DEMENTIA: “Development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia or a disturbance in executive functioning. Cognitive impairment must be sufficiently severe to cause impairment in the occupational or social functioning and must represent a decline from a previously higher level of functioning.” – American Psychiatric Association’s Diagnostic and Statistical manual of mental disorders (DSM-IV)

Common pathologic findings in dementia:
- Loss of neurons (clinical features depend on particular population of neurons affected)
- Intracellular accumulation of abnormally configured proteins with formation of inclusion bodies (e.g. neurofibrillary tangles or Lewy bodies)
- Extracellular accumulation of abnormal proteins (in some neurodegenerative diseases), e.g. amyloid-beta in AD

Potentially treatable causes of dementia:
- Stroke
- Infections (CJD, syphilis, HIV)
- Neoplasms (primary or metastatic brain tumors)
- Drugs and toxins (barbiturates, alcohol, lead poisoning, other heavy metals, pesticides)
- Metabolic (hypothyroidism, liver failure, hypoglycemia)
- Vitamin deficiencies (thiamine, niacin, cobalamin)

NEURODEGENERATIVE DISORDERS PRIMARILY AFFECTING CEREBRAL CORTEX

Alzheimer’s disease
- Most common cause of dementia in elderly
- Most cases are sporadic, age is the major risk factor
- Minority of cases are familial (~10%) and have early onset of the disease
- Amyloid precursor protein (APP):
  *A transmembrane protein that plays a role in synaptic development
  *Gene on chromosome 21; patients with Down syndrome (trisomy 21) usually develop AD if live into 40’s-50’s
  *Normal metabolic pathway involves proteolytic cleavage by alpha-secretase into smaller fragments (implicated in neuroprotection) that are easily cleared from the CNS
  *Beta-secretase pathway leads to formation of amyloid-beta fragments that are deposited as amyloid plaques and result in AD
- Early-onset (autosomal dominant) AD: APP mutation (chr. 21), presenilin 1 and presenilin 2 mutations
- Apolipoprotein E allele €4 increases the risk of development of AD; ApoE allele €2 is protective
- Gross pathology:
  Diffuse cerebral atrophy (narrowing of gyri and widening of sulci); atrophy of the hippocampus; hydrocephalus ex vacuo (dilatation of ventricles secondary to loss of brain volume)
- Microscopic pathology:
  
  **Neurofibrillary tangles**: intracellular filamentous inclusions (seen in other conditions, not specific for AD) composed of hyperphosphorylated tau protein (microtubule associated protein)
  
  **Amyloid plaques**: deposits of amyloid-beta in neuropil (extracellular)
  
  **Cerebral amyloid angiopathy (CAA)**: amyloid deposits in walls of small and medium size arteries in subarachnoid space and superficial cortex; frequently seen in Alzheimer’s disease but can be seen independently; important cause of non-traumatic parenchymal brain hemorrhage; highlighted by Congo red stain and immunohistochemistry with antibodies against amyloid-beta

**Lewy body disease (or dementia with Lewy bodies)**
- Second (after AD) most common neurodegenerative cause of dementia
- Clinical features: dementia, hallucinations and parkinsonian signs
- Lewy body inclusions composed of alpha-synuclein are present in substantia nigra and the cortex (diffuse Lewy body disease)

**Frontotemporal lobar degeneration**
- Group of neurodegenerative diseases characterized by predominant destruction of the frontal and temporal lobes (parietal and occipital lobe are spared)
- Third most common neurodegenerative cause of dementia (after AD and DLB)

**Pick’s disease**
- Frontotemporal lobar degeneration with Pick bodies (tauopathy)
- Presents with behavioral and language symptoms
- Tau-positive globose cytoplasmic neuronal inclusions in neurons of hippocampal dentate gyrus and hippocampal pyramidal neurons as well as pyramidal neurons of the frontal and temporal cortex

**DISEASES OF THE BASAL GANGLIA**

**Idiopathic Parkinson’s disease**
- Degeneration of dopaminergic neurons of the substantia nigra that project to the striatum
- Clinical symptoms: features of parkinsonisms (Tremor at rest, Rigidity, Akinesia (or bradykinesia), Postural instability); dementia may develop later in the course of the disease
- Gross findings: pallor of substantia nigra
- Microscopic findings: alpha-synuclein containing inclusions in cytoplasm of pigmented neurons of substantia nigra and locus coeruleus (Lewy bodies)

