Spinal Muscular Atrophies (SMA)

Synonyms: ***PROGRESSIVE SPINAL MUSCULAR ATROPHY, PROGRESSIVE SPINAL ATROPHY***

Last updated: August 8, 2020

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:
  a) 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).
  b) 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.
2. **HYPOTONIA, ATROPHY, LOSS OF TENDON REFLEXES**
   After immediate neonatal period, spinal muscular atrophy is *most common cause of infantile hypotonia* ("floppy infant")!
3. **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*.

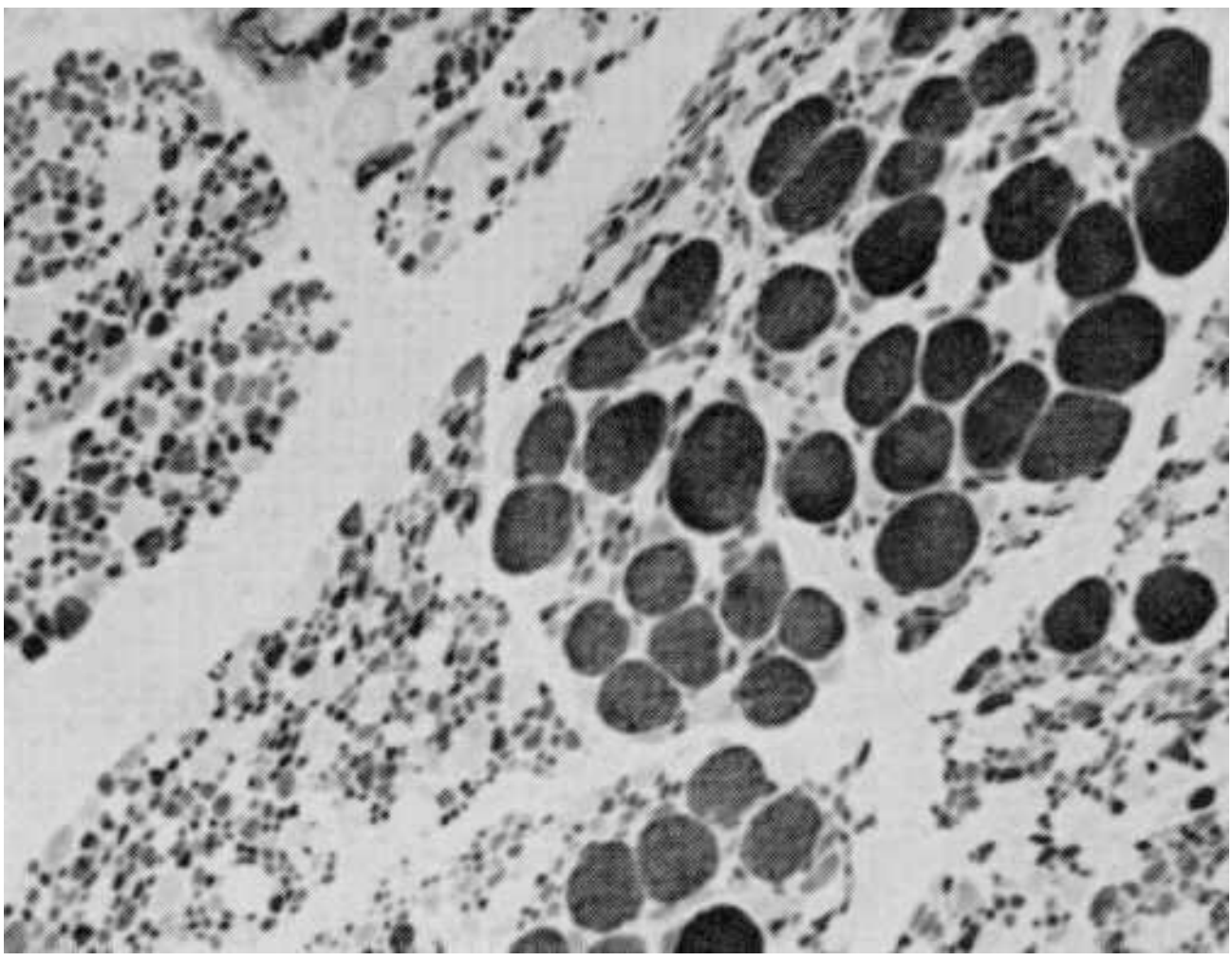
- mothers notice decreased intrauterine movements.
- one of most common forms of *floppy infant syndrome* (infants lie flaccid with little movement, unable to overcome gravity).
- tongue is often seen to fasciculate (rarely in limb muscles - because of ample subcutaneous fat).
- ultimately, **complete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

