Spinal Muscular Atrophy

Epidemiology	10-15 in 100,000 liver births (rare)
Genetics	➢ Autosomal recessive (consanguinity increases its risk) ➢ Genetic locus on chromosome 5 ➢ Secondary to SMN1 homozygous deletion (absent SMN1) ➢ SMN2 ▪ >99% identical to SMN1 (with the exception of **missing exon 7 in SMN2**) ▪ Less/non-functional (produces SMN proteins that mostly get degraded) ▪ Present in all patients with SMA (functions as "back-up" for SMN1) ▪ Milder SMA forms have >2 SMN2 copies
Pathophysiology	Degeneration of the anterior horn cells (and **α motor neurons**) due to lack of the protective **SMN proteins** ▪ Alpha motor neurons: - Main lower motor neurons (more abundant than gamma motor neurons) - Innervate extrafusal muscle fibers (while gamma motor neurons innervate intrafusal muscle fibers)
Types	Depends on the number of SMN2 copies ▪ Type 0: Fetal form ▪ Type 1 (Werdnig-Hoffman disease): Early infantile form (onset <6 months old) - **MOST COMMON form** ▪ Type 2: Late infantile form (onset 6-18 months old) ▪ Type 3 (Kugelberg-Welander disease): Juvenile form (onset >18 months old)
Clinical features	Hypotonia, weakness (progressive; proximal > distal), muscle atrophy, diminished/absent DTR, fasciculations (spares extraocular muscles & cognition) ▪ Type 0: Diminished fetal movements & IUD; **MOST SEVERE** ▪ Type 1: Severe hypotonia, weakness (progressive; proximal > distal), muscle atrophy, diminished/absent DTR, fasciculations (mainly of the tongue) in the **1st few weeks of life** - NEVER able to sit without treatment - Can affect muscles of sucking, chewing, swallowing & breathing (diaphragmatic involvement is late) - Most die before the age of 2 Y/O without treatment ▪ Type 2: Later onset and slower progression than type 1 - **Often able to sit but not walk** - Often does not affect sucking, chewing, swallowing & breathing - Can cause nasal speech, GERD, and scoliosis later in life ▪ Type 3: Later onset and slower progression than type 2; **MILDEST** - **Often ambulatory** (often presents with falls/difficulty climbing stairs) - Often does not affect sucking, chewing, swallowing & breathing - Can cause nasal speech, GERD, and scoliosis later in life
Newborn screening	➢ Detects defects in SMN1 gene ➢ Abnormal screening test → further testing to confirm Dx ➢ Best prognosis if treatment starts in the pre-symptomatic phase
Diagnosis	➢ CK can be normal or elevated ➢ Molecular genetic diagnosis by DNA probes in blood samples or in muscle biopsy ➢ Motor nerve conduction study is normal, except for **mild slowing in terminal disease** (this is an important distinguishing feature between SMA and peripheral neuropathy) ➢ EMG shows **fibrillation potential** and other signs of muscle denervation ➢ Muscle biopsy shows muscle atrophy
Management	➢ Supportive management (PT, OT, nutritional & respiratory support) ➢ Genetic therapy **(nusinersan; Spinraza)** ▪ Oligonucleotide splicing modulator ▪ Corrects exon 7 skipping in SMN2 (promotes the inclusion of exon 7 in SMN2) ▪ Dosing: - 12 mg intrathecally per administration - Initial: 4 loading doses; first 3 doses at 14-day intervals, fourth dose 30 days after the third dose - Maintenance: One dose every 4 months (life-long) ▪ Side effects: Headache, back pain, respiratory tract infections, thrombocytopenia, elevated urine protein ▪ Blood work (at baseline and prior to each dose and as clinically needed): - Platelet count, coags, quantitative spot urine protein testing ➢ Gene therapy **(onasemnogene abeparvovec-xioi; Zolgensma)** ▪ Adeno-associated virus vector-based gene therapy that targets the cause of SMA (delivers SMN1 gene) ▪ One dose IV administration ▪ Approved to treat children <2 Y/O with SMA type 1 ▪ Side effects: Thrombocytopenia, elevated liver enzymes/hepatitis and elevation of troponin-I ▪ Blood work: - Adeno-associated virus 9 (AAV9) antibody test BEFORE treatment (if antibodies are positive, child may not qualify) - Platelet count, liver enzymes and troponin-I BEFORE and regularly AFTER treatment for at least 3 months ▪ Steroid therapy (+PPI) is often needed following treatment to decrease the risk of hepatitis ▪ For more details and family resources → **https://www.zolgensma.com/** ➢ Requires F/U with NM neurologist