Neurodegenerative Diseases

Chronic, progressive and characterized by selective and symmetric loss of neurons in cognitive, motor, or sensory systems

DEMENTIAS

- 50 known causes of dementia
- > 50% of all demented patients have dementia of Alzheimer type (DAT)

DEMENTIA OF ALZHEIMER TYPE (DAT)

- most common form of dementing illness
- 1 in 10 over 65; 1 in 2 over 85
- 4th leading cause of death
- most frequent cause of institutionalization for long-term care

Etiology

- not known, no cure
- risk factors: family history of dementia, increasing age, Down syndrome; head injury, female sex, hypothyroidism, depression
- Protective: education, smoking, NSAIDS
- Chromosomes 1,14, and 21 have been implicated

Pathogenesis

- metabolism of amyloid precursor protein and its product β-amyloid (Aβ)
- phosphorylation and other post-translational modifications of tau protein (τ)
- oxidative stress

Three MAJOR Subtypes

1. **Alzheimer's Disease**
   - begins **before** the age of 65
   - 10-15% of cases familial (autosomal dominant)
   - Early clinical syndromes: loss of recent memory and initiative, difficulty in word finding and in performing calculations, and disorientation to time and place
   - Advanced stage: incontinent and bedridden
   - Time course: 2 – 20 years
   - almost no focal neurological deficits
   - GROSS: cerebral atrophy with thinning of gyri, widening of sulce, and hydrocephalus ex vacuo
   - HISTO:
     - **senile (neuritic) plaques**
       1. composed of a single core of extracellular amyloid (Aβ + other substances)
       2. surrounded by degenerating neuritic terminals which contain hyperphosphorylated τ, and reactive cells
     - **neurofibrillary tangles**
       1. consist of bundles of Paired Helical Filaments (PHF) and
       2. straight filaments, of which a major component is hyperphosphorylated τ
     - **neuronal loss**
     - granulovacular degeneration
     - Hirano bodies (bullet shaped)
     - congophilic angiopathy (deposition of amyloid in and around BV walls)
     - Loss of cholinergic neurons of the nucleus basalis of Meynert within the substantia inominata
     - Loss of serotonergic, noradrenergic and dopaminergic neurons at the brainstem

2. **Senile Dementia of Alzheimer Type**
    - begins at a **later** age (at or after 65)
    - **slower rate of progression**
    - more common than Alzheimer's disease
    - HISTO: identical to those in Alzheimer's disease
    - some studies have shown that nearly _ of all people > 85 have symptoms of the disease

3. **Down's syndrome with dementia**
    - Once Down Syndrome patients survive past the 3rd decade, they invariably develop the characteristic changes seen in DAT

LEWY BODY DEMENTIA

- considered by some to be the 2nd most common neurodegenerative form of dementia after the pure form of DAT and mixed DAT/vascular dementia group
- early dementia
- hallucinations, delusions, paranoia
- motor feature respond well to levodopa

PICK'S DISEASE

- progressive, sometimes familial disorder, with focal atrophy and sclerosis involving the frontal and temporal lobes
- Onset: 40-60 years
- Best clinical predictors: "frontal" dementia and depression
- early memory loss **does not** occur
- Patients have difficulty finding appropriate words or understanding everyday conversation
- End stage: mute, immobile, with memory loss
- GROSS:
    - severe atrophy of frontal and temporal lobes
    - **Remember: Posterior 2/3 of the Superior Temporal Gyrus are Characteristically spared**
- MICRO:
    - severe cortical neuronal loss
    - "Pick cells" (large swollen chromatolytic neurons) and "Pick bodies" (argyrophilic, tau-positive, cytoplasmic inclusions)
    - Severe white matter lobar gliosis

