Lower Motor Neurons
Motor Neuron Disorders
Neuropathy

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Outline

• Motor neurons
  – Upper and lower
• Motor neuron disorders
  – Anterior horn cell diseases
• Peripheral nerve disorders
  – Nerve root
  – Plexus
  – Nerve
Motor Neurons

- Upper motor neurons: Cell bodies in motor cortex, axons descend down through internal capsule, brainstem, and spinal cord to synapse on...
Motor Neurons

- Lower motor neurons: Cell bodies are anterior horn cells, axons exit ventral roots, join dorsal roots at intervertebral foramen and travel through nerves to muscles.
Phenomenology

• Upper motor neuron signs:
  – Weakness and slowness of movement
  – Increased tone (spasticity)
  – Hyperreflexia
  – Upgoing toes (Babinski’s sign)

• Lower motor neuron signs:
  – Weakness
  – Decreased tone
  – Hyporeflexia
  – Muscle atrophy
  – Fasciculations and cramps
Motor Neuron Disorders

• Spinal muscular atrophy
• Amyotrophic lateral sclerosis
Spinal Muscular Atrophy

• Type I (Werdnig-Hoffman)
  – Onset before 6 months of age

• Type II
  – Onset between 6 and 18 months of age

• Type III (Kugelberg-Welander)
  – Onset after 18 months of age

• Type IV
  – Adult-onset, third to fourth decade
Spinal Muscular Atrophy

• Autosomal recessive inheritance
• Due to homozygous deletion or point mutation of SMN1 gene on chromosome 5
• Severity of phenotype related to number of SMN2 copies
• Treatment for all types is largely supportive
• Nusinersen approved Dec 2016
• Gene therapy in Phase I trials
Spinal Muscular Atrophy

• SMA I: Werdnig-Hoffman Disease
  – Incidence 4-10/100,000
  – Manifests in first 6 months of life
  – Hypotonia with generalized (though proximally predominant) weakness, tongue fasciculations, abdominal breathing, weak cry, poor suck
  – Never sit
  – Only 8% of individuals reach age of 10 years
Spinal Muscular Atrophy

• SMA II: Intermediate form
  – Onset between 6 – 18 months of age
  – Child can sit independently but never walks
  – Otherwise symptoms mimic SMA I
  – Postural hand tremor
  – Prone to kyphoscoliosis and joint contractures
  – Two-thirds of individuals survive to age of 25 years
Spinal Muscular Atrophy

• SMA III: Kugelberg-Welander Disease
  – Onset after 18 months of age
  – Will sit and walk but never run
  – 40% still walking at 40 years of age
  – Postural hand tremor
  – Life expectancy not typically affected
Amyotrophic Lateral Sclerosis

• Neurodegenerative disorder characterized by loss of motor neurons in the spinal cord, brainstem, and motor cortex
  – Clinically, leads to a combination of UMN and LMN symptoms and signs
• Incidence roughly 1-2.5/100,000
• Etiology unknown and progression of the disease is relentless resulting in death
  – 10% cases familial, e.g. C9orf72, SOD1 mutations
The Iron Horse
ALS - Presentation

• 2/3 patients with limb-onset of symptoms
  – Weakness and wasting of distal limb musculature
  – Fasciculations and cramps
  – Lack of sensory symptoms

• 1/3 patients with bulbar-onset of symptoms
  – Dysphagia, dysarthria, dysphonia, chewing difficulty

• Most patients eventually develop respiratory muscle weakness
  – Dyspnea, orthopnea, signs of CO2 retention
  – Most deaths from ALS are due to respiratory failure
ALS - Treatment

- Riluzole: NMDA receptor antagonist
- Edaverone: Approved late 2017 – reduces oxidative stress
- Nutrition
- Physical and occupational therapy
- Speech and swallowing therapy
- Respiratory management
- Management of symptoms
  - Spasticity
  - Siallorhea
ALS - Prognosis

• Median survival from time of disease onset ranges from 24 to 36 months looking at data from several studies of the natural history of ALS
• Median survival from time of diagnosis ranges from 14 to 21 months in the same studies
• 3 year survival from onset roughly 40%
• 5 year survival from onset roughly 25%
Other Disorders of the Anterior Horn Cell

• Progressive bulbar palsy
• Progressive muscular atrophy
• Kennedy’s disease (x-linked spinal muscular bulbar atrophy)
• Infectious etiologies
  – Poliovirus, enteroviruses, West Nile virus, HIV
Nerve Root

- Degenerative disease of the spine
- Disc herniation
- Inflammatory or infectious
- Neoplastic
Radiculopathy