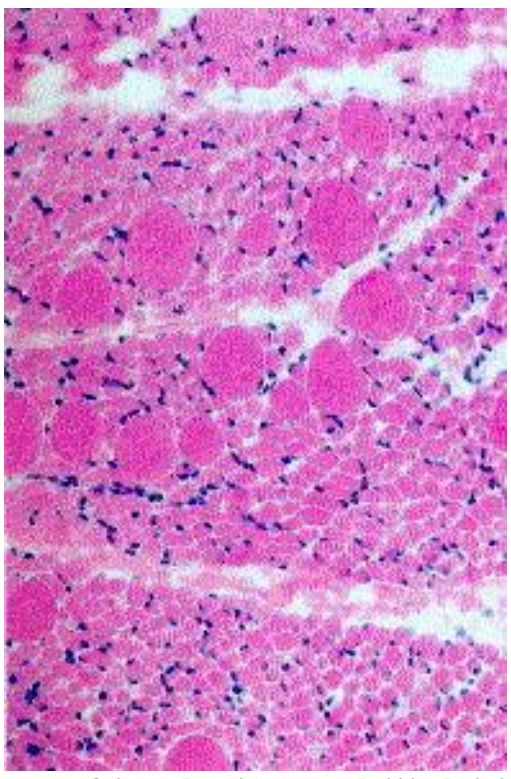
SMA type 3 (Kugelberg-Welander) – slowly progressive gait disorder in *late childhood or adolescence*.

- **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

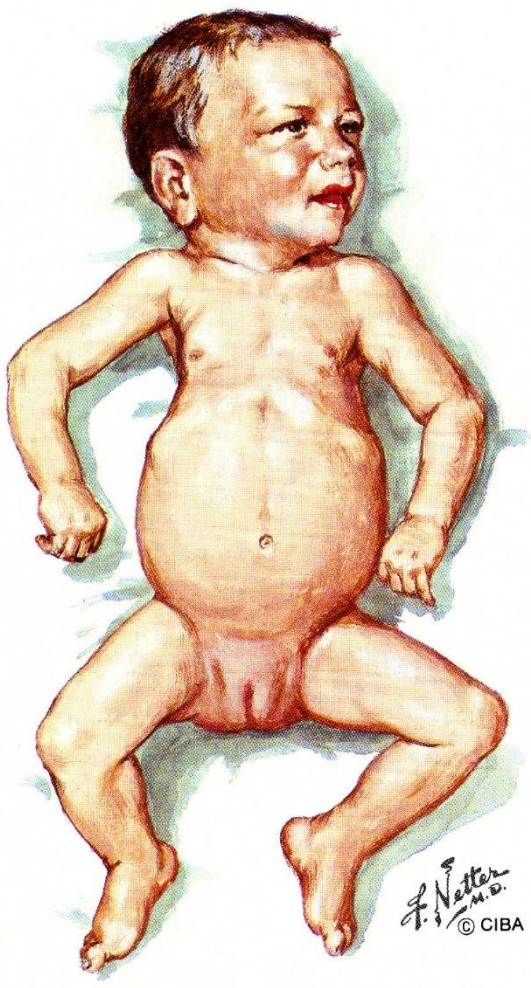
- **genetic test** – homozygous SMN deletion (sensitive test in 95% cases!).
  - prenatal testing is available only on research basis.
- **serum CK** can be elevated (correlates with illness duration);
  - in **SMA 3**, may be 20 times normal (in range of many myopathies!).
- **ECG** – normal.
- without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



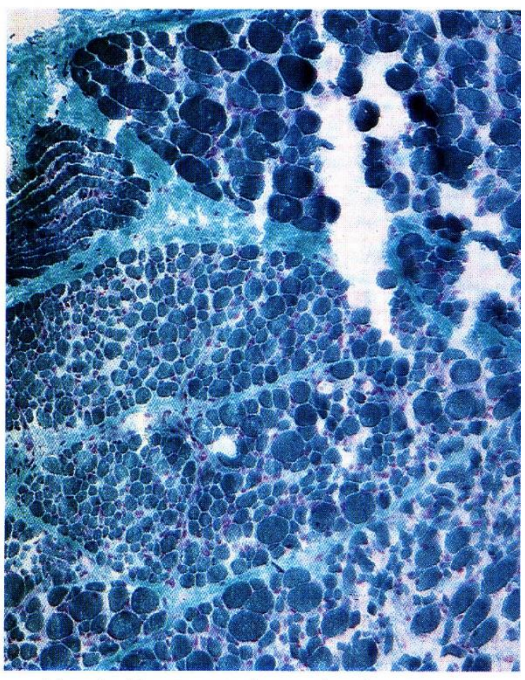


Source of picture: Ramzi S. Cotran "Robbins Pathologic Basis of Disease", 6th ed. (1999); W. B. Saunders Company; ISBN-13: 978-0721673356 >>

