MOTOR SYSTEM DISEASES

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Motor System Diseases

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Degenerative diseases

• Heterogeneous group
• Many are hereditary or genetic
• Classification originally clinically based
  • Usually a distinctive topography
  • Illustrate idea of selective vulnerability
• Often begin as nerve cell diseases
• Characterized by atrophy, neuronal loss, gliosis
Extrapyramidal disease

Involuntary movements
  Repetitive, random, purposeless
  Occur while at rest
Tremors are typical
Rigidity
  Stiffness, increased tone, slow movement
Parkinsonism (PS)

- Named for James Parkinson (1817)
  - English doctor, practiced in London
- Causes/types
  - Idiopathic=classic Parkinson’s disease (PD)
    - Affects 1-2 million people in US
  - Hereditary (25% cases)
  - Toxic
    - MPTP* and Cycad beans
    - Pesticides and herbicides possibly a cause
  - Head trauma, especially boxers

*1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine
Hereditary Parkinsonism
There are at least 10 known genes (Park 1-10)

- **α-synuclein (Park 1)**
  - Gene on Chr 4q21-23
  - α-synuclein is a normal phosphoprotein involved in synaptic vesicle transport
  - Numerous mutations in gene
  - Early onset, dominantly inherited disease

- **Parkin (Park 2)**
  - Gene on Chr 6q25-27
  - Normal parkin is a ubiquitin ligase
  - Numerous mutations or deletions
  - Juvenile, recessive parkinsonism
Is PS is a mitochondrial disease?

• Increased reactive oxygen species in mitochondria
  • MPTP (inhibits Complex I)
• ROS lead to free radical formation
  • Results in increased Mt membrane permeability
  • Leads to apoptosis
• ROS inhibits ubiquitin-proteolysis system
  • Increase in misfolded proteins → Lewy body formation
Misfolded protein response

- Proteins are folded into secondary and tertiary structures
- Chaperones, like heat shock proteins, help with folding
- Mutations, chaperone abnormalities or free radicals cause misfolding
- Misfolded proteins may have abnormal function or may aggregate
- Misfolding may lead to degradation or apoptosis
Clinical features

- Onset 50-70 years in classic PD
- Tremor at rest, typified by pill rolling
- Rigidity (stiffness)
- Bradykinesia (in slow motion)
- Soft speech, micrographia
- Dementia late in some cases
- Disability in 10-15 years (average)
Normal substantia nigra

Parkinson’s disease strikes the pigmented nuclei of brain
Parkinson’s disease

Loss of pigment in the substantia nigra

Due to loss of pigmented neurons

Results in injury to the dopaminergic system
• PET scanning shows diagnostic findings
• Use 18 fluorodopa and measure brain uptake
• Find signal loss in putamen in PD
• Test is based on loss of substantia nigra (dopaminergic) projections to corpus striatum
PET scan-Parkinson’s disease

Signal loss in corpus striatum
Parkinson’s disease

Normal substantia nigra

Loss of pigmented neurons
Parkinson’s disease

Laminated Lewy body

Lewy bodies-cytoplasmic, round, eosinophilic with a halo
Lewy bodies

Ubiquitin staining

Composed of filaments including \( \alpha \)-synuclein
Summary of events

MPTP
- Inhibits complex I

ROS
- Free radicals
- Mt membrane permeability
- Apoptosis

α-synuclein mutations
- Inhibition of ubiquitin-proteolysis system
- Lewy bodies
Treatment strategies

• Anti-oxidants - combat ROS
• Co-enzyme Q - promote Mt integrity
• Dopamine agonists \(\rightarrow\) anti-apoptosis
  • Pramipexole (D\textsubscript{2} receptors) in clinical trials for this effect
Diffuse Lewy body disease

• Dementia
• Parkinsonian features
• More rapid course than classic PD
• Lewy bodies in cerebral cortex and brainstem
Progressive supranuclear palsy

• Sometimes called atypical PD
  • Sporadic disease
• Onset 40-60 years, more common in men
• Wide-eyed vacant stare, vertical gaze palsy
• Rigidity, tremors, weak, spastic
• Dysarthria, dysphagia
• Dementia
• Progressive, fatal in 5 years
Vacant stare
Michael Emerson (Mr. Finch) in Person of Interest
PSP pathology

- Widespread loss of neurons
  - Cerebral cortex
  - Globus pallidus, substantia nigra
  - Colliculi, periaqueductal grey, brainstem nuclei
- NFT (neurofibrillary tangles) in neurons and glia
  - Huge, round (globose), not flame shaped
  - 15 nm filaments, contain 4R tau protein
PSP pathology

Globose NFT-large, round, bulbous
Silver stain

Globose tangle-tau stain (red)
Huntington’s disease

• Named for George Huntington (1872)
  • Newly minted doctor from Long Island
• Autosomal dominant inheritance
• Disease locus on Chromosome 4p16.3
  • Gene product is **huntingtin**, 348 kd protein
  • Gene codes for the polyglutamine region of protein
  • Disease associated with ↑ CAG repeats (37-250)
    • Normal gene only has 9-34 trinucleotide repeats
• Mutant huntingtin has ↑ glutamine segments
  • Abnormally shaped protein is dysfunctional
  • Abnormal protein disrupts axonal transport and synaptic transmission (Arch Neurol 68: June 2011)
Clinical features

