**Spinal Muscular Atrophies (SMA)**

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

Last updated: August 8, 2020

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**ETIOPATHOPHYSIOLOGY**

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**EPIDEMIOLOGY**

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**CLINICAL FEATURES**

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**DIAGNOSIS**

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**TREATMENT**

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**PROGNOSIS**

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**OTHER FORMS OF LMN DEGENERATION**

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

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

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

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**SPINAL MUSCULAR ATROPHIES (SMA)**

Autosomal recessive SMA types I, II, III (allelic heterogeneity) have been linked to **SMA1-SMA4** - 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!
  - 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 SMN (telomeric copy of SMN) → SMA type I; mutations that convert SMN 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 focus 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.

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**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 ≈ 4-5%.

**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), atrophy, respiratory / nutritional / sleep problems. No sensory symptoms or loss, no myalgias! No heart involvement! Intelligence normal! (children often appear brighter than their normal peers!)

2. HYPOTONIA, ATROPHY, LOSS OF TENDON REFLEXES

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

3. CEREBRAL NERVE PALSYs (CN3, 4, 6 are typically spared!).

SMA type I (Werdnig-Hoffmann) - evident at birth or soon thereafter, always before age 6 months.
mothers notice decreased intrauterine movements.

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!).
  \[ \text{prenatal testing is available only on research basis.} \]
- serum CK can be elevated (correlates with illness duration);
  \[ \begin{align*}
  \text{in SMA 3, may be 20 times normal (in range of many myopathies!)}
  \end{align*} \]
- 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]
S PINAL MUSCULAR A TROPHIES (SMA)

TREATMENT

- Multidisciplinary approach aimed at preventing contractures, skeletal deformities, respiratory complications, and social isolation.

NUSSERBERG (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.


RISDIPLAM (Evrysdi®) taken by mouth or via a feeding tube – gene-spllicing 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

Polymyelitis – 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 bulbar muscular atrophy (preferentially bulbar* → distal limb muscles).
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:

**BIBLIOGRAPHY for ch. “Spinal Disorders” → follow this LINK >>**