Cheyenne

Neurological Disorders II

Transmissible Spongiform Encephalopathy

-E.g...Bovine Spongiform Encephalopathy (BSE="mad cow disease"), Creutzfeldt-Jakob disease, scrapie (animal only)

-Sporadic: Can be infectious or genetic.

-Caused by “protein infectious agents” (prions). Found in neutral membranes important for synaptic function and myelin. Normal amino acid 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) Protons. 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: Enzymes that trigger cell death (a.k.a apoptosis)

Parkinson’s Disease: classified as a movement disorder

Symptoms:

-Ridgidity, slow movement absence of reflexes, tumors at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia, and akinesia.

-Initially: little intellectual impairments. As it progresses speech impairments, decreased Short Term Memory, slower problem-solving and slower visual spatial skills.

-In general not hereditary. Sporadic. Affects 0.5% of adult population, slow progression (-20 years)

-No single cause (genetic, strokes, tumors, infections...) No cure.
Neural structures affected:

- Defeberation of Pars Compacta region of Sub Nigra → Basal Ganglia
- Caused by death of dopamine neurons
- Decreased activity of 4 areas that receive inputs from 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 defect on chromosome 4: the protein (α-synuclein) produced is misfolded.
- Toxic gain of functions: produced of a toxic protein by 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 functions

- Not only genetic: other possible mechanisms include decreased mitochondrial activity and iron build-up.

Ubiquitin + Misfolded protein → “tagged” misfolded protein → proteasomes → amino acids

Treatments:

- MAO inhibitors (e.g. deprenyl) prevents the destruction of monoamines. Slows down progression of PD
- L-Dopa: promote the production of dopamine. Side effects (hallucinations). Effects are temporary. Eventual complete destruction of dopamine neurons.
- Direct fetal dopamine cell transplantation in Basal Ganglia. Side effects (involuntary movement)
- 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 in Supplemental Motor Area → Decrease PD symptoms
- Neuroprotective agents - chemicals that protect the brain. Control α-syncline.
- Stem cells - increase dopamine secretion.

**Huntington’s Disease**

![Normal brain vs Huntington's disease]

**Symptoms:**

- Uncontrollable and excessive movements. Uncoordinated activation of more programs.
- Rare, Associated with dementia. Symptoms appear after 35 years old, death 15 years after onset.
- 1630’s Witches of Bures (UK)
- Neural substrate: Degeneration of caudate and putamen: affect GABA and ACh cells in the Basal Ganglia. Enlarged ventricles

**Treatments:**

- No treatments 1/10,000 people. Management therapies.
- Gene is identified, and tests exists to determine whether it is present.
- Research focuses on Gene therapy.

Alzheimer’s Disease

Symptoms:
- Affect 10% of the > 65 y/o population 50% if > 85 y/o.
- 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 the hippocampus, frontal and temporal cortex, raphe nucleus and locus coeruleus.
- Development of:
  - $\beta$-Amyloid plaques: Accumulation of $\beta$-Amliod...cell death.
  - Neurofibrillary triangles: Dead microtubules. Also in Down syndrome.

Treatment:
- No cure. Causes unclear. Gene mutation on chromosome 21 (amyloid gene)
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).

Treatments:
- No cure.
- Drug that decrease glutamate release, improve symptoms. Gene therapy

Neural substrate:
- Degenerative of spinal cord motor neurons and cranial nerves. Excitotoxicity