**Huntington’s disease**
- Clinical features: chorea, psychiatric symptoms progressing to dementia and cachexia
- Autosomal dominant due to abnormal expansion of CAG triplet repeats in huntingtin gene
- Number of repeats inversely correlates with the age of onset (>35 repeats is abnormal)
- Degeneration of GABA-containing neurons in the striatum with progressive atrophy of the caudate and putamen

**DISEASES OF CEREBELLUM AND SPINAL CORD**

**Multiple system atrophy**
- Sporadic and progressive disease
- Combinations of symptoms including: parkinsonism (due to striatonigral degeneration), cerebellar ataxia (due to olivopontocerebellar atrophy) and autonomic dysfunction
- Gross: atrophy and grey-green discoloration of putamen; substantia nigra, cerebellum, pons and olivary nucleus also atrophic
- Microscopic pathology: glial cytoplasmic inclusions containing alpha-synuclein in affected areas

**Amyotrophic lateral sclerosis**
- Degeneration of upper motor neuron (spasticity and hyperreflexia)
- And lower motor neuron (muscle weakness and atrophy)
- 5-10% familial with subset having mutations in the **superoxide dismutase gene (SOD1)** on chromosome 21 (most autosomal dominant but other patterns of inheritance also occur)
- Most cases are sporadic
- Some patients also have frontotemporal dementia
- Gross findings: spinal cord anterior nerve roots are atrophic (posterior sensory roots are normal)
- Loss of motor neuron in anterior horns of the spinal cord and motor cortex
- Characteristic inclusions in surviving motor neurons (TDP-43-positive)
- Loss of myelin in corticospinal tracts

**Spinal muscular atrophy**
- **Werdnig-Hoffmann disease (SMA I)**
  *Autosomal recessive
  *Affects fetus and newborn → “floppy baby”
  *Degeneration of lower motor neurons (anterior horn cells) → neurogenic atrophy of distal muscles
- **Kugelberg-Walander Disease (SMA II):**
  *Similar to Werdnig-Hoffmann disease but presents after 3 months of age or later
  *Course is progressive but slower
  *Compatible with normal life span
- **SMA III** (Rare):
  *Onset in infancy to early adolescence;
  *AR or sporadic
- All are caused by mutations in the survival of motor neuron (SMN) genes, SMN1 and SMN2 on chromosome 5
**Friedreich’s ataxia**
- Most common form of hereditary ataxia
- Autosomal recessive
- Trinucleotide repeat GAA (glutamic acid) in frataxin gene on chromosome 9
  - Frataxin is essential for mitochondrial iron regulation
- Degeneration of cerebellum → ataxia
- Degeneration of spinal cord tracts → loss of sense of vibration and proprioception, muscle weakness, loss of deep tendon reflexes
- + electrical conduction and structural anomalies of heart, hypertrophic cardiomyopathy → ~50% of deaths due to cardiac cause

**VASCULAR DEMENTIA**
- Second most common cause of dementia
- AD and cerebrovascular disease frequently co-exist = mixed dementia
- Subtypes:
  - Multi-infarct dementia: multiple strokes
  - Single stroke involving a strategic site (e.g. thalamus)
  - Subcortical small vessel disease (involving subcortical white matter)
- Causes: hypertension, atherosclerosis, vasculitis, CAA

**TOXIC AND METABOLIC DISORDERS**

**Ethanol toxicity**
- Wernicke’s syndrome (thiamine, B1, deficiency) – hemorrhage and subsequent atrophy of mammillary bodies and cerebellar vermis
- Central pontine myelinolysis – due to rapid correction of electrolyte imbalances, especially chronic hyponatremia; triangular demyelinating lesion in the midline of basis pontis
- Cortical atrophy

**Methanol toxicity**
- Necrosis and cavitation of the putamen

**Carbon monoxide poisoning**
- Hemorrhagic necrosis of globus pallidus

**Subacute combined degeneration**
- Vitamin B12 deficiency
- Causes: pernicious anemia, chronic gastritis, surgical resection, tumors, strict vegetarianism/veganism
- Symptoms: megaloblastic anemia, neurologic symptoms (mechanism unknown): weakness, paresthesias of hands and feet → loss of sense of vibration → ataxia
- Myelin loss in posterior and lateral columns of the spinal cord
Hepatic encephalopathy
- In acute or chronic liver disease
- Acute: brain edema
- Chronic: Alzheimer’s type II astrocytes secondary to elevated ammonia level