HUNTINGTON'S DISEASE

- Severe degenerative disease
- Autosomal dominant with complete penetrance
- ONSET: 35-40; last 15-20 years
- Progressive choreiform movements, dementia, delusions, hallucinations, paranoia, depression, drastic mood Changes, and loss of weight occur.
- **Chromosome 4**; expansion of CAG trinucleotide beyond 35 repeats within its coding region
    - **strong inverse correlation between CAG length and age of onset exists (juvenile form)**
- GROSS:
    - Severe progressive atrophy of the neostriatum (caudate and putamen)
- MICRO:
    - Massive preferential loss of the medium spiny GABAergic projection neurons and gliosis
    - Selective sparing of the large aspiny neurons
    - Cortical neuronal loss occurs later
    - Intranucleur inclusions found only in affected areas

Other Forms of Dementia

NORMAL (INTERMITTENT) PRESSURE HYDROCEPHALUS

- progressive dementia, gait disorders, urinary incontinence, and urgency
- enlarged ventricles with normal or minimally elevated CSF pressure
- Shunting of CSF is beneficial in 2/3 of patients; 1/3 DAT pathology is found

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PARKINSONISM

- symptom complex
- tremor at rest, rigidity, difficulty in initiation of movement, and reduction of postural reflexes

PARKINSON'S DISEASE

- unknown etiology
- occurs predominantly in the 6^{th} and 7^{th} decades
- 20-30& of patients with Parkinson's disease become demented
- GENETICS:
  - mutation of α-synuclein, a presynaptic protein, has been found on the gene of a subset of autosomal dominant familial Parkinson;s disease located on chromosome 4.
- GROSS:
  - depigmentation of substantia nigra and to a lesser estent the locus cerelus
  - atrophy of the brain stem and cerebral cortex
- MICRO:
  - severe neuronal loss in pigmented nuclei
  - accompanied by gliosis
  - **Lewy Bodies**: eosinophilic, intracytoplasmic inclusions with distinctive core and peripheral halo
    - made of neurofilaments, αsyneclein, ubiquitin, and proteosomal subunits
    - contain a core of filaments and granular material
    - outer zone of loose radiating filaments
    - also present in 4-13% of "normals" from 60-90 years of age
- MPTP intoxication
  - converted to MPP^+ by MAO-B in glial cells
  - MPP^+ selectively toxic to neurons of the substantia nigra

Treatment of Parkinsonism

- levodopa as replacement therapy for dopamine deficiency
- Dopamine deficiency = Parkinsonism
- Surgical Treatment: reserved for disabling, medically refractory problems
- Pallidotomy or subthalamic nucleotomy reduces the excessive cortical inhibition by the ventrolateral thalamus

Striatonigral degeneration

- clinically indistinguishable from Parkinson's disease
- Severe neuronal loss and gliosis in the substantia nigra and putamen
- **LEWY BODIES ARE NOT PRESENT**
- Putaminal pigmentation

Parkinsonism-Dementia-Amyotrophic lateral sclerosis of the Western Pacific

- found in the indigenous Chamorro adults in the island of Guam and Kii peninsula of Japan
- manifested by parkinsonism, dementia, and motor neuron disease
- GROSS:
  - cortical atrophy
  - depigmentation of substantia nigra and locus cerelus
- MICRO:
  - neurofibrillary tangles and granulovacuolar degeneration
  - NO amyloid accumulation

PROGRESSIVE SUPRANUCLEAR PALSY

- progressive neurological disorder of gait and balance
- Clinical features
  - paralysis of vertical eye movements
  - axial rigidity > limb rigidity
  - nuchal extension
  - early falls
  - subcortical dementia
  - psuedobulbar palsy
  - HTN
- selective degeneration of the subthalamic nucleus, the substantia nigra, and possibly the pallidum

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HALLERVORDER-SPATZ DISEASE

- most commonly begins in childhood as a dystonic syndrome
- rust brown discoloration of the globus pallidus and the reticular portion of the substantia nigra due to disposition of an iron-containing pigment
- axonal spheroids

MULTIPLE SYSTEM ATROPHY (MSA)

