

DEGENERATIVE DISEASES

MODULE



Objectives:

1. Degenerative diseases characterized primarily by cerebral cortex lesions: For each of the following diseases, describe (as appropriate) etiology/pathogenesis of lesions, location of lesions, clinical features and course of the disease, diagnostic tests, inheritance pattern and genetic mechanism, gross pathology, microscopic pathology

- Alzheimer disease
- Pick disease (frontotemporal dementia)
- Dementia with Lewy bodies

2. Degenerative diseases characterized primarily by basal ganglia lesions: For each of the following diseases, describe (as appropriate) etiology/pathogenesis of lesions, location of lesions, clinical features and course of the disease, diagnostic tests, inheritance pattern and genetic mechanism, gross pathology, microscopic pathology

- Huntington disease
- Parkinson disease; parkinsonism syndrome
- Wilson disease

3. Diseases with spinal cord and/or cerebellum involvement: For each of the following diseases, describe (as appropriate) etiology/pathogenesis of lesions, location of lesions, clinical features and course of the disease, diagnostic tests, inheritance pattern and genetic mechanism, gross pathology, microscopic pathology

- Amyotrophic lateral sclerosis
- Friedreich ataxia

4. Prion diseases:

- Discuss characteristics and replication mechanism (conformational change) of the "prion," the agent in transmissible spongiform encephalopathies.
- Know that prion diseases can be sporadic, genetic, or infectious.
- Understand the role of codon 129 of the PrP gene in determining disease characteristics.
- For Creutzfeldt-Jakob (C-J) disease, describe age of onset, pathogenesis, clinical signs and symptoms, gross and microscopic pathology. Understand the general characteristics of other prion diseases, including variant CDJ, in humans.

I. General principles

Degenerative diseases are characterized by progressive neuronal degeneration and loss in disease-specific regions. The disease arises without any clear inciting event in a patient without previous associated neurologic deficits. In most disorders, the etiology is unknown. The most common manifestations involve at least one of the following: dementia, movement disorders, weakness or sensory loss due to spinal cord involvement. Dementia may be caused by a degenerative disease, or may be caused by multiple small infarcts (vascular dementia) or other disorders. Part A covers disorders characterized primarily by dementia (primary cortical involvement) and Part B covers disorders involving primarily the basal ganglia and/or spinal cord.

A. Clinical Signs

1. **Signs and Symptoms** are predictable and dependent upon the area of the nervous system involved.
 - a. **Cerebral Cortex** - degeneration (progressive loss of neurons and secondary white matter lesions) leads to dementia with impairment of intellectual function and judgement; memory loss is common.
 - b. **Basal Ganglia** - lesions lead to a variety of movement disorders and sometimes to "subcortical dementia"
 - c. **Spinal Cord** - degeneration of corticospinal tract causes weakness and spasticity; lesions in posterior columns cause loss of position sense; loss of motor neurons (anterior horn and motor cranial nerve nuclei cells) cause weakness and flaccidity.
2. Some of the disorders have an **hereditary** pattern and family history can be used for screening.

B. Histopathology

Each of the degenerative diseases has **neuronal loss** and a resulting glial reaction seen in disease-**specific regions** of the brain. There may also be disease-specific microscopic changes, such as inclusion bodies, that are part of the diagnostic criteria. The inclusions seen in several of the diseases are comprised of cytoskeletal components.

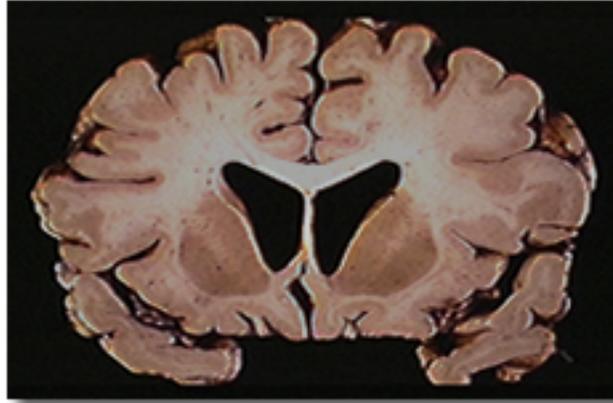
II. Diseases primarily affecting the cerebral cortex

A. **Alzheimer Disease (AD)** - deposits of both **tau** (neurofibrillary tangles) and **amyloid** (neuritic plaques)

1. **Age of Onset:** Usually after 40 years; incidence increases with increasing age.
2. **Incidence:** Occasionally familial (about 10% of cases), some with autosomal dominant inheritance pattern; usually sporadic; affects 10% of

persons over 65; nearly 50% of those over 85. Pathological changes identical to those observed in AD occur in almost all patients with trisomy 21 (Down's syndrome) who survive beyond 45 years. The incidence is increased in individuals homozygous for the apoE4 allele. There are autosomal dominant familial forms (rare) with a mutation in the presenilin 1 or presenilin 2 gene (genetic testing is available).

