogenic gene:
    1. contiguous deletion of nearby **neuronal apoptosis inhibitory protein gene (NAIP)** is associated with most severe phenotype (occurs in 45-65% **SMA type I** and in 20-40% **SMA type II and III** cases).
    2. homozygous deletions in exons 7 and 8 in **SMNt (telomeric copy of SMN)** → **SMA type I**; mutations that convert SMNt to centromeric copy (**SMNc**) → **SMA type II and III**.
* SMN protein is implicated in the trafficking of RNA in and out of the nucleus and in the formation of complexes that are important in RNA splicing.
* SMN locus on chromosome 5 has two almost identical copies of the SMN gene - one produces a full length SMN protein, whereas the second expresses a small amount of full-length SMN and a shortened SMN; loss of full-length SMN from mutations at the main locus can be mitigated to some degree by the shortened SMN protein expressed at the second locus.

Epidemiology

**SMA type I** (most common SMA) incidence ≈ 4-10 in 100,000 (2nd most common neuromuscular disease, following Duchenne muscular dystrophy).

* similar numbers are affected with milder forms and forms with later onset.
* *carrier frequency* of **SMNt mutation** - 1 in 50.

Clinical Features

Clinical hallmarks:

1. Insidious onset of symmetrical **weakness**.
   * proximal muscles > distal muscles.
   * legs > arms.
   * *greatest decline in muscular power occurs at onset*\* and then slows (i.e. great loss of motoneurons initially, followed by stabilization in any remaining neurons) - difference between SMAs and other neurodegenerative disorders.

\*results in ***large number of complications***: scoliosis, contractures (e.g. arthrogryposis multiplex congenita), disuse atrophy, respiratory / nutritional / sleep problems.

1. **Hypotonia, atrophy, loss of tendon reflexes**

After immediate neonatal period, spinal muscular atrophy is *most common cause of infantile hypotonia* (“floppy infant”)!

1. **Cranial nerve palsies** (CN3, 4, 6 are typically spared!).

No sensory symptoms or loss, no myalgias!

No heart involvement!

Intelligence normal! (children often appear brighter than their normal peers!)

**SMA type 1 (Werdnig-Hoffmann)** - evident at birth or soon thereafter, always *before age 6 months*.

* mothers notice decreased intrauterine movements.
* one of most common forms of *floppy infant syndrome* (infants lie flaccid with little movement, unable to overcome gravity).
* tongue is often seen to fasciculate (rarely in limb muscles - because of ample subcutaneous fat).
* ultimately, **complete flaccid quadriplegia** results with **compromised respiration**.
* all dead by age 4 yrs.

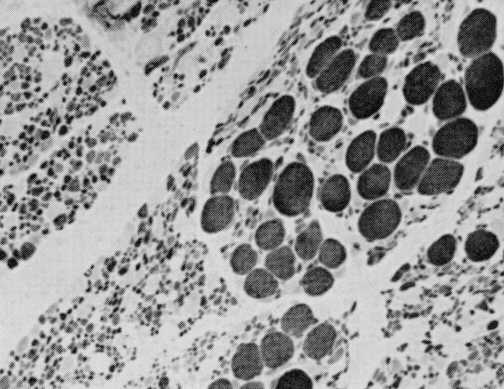
**SMA type 3 (Kugelberg-Welander)** – slowly progressive gait disorder in *late childhood or adolescence*.

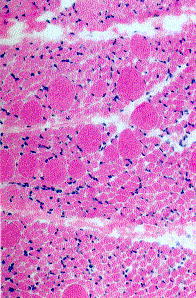
* **proximal** limb muscle weakness and wasting (simulates muscular dystrophy!); tendon reflexes are lost.
* relative sparing of bulbar muscles.
* *course relatively benign* - many continue to function socially with normal life span (others may be handicapped); many children are highly intelligent.