• Age of onset 30-50 years
• Choreiform movements (chorea=dance [Gr])
  • Nonrepetitive, purposeless, sudden rapid movements
  • Involuntary, twisting or jerky
  • Embarassing, interfere with motor function and sleep
• Personality changes; Dementia later
• Survival after diagnosis is 15 years (average)
• HD2 clinically similar
  • Described in African families
  • Disease locus on Chr 16q
    • Associated with excessive numbers of CTG repeats
Huntington’s disease

 Strikes caudate & putamen
Huntington’s disease

Atrophy of caudate nucleus and putamen + cortex
Huntington’s disease

Ventricles dilated and caudate nuclei are “gone”
Huntingtin inclusions

Intranuclear inclusions
Within neurons
Contain mutant protein
Cerebellar ataxias

Involuntary movements (often tremors)
Initiated or made worse by intentional movement
Unlike movements in Parkinsonism and Huntington’s disease
Unsteady gait
Involuntary movements/ataxia

• Involvement of cerebellum
• Causes
  • Friedreich’s ataxia
  • Spinocerebellar ataxias (atrophies)
• Often hereditary
• Slowly progressive disease
Friedreich’s ataxia

- Named for Nicholas Friedreich (1881)
- Onset in older children, young adults
- Staggering, ataxic gait
- Dysarthria, nystagmus
- ↓ vibratory sensation, proprioception
- Babinski responses and weakness
- ↑ incidence of diabetes (30% patients)
- 15 year survival (average) after diagnosis
Friedreich’s ataxia

• Familial, recessive inheritance
• Disease may be due in part to impaired mitochondrial function
• Disease locus on Chr 9q13-21
  • Gene product is frataxin
• Disease associated with ↑ GAA repeats (90-1359)
  • Normal gene only has 6-36 trinucleotide repeats
Friedreich’s ataxia

• Expanded GAA repeats located in an intron
  • Regulation of protein synthesis is altered
  • Loss or shortage of frataxin occurs
• Frataxin is normal protein located on inner Mt membrane
  • Involved in biosynthesis of proteins
  • Play role in mitochondrial electron transport & aconitase function
Friedreich’s ataxia

Cerebellar cortical atrophy, all three layers
And the dentate nucleus
Friedreich’s ataxia

Damage to dorsal columns, pyramidal tracts and spinocerebellar tracts
Damage to dorsal root ganglia and posterior roots, Clark’s columns
Friedreich’s ataxia

Cardiomyopathy (myocarditis)

Giving rise to CHF and arrhythmias
Spinocerebellar degenerations

• Several types are reported (SCA 1-7)
• Autosomal dominant inheritance
• Usually caused by increased CAG repeats
  • Genes code for polyglutamine portions of different proteins
Motor neuron diseases

Muscular weakness is the predominant feature
May involve upper or lower motor neurons or both
Spasticity
Hyper-reflexia
Babinski responses

Weakness, distal early
Flaccidity
Atrophy & fasciculations

No bladder or eye sxs
Motor neuron diseases

• Lead to neurogenic atrophy in muscle when lower motor neurons are affected
• Loss of trophic influences of nerve on muscle
• Atrophy of muscle on physical exam
  • Distal more than proximal early
• Small angular fibers
• Grouped atrophy
• Type grouping
Amyotrophic lateral sclerosis (ALS)

- 5 cases/100,000
  - 800,000 people affected
- Onset mid- to late 50s
- Diverse causes/risk factors
  - Trauma, genetic
- Progressive course with 3-5 year survival
Amyotrophic lateral sclerosis

- Most cases are sporadic (90-95% patients)
- Familial cases have dominant inheritance
  - Juvenile onset
  - Example disease is locus on chromosome 21q 22
  - Mutations in Cu/Zn SOD gene
  - Neurons are killed by free radicals normally eliminated by SOD
At least 26 genes involved in ALS
Sporadic ALS

- Intracytoplasmic inclusions of TDP-43* in neurons (also SOD-1, ubiquitin)
  - Truncated, hyperphosphorylated fragments
- TDP-43 is normal protein involved in preventing apoptosis
- TDP-43 also found in some cases of FTD with motor neuron disease

*Transactive response (TAR) DNA binding protein-43
ALS

Advanced disease
Marked muscle atrophy
Sparing of facial and eye muscles
ALS

Small (atrophic) anterior roots

Wallerian degeneration of pyramidal tracts
ALS

Central chromatolysis

Loss of motor neurons
Infantile spinal muscular atrophy

- Onset in infancy (type 1)
- Genetic disease
  - Mutation in SMN 1 gene, chr 5
- Purely an anterior horn cell disease
- Progressive and fatal

SMN = survival motor neuron gene
SMA 1-floppy infant
SMA 1-loss of anterior horn cells
SMA 1- grouped atrophy
Learning Objectives

• The student should know each of the following with regard to the diseases discussed:
  • Pathogenesis/etiology
  • Epidemiology
  • Clinical features
  • Pathology
  • Natural history/course
  • Treatment strategies where discussed in lecture
Learning Objectives

• The student should know each of the following definitions:
  • Degenerative disease
  • Selective vulnerability
  • Parkinsonism/Parkinson’s disease
  • Ataxia
  • Chorea
  • Motor neuron disease
THE END
Identify the three diseases