Neurological Disorders II

Developmental Disorders:
-inherited metabolic disorders: deficiency in the production of an enzyme; genetic bases
   -PKU: (Phenylketonuria): deficit in phenylalanine -> tyrosine conversion.
     -lack of myelination, mental retardation if untreated
     -mental retardation if untreated
     -detectable at birth. Preventable by appropriate diet (low protein)
   -lack of vitamin b6: damage to thalamus and cerebellum
   -lack of (milk) glucose metabolism (galactosemia): damage to cerebellum and cortex
     -Eastern European Jewish population
     -There is a retinal diagnosis
   -Down syndrome: congenital ('born with')
     -1/700 children; 350,000 people in the US
     -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 Sup. Temp. Gyrus (Wernike’s area)
     -mild to severe mental retardation. Can learn to have almost normal lives
     -no cure
     -research:
       -focused on avoiding associated diseases (heart condition, epilepsy, hearing/ vision deficits); determine gene over-expression pattern

-Transmissible Spongiform Encephalopathy
   -mad cow disease or creutzfeldt-jakob disease, scrapie (animals only)
   -sporadic: can be infectious or genetic
   -caused by ‘protein infectious agents’ (prions)
   -found in neural membranes
   -important for synaptic function and myelin
   -normal aminoacid composition, but misfolding
   -symptoms similar to alzheimer’s, but faster and deadlier
   -no known treatments in humans
   -for animals there is genetic manipulations in mice
   -figure 14.9

Degenerative Disorders
-Scapies:
  -can be treated by late onset destruction of (normal) Prions
  -Prions are useful for development
  -treatment invokes a prion-destructive protein produced after 12 weeks (mice)
Possible genetic therapies: selective activation of cell death in infected cells only; use caspases: Enzyme that triggers cell death (a.k.a. Apoptosis)

**Parkinson's Disease:** (classified as movement disorder)

**Symptoms:**
- Rigidity, slow movement, absence of reflexes, tremor at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia (slow movement), and akinesia (no movement at all)
- Initially, little intellectual impairments. As it progresses: speech impairments, decreased short term memory, slower problem-solving and slower visual spatial skills
- Mood changes (depression and anxiety)
- Not hereditary
- Sporadic
- Affects 0.5% of adult population and slow progression (~20 years)
- No single causes (genetic, strokes, tumors, infections)
- No cure

**Degeneration of the Basal Ganglia**
- Neural structures affected & related to Parkinson's
  - Degeneration of pars compacta region of Sub. Nigra -> basal ganglia
  - Caused by cell death of dopamine neurons
  - Decreased activity of 4 areas that receive inputs from the basal ganglia:
    - Motor cortex, oculomotor and associative areas, limbic system, orbitofrontal cortex

**Physiological Mechanisms of PD**
- Lack of dopamine: nigro-striatal dopaminergic neurons almost gone
- Lewy bodies: protein 'growth' within dopamine cells
- Possibly due to a defect on chromosome 4: the protein (a-synuclein) produced is misfolded
  - Toxic gain of function: production of a toxic protein by a faulty gene
    - Figure 14.11
  - Mutation on chromosome 6: parkin gene
  - Ubiquitin tags faulty/ misfiled protein
  - Tagged proteins are destroyed by proteasomes
  - Parkin gene helps in ubiquitin tagging
    - Mutation -> loss of parkin function
  - Not only genetic: other possible mechanisms include decreased mitochondrial activity and iron build-up
  - Ubiquitin + misfolded protein -> parkin -> 'tagged' misfolded protein -> proteasomes -> amino acids
    - Figure 14.12

**Treatments:**
- MAO inhibitors (deprenyl): prevents the destruction of monoamines
  - Slows down progression of PD
-L-Dopa: promote the production of dopamine; side effects (hallucinations). Effects are temporary. Eventually complete destruction of dopamine neurons
  - Direct fetal dopamine cell transplantation in Basal Ganglia. Side effects: involuntary movements
  - Pallidotomy: precise lesions of the globus pallidus:
    - sub. Nigra -> dopamine (inhibitory) -> glob. Pall. (inhibitory) -> motor systems
    - subthalamic nucleus (excitatory) -> glob. Pall. (inhibitory) -> motor systems
  - Deep brain inhibitory stimulation of subthalamic nucleus (STN)

-Figure 14.13
-Current Research on PD
- Gene therapy: modified virus that inhibits STN -> increase activity in Supplemental Motor Area -> Decrease PD symptoms
- Neuroprotective agents - chemicals that protect brain. Control a-synuclein
- Stem cells - increase dopamine secretion

Quiz:
True: Meningiomas are tumors originating in the meninges
True: Gliomas are tumors originating in glial cells
In the brain an obstructive blood clot that travels through the blood stream is called a _____. It can cause a stroke.
In the brain, an obstructive blood clot, that remains in place is called a _____. It can cause a stroke.
During a stroke, cell death is due to:
  - not enough oxygen
False: a malignant tumor can easily be removed surgically
False: Fetal Alcohol Syndrome is induced by a virus

Degenerative Disorders:
-Huntington’s Disease:
  - symptoms: uncontrollable and excessive movements. Uncoordinated activation of motor programs
  - rare, associated with dementia. Symptoms appear after 35 years old, death after 15 years from onset
  - terminal disease; hereditary (dominant gene, C4); misfolded protein (huntingtin) accumulation. 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
  - caudate putamen -> inhibits/ no GABA -> prefrontal cortex and motor cortex (excitatory) -> motor activity/ plans
  - treatment:
none; 1/10,000 people get it
-management therapies
-gene is identified, tests exist to determine whether it is present in a person or not
-research focuses on gene therapy because it is only genetic
-Alzheimer’s disease
-symptoms:
  -affects 10% of people 65+ years old and 50% if 85+ years old
  -progressive: depression, loss of memory and mental function (dementia)
  -resembles anterograde amnesia of declarative memory
  -down syndrome develops sometimes into alzheimer’s
  -terminal disease
-neural substrate: degeneration of ACh center (nuc. Basalis)
  -degeneration of the hippocampus, frontal and temporal cortices, raphe nucleus and locus coeruleus
  -neurofibrillary tangles. Dead microtubules. Also in down syndrome
-treatment: no cure; causes unclear; gene mutation on chromosome 21 (amyloid gene)

SKIP FIGURES: 14.16 - 14.18 and p.380 (starting at APP) to p. 382 (before ALS)