Spinal muscular atrophy

Genetics

-Genes: SMN1 (SMNT), SMN2 (SMNC) (survival motor neuron protein 1 and 2; 5q12.2-q13.3)

-AR

Clinical findings/Dysmorphic features

-Arthrogryposis multiplex congenita (congenital joint contracture in >2 areas of body)

-Progressive degeneration and loss of anterior horn cells in the spinal cord (i.e. lower motor neurons) and the brain stem nuclei --> muscle weakness and atrophy

-Onset of weakness ranges from before birth to adolescence/young adulthood

-Weakness is symmetric, progressive, proximal > distal

-SMN1-associated SMA spans a continuum without clear delineation of subtypes

-Complications: poor weight gain, FTT, restrictive lung disease, scoliosis, joint contractures

-Loss of deep tendon reflexes

Etiology

-Incidence 4-10 in 100,000; Carrier frequency: 1:50 – 1:100

Pathogenesis

-Role for SMN protein in snRNPs (small nuclear ribonuclear proteins) biogenesis and function

-Reduced SMN lowers the capacity of cells to assemble snRNPs --> altered levels of spliceosomal components and defects in splicing --> impaired production of specific mRNAs and proteins

Genetic testing/diagnosis

-Targeted analysis: deletion of SMN1 exon 7 deletion (95-98%), SMN1 sequencing (2-5%)

-Carriers with 2 SMN1 in cis (~4% of the population) will be misdiagnosed as non-carriers

-Quantitative PCR and MLPA to detect single-exon deletions or duplications (SMN1 and SMN2 are nearly identical --> gene-targeted microarray cannot be used to determine copy number)

-SMN1 sequencing cannot determine whether an inactivating variant is in SMN1 or SMN2 -->

1) Establish that the inactivating variant has previously been reported in SMN1

2) Sequence a long-range PCR product or a subclone of SMN1

Others

-Increase in SMN2 copies often improves phenotype; absence of both SMN genes --> lethal

-SMN2 predominantly produces protein that is lacking in exon 7 (splice site variant in SMN2)

-Treatment: SPINRAZA® (nusinersen); ASO targeted to SMN2 --> increased exon 7 inclusion

-Newborn with weakness, hypotonia, absent reflexes, and tongue fasciculations