- distribution and frequency of argyrophilic oligodendroglial inclusions are considered by some to be characteristic of MSA
- only 20% show good initial response and 13% sustained response to levodopa treatment

Olivopontocerebellar atrophy

- most common form of MSA
- Clinical Presentation
  - ataxia
  - rigidity
  - oculomotor symptoms
- Neuronal loss and gliosis in pons, olives, cerebellum, and other areas

Shy-Drager's Sydrome

- Parkinsonism or spinocerebellar ataxia symptoms + autonomic disturbances
- due to neuronal degeneration in the dorsal vagal nucleus, hypothalamus, lateral horns of the spinal cord, and the sympathetic ganglia

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DISORDERS OF TRINUCLEOTIDE (CAG) REPEATS

- CAG repeat extension are implicated in 8 neurodegenerative diseases
- all exhibit anticipation
- the repeat is located in the coding region of the gene involved and in all is translated into a stretch of polyglutamines in the respective proteins
- characterized by autosomal dominant or X-linked inheritance, onset in midlife
- see table on p. 501

FRIEDREICH'S ATAXIA

- most common inherited progressive ataxia (autosomal recessive)
- chromosome 9; homozygous expansion of GAA repeats in the first intron of the frataxin gene
- Clinical Presentation
  - before 20 years of age
  - ataxia of all four limbs
  - cerebellar dysarthria
  - areflexia of the lower limbs
  - sensory loss
  - pyramidal signs
  - cardiomyopathy
  - skeletal deformities
  - diabetes
- Low Frataxin levels
  - inner mitochondrial membrane protein that transports iron out of mitochondria
  - with loss, Fe accumulated in the mito. matrix and stimulates the conversion of H_2O_2 to OH by the Fenton Reaction
  - this inactivated the mito. Fe-S center enzymes which in turn decreases energy production
- loss of neurons with large bodies and extensive axon elongations associated with dorsal root ganglia, dorsal roots, dorsal columns, Clarke's columns, spinocerebellar tracts, and pyramidal tracts

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MOTOR NEURON DISEASES

- Degeneration of lower motor neurons causes muscle atrophy and weakness
- Death of upper motor neurons causes increased muscle tone, hyperreflexia, and extensor plantar responses (Babinski's sign)

AMYOTROPHIC LATERAL SCLEROSIS (ALS) (LOU GEHRIG'S DISEASE)

Sporadic

- mean age of onset: 60 years
- Begins with: impairment of fine finger movement, weakness, and wasting of the muscles of the hand
- Later: spreads to lower limbs, back of the neck, tongue, pharynx, and larynx
- Time course: 2-7 years
- Degeneration of motor neurons in the spinal cord and brainstem and degeneration of pyramidal tracts
- Loss of Betz cells seen in some cases
- severe atrophy of anterior spinal roots
- Intact mental capacity
- Therapy: riluzole and insulin-life growth factor

Familial

- 8% of all cases
- Extra features: 1) eosinophilic intracytoplasmic inclusions in snterior horn cells 2) degeneration of posterior columns, Clarke's column, and spinocerebellar tracts
- Neurofilamentous accumulation in cells bodies and proximal axons are a common feature of sporadic and familial cases of ALS

Guamanian

FAMILIAL SPINAL MUSCULAR ATROPHY (SMA)

- two genes on chromosome 5q13, SMN and NAIP, are associated with the disease
- Three forms according to severity

Infantile spinal muscular atrophy (Werdnig-Hoffmann disease, SMA I)

- onset: may be in utero
- muscular weakness with hypotonia
- eventually all muscles except eye muscles affected (infant assumes a “frog position”
- difficulty in suckling, swallowing, and breathing
- patients die within first 2 years

Intermediate form (chronic or arrested WHD, SMA II)

Kugelberg-Welander syndrome (SMA III)

- most benign form of familial SMA
- proximal weakness, waddling gait, and difficulty climbing stairs follow normal motor development
- respiratory system unaffected
- good prognosis