Diagnosis

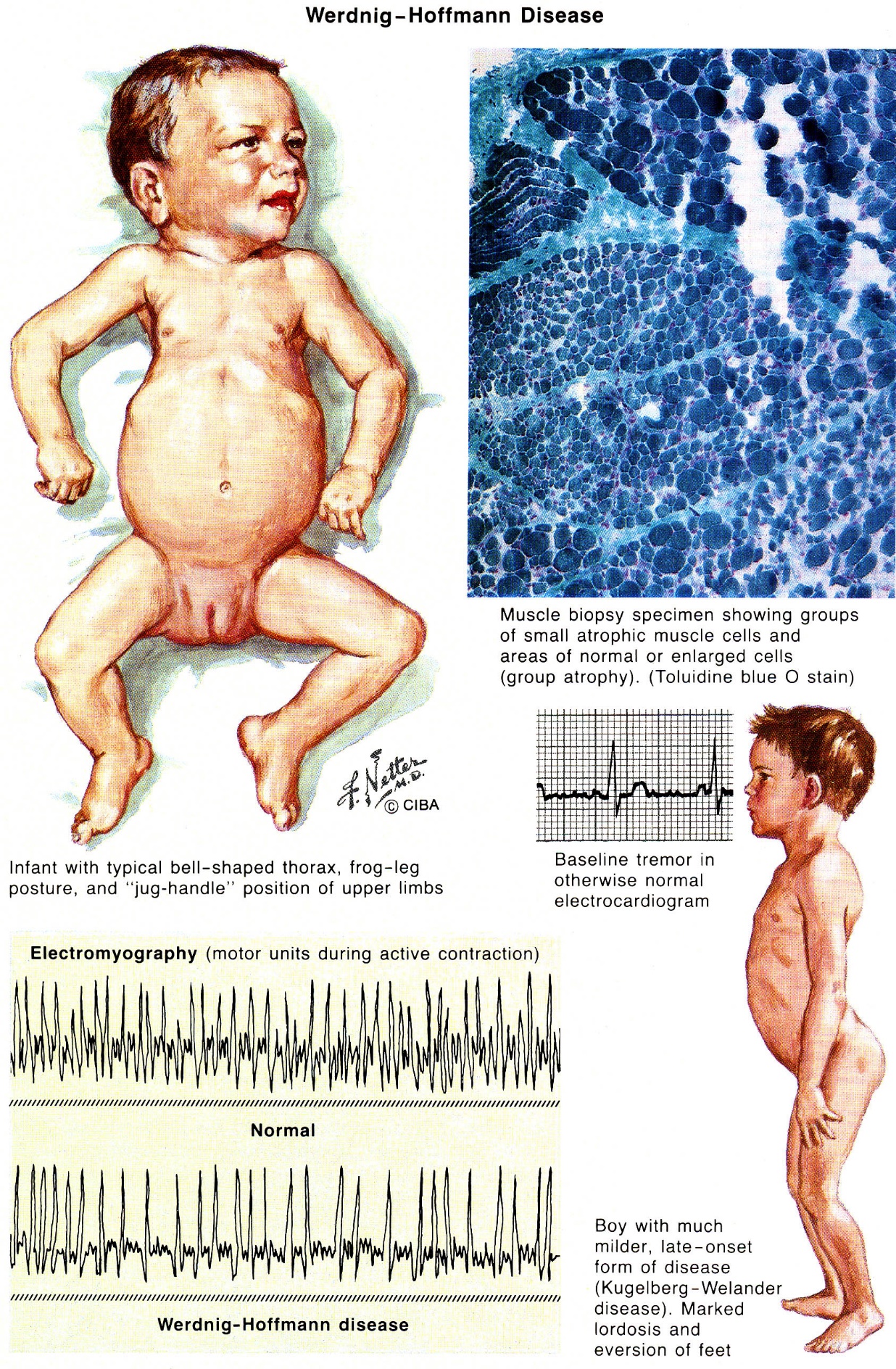
* + - **genetic** **test** – homozygous SMN deletion (sensitive test in 95% cases!).
      * prenatal testing is available only on research basis.
    - **serum CK** can be elevated (correlates with illness duration);
      * in **SMA 3**, may be 20 times normal (in range of many myopathies!).
    - **ECG** – normal.
    - without DNA diagnosis, it is essential to verify neurogenic process via:

1. **EMG** – denervation.
2. **nerve conduction studies** – normal.
3. **muscle biopsy** (with histochemistry) – denervation & reinnervation: large numbers of atrophic fibers, often only few micrometers in diameter; atrophic fibers often involve entire fascicle (**panfascicular atrophy**!!!); scattered groups of large fibers that are 2-4 times normal size. [also see p. D30 >>](http://www.neurosurgeryresident.net/D.%20Diagnostics\D30-39.%20Biopsy%20(brain,%20nerve,%20muscle)\D30.%20Muscle%20Biopsy%20and%20Serum%20Markers.pdf)





[Source of picture: Ramzi S. Cotran “Robbins Pathologic Basis of Disease”, 6th ed. (1999); W. B. Saunders Company; ISBN-13: 978-0721673356 >>](http://www.amazon.com/gp/product/0721601871)



Treatment

* multidisciplinary approach aimed at *preventing contractures, skeletal deformities, respiratory complications, and social isolation*.

nusinersen (Spinraza®) intrathecal injection - antisense therapy - the first FDA approved drug to treat children and adults with spinal muscular atrophy.

* sham-controlled study in 78 children with infantile SMA showed that treatment with nusinersin leads to a 50% reduction in deaths or early ventilation.

Finkel RS, Mercuri E, Darras BT, et al; ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377:1723-1732.

Prognosis

Earlier onset – more rapid decline.

Other Forms of LMN degeneration

**Poliomyelitis** – viral disease of LMN – see [p. 259 (1) >>](../USMLE%202/Infection%20(201-300)/259%20(1).jpg)

* do not map to 5q11.
* most are *autosomal recessive*.

**Fazio-Londe disease (progressive bulbar palsy of childhood)** - **brainstem** LMN degeneration of all brainstem nuclei (vs. most juvenile SMAs).

* presents in late childhood or adolescence with stridor → ptosis, dysarthria, facial palsy, dysphagia.
* weakness of arms & legs may occur later, and respiration may be affected.
* death in early childhood?

**Scapuloperoneal and facioscapulohumeral SMA forms**

* distinction from *muscular dystrophy* depends on **DNA analysis**.

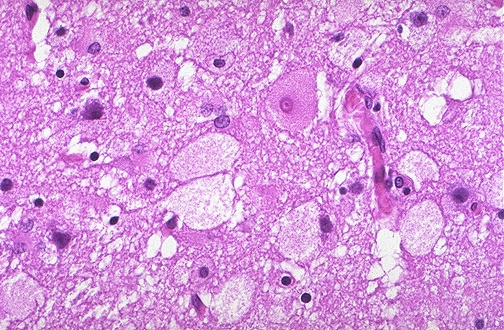
**Kennedy's disease** - X-linked recessive disorder (**expansion of CAG trinucleotide repeats** in first exon of androgen receptor gene Xq11-12) - affects males:

* 1. ***progressive bulbospinal muscular atrophy*** (preferentially **bulbar**\* → **distal** limb muscles) \*incl. ocular!
  2. ***endocrine dysfunction*** – androgen insensitivity (testicular atrophy, gynecomastia, oligospermia), diabetes mellitus.
  3. subtle *sensory sign*in some patients. (e.g.abnormal sensory-evoked potentials, affected spinal sensory tracts, distal degeneration of sensory axons).
* midlife onset, after age 40 yrs. (direct correlation between number of -CAG- repeats and disease severity).
* most common form of adult-onset SMA!
* may be readily screened from blood **DNA analysis**.
* slowly progressive, normal lifespan.

**Adult Tay-Sachs disease** (hexosaminidase A deficiency)

* primarily in Ashkenazi Jewish families.
* adult-onset (vs. classical Tay-Sachs disease), very slowly progressive.
* dysarthria and cerebellar atrophy.

Baby with Tay-Sachs disease - enlarged, pale neurons:



[Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD) >>](http://library.med.utah.edu/WebPath/webpath.html" \t "_blank)

Bibliography for ch. “Spinal Disorders” → follow this [link >>](http://www.neurosurgeryresident.net/Spin.%20Spinal%20Disorders\Spin.%20Bibliography.pdf)

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