Neurological Disorders (part 2)

Developmental Disorders

- **Inherited Metabolic Disorders**: deficiency in production of an enzyme
  - Genetic Bases
    - PKU: deficit in phenylalanine --> tyrosine conversion
      - Lack of myelination
      - Mental retardation if untreated
      - Detectable at birth and prevented by low protein diet
      - Lack of vitamin B6: damage to thalamus and cerebellum
      - Lack of (milk) glucose metabolism (Galactosemia): damage to cerebellum/cortex
  - Tay-Sachs Disease: inability to breakdown cellular waste products.
    - Accumulation of waste in brain, death.
    - Retinal diagnosis, common in eastern European Jewish pop.
  - Down Syndrome: congenital (born with)
    - 1/700 children have it
      - Extra chromosome 21 in mother's ovum. Over expression of genes, can be detected before birth
      - 10% less brain, less neurons in frontal lobe and superior Temp. gyrus (Wernicke's area)
      - Mild to severe mental retardation. Can learn to live almost normal lives. No cure
      - Research: focused on avoiding associated diseases (heart condition, epilepsy, hearing/vision
      - issues…) and trying to determine how to control the gene over-expression pattern

Degenerative Disorders

- **Transmissible Spongiform Encephalopathy**: Mad Cow Disease
  - Sporadic: can be infectious or genetic
  - Caused by 'protein infectious agents' (prions)
• Found in neural membranes, important for synaptic function and the production of myelin
• Normal amino acid composition, but misfolding
• Symptoms similar to Alzheimer's but faster and deadlier
• No known cure or treatments in humans but there is genetic manipulations in mice.

- **Scrapie:**
  - Can be treated by late onset destruction of (normal) prions
  - Prions are useful for development so cannot be immediate
  - In mice: Treatment involves a prion-destructive protein produced after 12 weeks

- **Possible genetic therapies:**
  - Selective activation of cell death in infected cells only.
  - Uses Caspases: enzyme that triggers cell death (apoptosis)

- **Parkinson's Disease:** classified as movement disorder
- **Symptoms:**
  - Rigidity, slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movement), posture and walking abnormalities, bradykinesia and akinesia
  - Initially, little intellectual impairments:
    - As it progresses: speech impairments, decreased short term memory and slower visual spatial skills
  - Mood changes, depression, anxiety
  - In general not hereditary. Sporadic. Affects .5% of population, slow progression (~20 yrs.)
  - No single cause. No cure.
  - Degeneration of Basal Ganglia

- **Neural Structures Affected:**
  - Degeneration of Pars Compacta region of substantia nigra --> basal ganglia
  - Caused by cell death of dopamine neurons
  - Decreased activity in 4 areas that receive inputs from the basal ganglia
    - Motor complex
- Oculomotor and associative areas
- Limbic systems
- Orbitofrontal cortex

- **Physiological Mechanisms of PD**
  - Lack of dopamine
  - Nigro-striated dopaminergic neurons almost gone
  - Lewy bodies: protein 'growth' within dopamine cells
  - Possible due to defect on Chromosome 4: protein produced (a- synuclein) is misfolded
  - Toxic gain of function- production of a toxic protein by a faulty gene
  - Mutation on chromosome 6: **Parkin Gene**
    - Ubiquitin tags faulty/misfolded protein
    - Tagged proteins are destroyed by proteasomes
    - Parkin gene helps in ubiquitin tagging
  - Mutation--> loss of Parkin function (no tagging of misfolded proteins)
  - Not only genetic: other possible mechanisms include decreased mitochondrial activity
    and iron buildup

- **Treatments:**
  - MAO inhibitors: (deprenyl) ability to prevent destruction of monoamines
    - Slows progression
  - L DOPA- promote production of dopamine
    - Side effects (hallucinations)
    - Effects are temporary. Eventual complete destruction of dopamine neurons
  - Direct fetal dopamine cell transplantation in the Basal Ganglia
    - Side effects (involuntary movements)
  - Pallidotomy: precise lesions of the Globus Pallidus
  - Deep brain inhibitory stimulation of sub-thalamic nucleus (STN)