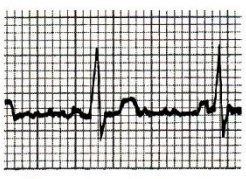
Werdnig–Hoffmann Disease



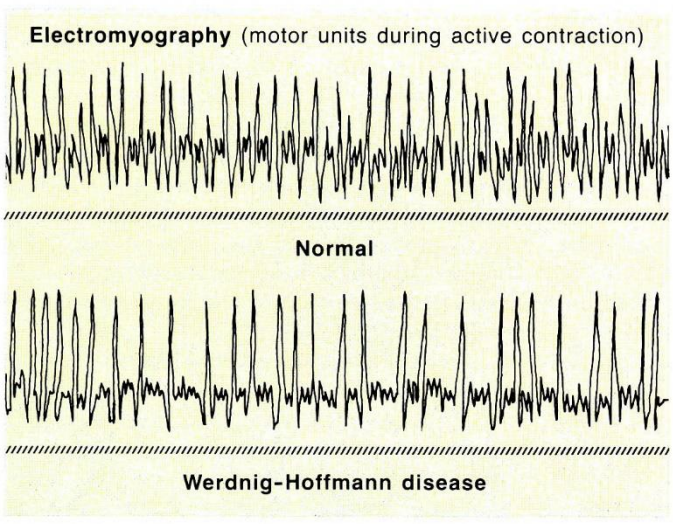
Infant with typical bell-shaped thorax, frog-leg posture, and "jug-handle" position of upper limbs

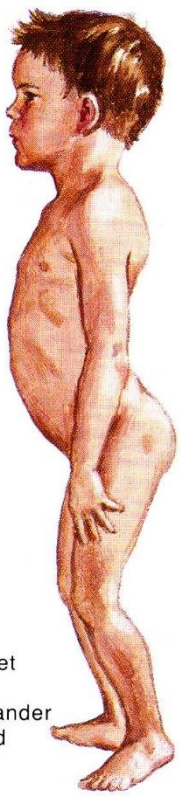


Muscle biopsy specimen showing groups of small atrophic muscle cells and areas of normal or enlarged cells (group atrophy). (Toluidine blue O stain)



Baseline tremor in otherwise normal electrocardiogram





Boy with much milder, late-onset form of disease (Kugelberg-Welander disease). Marked lordosis and eversion of feet

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.

RISDIPLAM (Evrysdi®) taken by mouth or via a feeding tube – gene-splicing modulator that increases production of survival of motor neuron protein (SMN), needed for survival of motor neurons - FDA approved for treatment of SMA in adults and children age 2 months or more.

PROGNOSIS

Earlier onset – more rapid decline.

Other Forms of LMN degeneration

Poliomyelitis – viral disease of LMN – see p. 259 (1) >>

- 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:

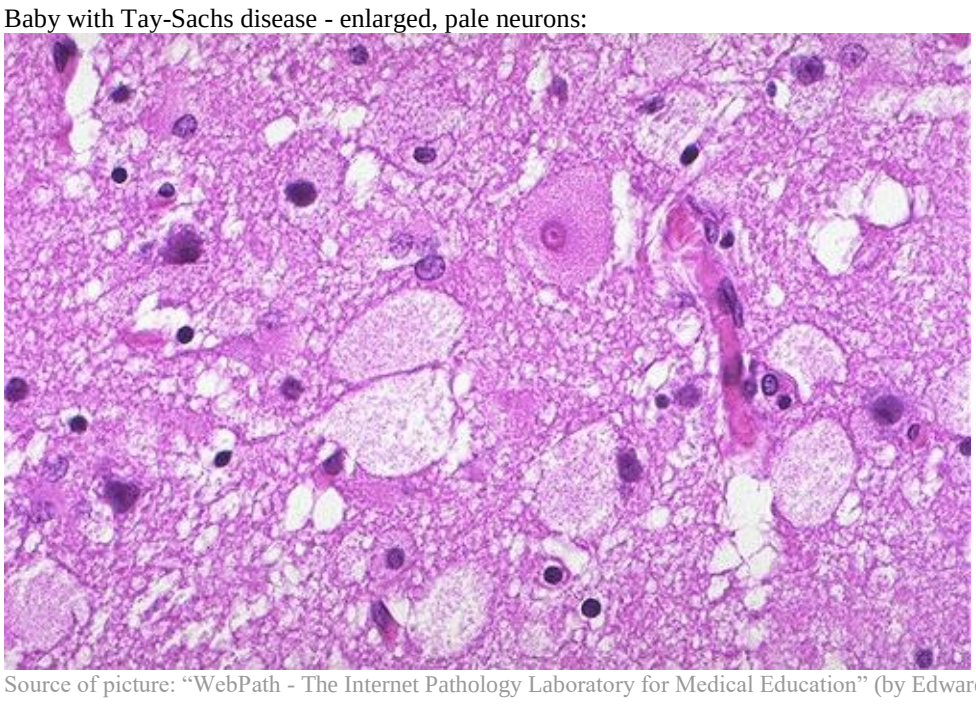
1) ***progressive bulbospinal muscular atrophy*** (preferentially **bulbar*** → **distal** limb muscles) *incl. ocular!
2) ***endocrine dysfunction*** – androgen insensitivity (testicular atrophy, gynecomastia, oligospermia), diabetes mellitus.
3) subtle *sensory sign* in some patients. (e.g. abnormal 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) >>

BIBLIOGRAPHY for ch. "Spinal Disorders" → follow this LINK >>