Degenerative Disorders

- E.g.: Bovine Spongiform Encephalopathy (BSE = ‘mad cow disease’), Creutzfeldt-Jakob disease, scrapie (animals only)
  - Sporadic: can be genetic or infectious
    - Caused by ‘protein infectious agents’ (prions). Found in Neural membranes, important for synaptic function and myelin. Normal aminoacidic composition, but misfolding
    - Symptoms similar to Alzheimer’s, but faster and deadlier
    - No known treatments in human. Genetic manipulations in mice.
  - Scrapie can be treated by late onset destruction of (normal) prions. Prions are useful for development. Treatment involves 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 a movement disorder
  - Rigidity: slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia (slow movements), and akinesia.
  - Initially, little intellectual impairments. As it progresses: speech impairments, decreased short term memory, slower problem solving and slower visual spatial skills
  - Mood changes, including depression. Anxiety also common
  - In general, not hereditary. Sporadic. Affects .5% of adult population, slow progression (20 years)
  - No single causes (genetic, strokes, tumors, infections...) no cure.

- Degeneration of the Basal Ganglia
  - Neural structures affected
    - Degeneration of Pars Compacta region of Sub. Nigra → Basal Ganglia
    - Caused by death of dopamine neurons
    - Decreased activity of 4 areas that receive inputs from the basal ganglia:
      - Motor cortex, oculomotor and associative area, 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.
  - Mutation on chromosome 6: parkin gene
  - Ubiquitin tags faulty/misfolded protein
  - Tagged proteins are destroyed by proteosomes
• 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
• Misfolded protein + ubiquitin → (parkin) ‘tagged’ misfolded protein → proteosomes → amino acids

- Parkinson’s Disease
  o Treatments:
    ▪ MAO inhibitors (e.g., diphenyl): prevents the destruction of monoamines. Slows 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:
      ▪ Deep brain inhibitory stimulation of subthalamic nucleus (STN)

- Current research on PD
  o Gene therapy: modified virus that inhibits STN → increase activity in Supplemental Motor Area → Decrease PD symptoms
  o Neuroprotective agents – chemicals that protect the brain. Control a-synuclein.
  o Stem cells – increase dopamine secretion

- Degenerative Disorders
  o Huntington’s Disease
    ▪ Symptoms:
      • Uncontrollable and excessive movements. Uncoordinated activation of motor programs
      • Rare, associated with dementia. Symptoms appear after 35 years old, death 15 years after onset
      • Terminal disease. Hereditary (dominant gene, C4) Misfolded protein (huntingtin) accumulation. Toxic gain of function
        ▪ 1630’s witches of Bures (UK)

- Huntington’s Disease
  o Caudate Putamen → Prefrontal Cortex, Motor Cortex → Motor Activity/plans
  o Treatment:
    ▪ No treatment. 1/10,000 people. Management therapies.
    ▪ Gene is identified, and tests exist to determine whether it is present.
    ▪ Research focuses on Gene therapy

- Degenerative Disorders
  o Alzheimer’s Disease
    ▪ Symptoms
      • Affects 10% of the > 65 yo population. 50% if >85 yo
• Not entirely hereditary
• Progressive: depression, loss of memory and mental function (dementia). Resemble anterograde amnesia of declarative memory.
• Down syndrome develops sometimes into Alzheimer’s
• Terminal disease
  ▪ Neural Substrate
    • Degeneration of Ach center (nuc. Basalis)
    • Degeneration of hippocampus, frontal and temporal cortices, rah nucleus and locus coeruleus.

- Alzheimer’s Disease
  o Neural Substrate
    ▪ Development of:
      • B-Amyloid plaques: accumulation of B-Amyloid... cell death
      • Neurofibrillary tangles. Dead microtubules. Also, in down syndrome
  → Skip: Fig 14.16-14.18 and p 380 (starting at APP)-382 (before ALS)
  o Treatments: no cure. Causes unclear. Gene mutation on chromosome 21 (amyloid gene)

- Degenerative Disorders
  o Amyotrophic Lateral Sclerosis (Lou Gehrig’s disease)
    ▪ Symptoms: stiffness of movement, exaggerated reflexes, muscular atrophy, paralysis, terminal disease (5-10 years after onset). No dementia
    ▪ Mostly sporadic cases (1/20,000)
    ▪ In some cases, related to chromosome 21 (misfolding of protein, toxic gain of function)
  o Neural Substrate: Degeneration of spinal cord motor neurons and cranial nerves. Ecotoxicity.
  o Treatment: no cure. Drug that decrease glutamate release, improve symptoms. Gene therapy.

- Degenerative Disorders
  o Multiple sclerosis (MS)
    ▪ Symptoms: Complex and very diverse. Slowly evolving. Not hereditary, not contagious. More women than men (20-30 yo). Loss of motor coordination, tremor, numbness...
    ▪ Neural substrate: autoimmune disease. Degeneration of myelin and formation of sclerotic plaques.
    ▪ Treatment: genetic component (Romani and Asians are low risk), environmental component (childhood in cool climates are high risk). Influencing the immune system. No cure. Partial recovery.

- Infectious Diseases
  o Encephalitis and Meningitis
  o Symptoms:
- Fever, irritability, nausea → Convulsion, delirium
- 10% is terminal, 20% results in permanent brain damage. Deafness
  - Neural Substrate:
    - Viral infections (mosquitoes or STDs), bacteria, fungi
    - Encephalitis: affect the whole brain
    - Meningitis: affects the meninges.