- **Current research on PD:**
  - Gene therapy: modified virus that inhibits STN --> increase activity of Supplemental
    Motor Area --> decrease PD symptoms
Neuroprotective Agents: chemicals that protect brain. Control a-synuclein protein that is misfolded

Stem Cells: increase dopamine secretion

- Huntington's Disease
  - Symptoms
    - Uncontrollable and excessive movements. Uncoordinated activation of motor programs
  - Rare, associated with dementia. Symptoms appear after 35 years and death occur after 15 years of onset
    - Toxic gain of function
  - 1630's Witches of Bures (UK)
  - Neural Substrate: degeneration of caudate and putamen.
  - Affect: GABA and Ach cells in the basal ganglia.
    - Enlarged ventricles.

- Treatment:
  - None, just management therapies
  - 1/10,000 people
  - Gene is identified and tests exist to determine whether it is present
  - Research focuses on Gene Therapy

- Alzheimer's
  - Symptoms:
    - Affects 10% of < 65 yrs old and > 50% of 85 yrs old population
    - Not entirely hereditary
    - Progressive- depression, loss of memory and mental function (dementia)
      - Resemble anterograde amnesia in declarative memory
      - Down syndrome can develop into Alzheimer's
      - Terminal disease
Neural Substrate:
• Degeneration of Ach center (Nucleus Basalis)

• Degeneration of the hippocampus, frontal and temporal corticles, rape nucleus and locus coeruleus

• Development of:
  ▪ B- Amyloid plaques: Accumulation of them = cell death
  ▪ Neurofibrillary tangles. Dead microtubules also in down syndrome

Treatment:
• No cure, causes unclear, gene mutation on chromosome 21 (amyloid gene)

Amyotrophic Lateral Sclerosis (ALS)
Symptoms:
• Stiffness, exaggerated reflexes, muscular atrophy, terminal (5-10 years after onset). No dementia

• Mostly sporadic

• Some have noticed relationship between ALS and chromosome 21 (misfolding protein = toxic gain of function)

Neural substrate:
• degeneration of spinal cord motor neurons and cranial nerves. Excitotoxicity

Treatment:
• No cure, drug that deceases glutamate release, improves symptoms. Gene therapy

Multiple Sclerosis (MS)
Symptoms:
• Complex and diverse. Slowly evolving, not hereditary and not contagious
• More women than men (20-30 yrs old)
• Loss of motor coordination, tremors, numbness

Neural substrate:
• autoimmune disease. Degeneration of myelin and formation of sclerotic plaques

Treatment:
• Genetic component (gypsies and Asians are low risk), environmental component (childhood in cool climates are high risk). Influencing the immune system.
• No cure
• Partial recovery
Infectious Diseases

- **Encephalitis and Meningitis**
  - Symptoms:
    - Fever, irritability, nausea --> convulsion, delirium
    - 10% terminal, 20% results in permanent brain damage
  - Neural Substrate:
    - Viral infections (mosquitoes or STD), bacteria, fungi
    - Encephalitis- affects whole brain
    - Meningitis- affects meninges
  - Treatment: none in general
    - **Herpes Simplex (cold sores)** - virus lives inside spinal ganglion
    - Encephalitis results from break out to the brain (rare) in frontal and temporal lobes primarily
    - No cure
  - **Polio** - damage to all motor neurons (brain and spinal cord)
    - Vaccine (founded by Jonas Stalk)
  - **Rabies** - fever and headaches --> convulsions, seizures, death within a week
    - Affects cerebellum and hippocampus.
    - Vaccine
  - **AIDS (no HIV)** - brain damage in 75% of cases in untreated. Due to excess of CA2+ through NMDA receptors (excitotoxicity). Hippocampus and Cortex
  - **Meningitis** - headache and stiff neck --> convulsion, death,
    - Damage resulting in impaired blood/CSF circulation. Cranial nerve damage
    - Treatable with antibiotics and vaccine

***Skip: Fig. 14.16-14.18 and page 380 (starting at APP)-382 (Before ALS)***