Far lateral cervical disc herniation causes compression of the nerve and the dorsal root ganglion.
Radiculopathy

- Neck or back pain usually present
- Pain and mild sensory loss in distribution of nerve root (dermatomal pattern)
- Weakness rare due to myotomal overlap of muscle innervation
- Treatment either surgical or conservative
- Most cases are self-limited but may recur with time
Plexus

Note: Usual composition shown. Prefixed plexus has large C4 contribution but lacks T1. Postfixed plexus lacks C5 but has T1 contribution.
Causes of Plexopathy

• Trauma
  – Birth trauma
    • Erb’s palsy: upper trunk injury
    • Klumpke’s palsy: lower trunk injury

• Inflammatory/Autoimmune
  – Parsonage-Turner syndrome

• Neoplastic invasion (lung, lymphatic, breast)
• Radiation exposure
• Structural anomalies
Nerve

- Mononeuropathies
- Polyneuropathies
Mononeuropathies

• Strictly defined as injury to a single nerve
• Common examples:
  – Bell’s palsy (CN VII)
  – Carpal tunnel syndrome (median neuropathy at the wrist)
  – Ulnar neuropathy at the elbow
  – Saturday night palsy (radial neuropathy at the spiral groove)
  – Common peroneal neuropathy at the fibular neck
Bell’s Palsy

• Annual incidence 13-34 cases/100,000 population

• No race, gender, or geographic predilection
  – Risk is three times greater during pregnancy (particularly first trimester) and first post-partum week

• Idiopathic, though most commonly thought to be caused by HSV-1 activation/infection
  – Other viral infections: VZV, CMV, EBV, etc
Bell’s Palsy
Polyneuropathy

• Types of fibers involved:
  – Sensory
    • Small fibers (A delta, C fibers)
    • Large fibers
  – Motor
  – Autonomic
    • Small fibers

• Pathophysiology
  – Axonal
  – Demyelinating
Causes of Polyneuropathy

- Axonal Neuropathies
  - Diabetes mellitus/dysglycemia
  - Amyloidosis or plasma cell dyscrasias
  - Vasculitis, e.g. polyarteritis nodosa, Churg-Strauss syndrome
  - Paraneoplastic
  - Nutritional, e.g. vitamin B1, B6, B12, E deficiency
  - Infectious, e.g. viral (especially HIV)
  - Secondary to toxins, e.g. arsenic, lead, thallium
  - Secondary to metabolic disturbances, e.g. liver failure, uremia, sepsis
  - Secondary to medications, e.g. chemotherapeutic agents, antibiotics
  - Hereditary (Charcot-Marie-Tooth disease type 2)
  - Immune-mediated, e.g. axonal variants of AIDP also known as AMAN and AMSAN, also Sjogren’s and other collagen vascular diseases
  - Idiopathic
Causes of Polyneuropathy

• Demyelinating neuropathies
  – Immune-mediated: Guillain-Barre Syndrome (AIDP), CIDP (chronic inflammatory demyelinating polyneuropathy)
  – Hereditary: e.g. Charcot-Marie-Tooth disease types 1, 3, and 4
  – Paraneoplastic: MGUS (IgM), hematologic malignancies
  – Infectious: diphtheria
Guillain-Barre Syndrome (AIDP)

- Most common cause of acute weakness in Western countries
- Incidence: 0.6 to 1.9/100,000 population
- Antecedent illness
  - Viral syndrome (URI, gastroenteritis) precedes illness in about 2/3 of cases, typically 1-3 weeks before development of neurological symptoms
- Fairly rapidly progressive ascending weakness and sensory symptoms
Guillain-Barre Syndrome (AIDP)

• Motor symptoms (weakness) usually predominate over sensory symptoms
• Areflexia on examination
• Albuminocytologic dissociation in CSF
  – No white blood cells, elevated protein
• EMG and nerve conduction studies demonstrate a demyelinating neuropathy
Guillain-Barre Syndrome (AIDP)

- Treatment
  - IVIg or plasmapheresis
  - Respiratory management
  - Treatment of dysautonomia
  - Physical and occupational therapy
Guillain-Barre Syndrome (AIDP)

- Course
  - Symptoms progress over the first 1 to 2 weeks in most patients
  - 95% of patients reach their nadir by 4 weeks
  - Plateau phase for 1 to 4 weeks
  - Improvement ensues, however rate variable and dependent on severity of symptoms at nadir (usually over 2-12 months)
  - Relapses in 2 to 10%
  - CIDP in 2%
Guillain-Barre Syndrome (AIDP)

• Prognosis
  – Majority of patients (80%) have no or minor sequelae
  – Permanent disabling symptoms in 5-10%
  – Mortality < 5%