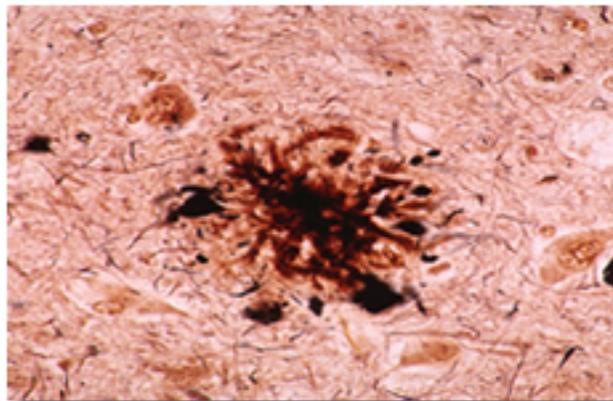
3. **Location of Lesions:** cortex; hippocampus; basal forebrain, especially basal nucleus of Meynert (which contains cholinergic neurons projecting to cortex); and other regions.
4. **Clinical Presentation:** diagnosis difficult in early stages--often equivocal. Clinical diagnosis (80-90% accurate) is made by presence of dementia and exclusion of other conditions. The definite diagnosis must be established by postmortem brain examination. Initial symptoms include behavioral changes; impaired judgement; loss of memory, especially recent; loss of intellect.
5. **Pathogenesis:**
 - (a) loss of cholinergic neurons in the basal nucleus of Meynert and other basal forebrain nuclei results in a deficiency of acetylcholine in the cortex; there are abnormalities in other neurotransmitters also.
 - (b) amyloid deposition may be an early and critical event in neuritic plaque formation. The development of amyloid deposits has been inferred to arise from abnormal processing of the normal molecule, amyloid precursor protein (APP), with accumulation of amyloid β -peptide ($A\beta$). $A\beta$ appears to be neurotoxic after aggregation. In some pedigrees with familial AD, the disease appears to be linked to a point mutation within the coding region of the APP gene on chromosome 21; however, other familial pedigrees are linked to genes on other chromosomes.
 - (c) Mutations in presenilin-1 or presenilin-2 cause are linked to early-onset AD, with increased $A\beta$ production.
6. **Gross Pathology:** cortical atrophy, decreased brain weight, enlarged ventricles



DEG 01

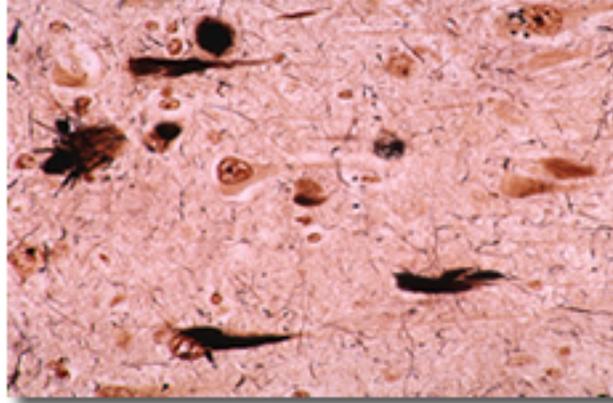
This coronal section shows cortical atrophy indicated by narrow gyri and wider sulci; the arrow points to a widened sulcus. The ventricles are enlarged as a result of decreased volume of the brain parenchyma.

7. **Microscopic Pathology:** nerve cell loss, gliosis, neuritic (senile) plaques, neurofibrillary tangles, amyloid deposition in blood vessels. **Neuritic plaques** are spherical collections of dilated silver-staining neuritic processes surrounding a central amyloid core, the major component of the plaque core is A β . **Neurofibrillary tangles** are an intracellular accumulation of paired helical filaments containing abnormally hyperphosphorylated forms of the protein tau, a protein that enhances microtubule assembly. Both neuritic plaques and neurofibrillary tangles may be present to a lesser extent in non-demented elderly persons. **Large numbers of neuritic plaques and neurofibrillary tangles are the main diagnostic criteria for Alzheimer disease.**



DEG 02

This silver-stained section from the cortex shows a neuritic plaque in the center – an extracellular collection of degenerating neuritic processes (dark stain) and other elements surrounding a central amyloid core. Two normal neuron cell bodies are indicated by the arrows.



DEG 03

large numbers of neurofibrillary tangles in cortex
---composed of tau protein
---intracellular accumulation
---paired helical filaments

B. Dementia with Lewy Bodies (DLB) - alpha-synucleinopathy

1. **Age of Onset:** elderly; second commonest cause of dementia after AD
2. **Location of Lesions:** cortex, basal ganglia, substantia nigra
3. **Clinical Presentation:** dementia, parkinsonism, fluctuation in severity of condition on a day-to-day basis, early development of hallucinations. Patients are unresponsive to anti-Parkinson medication and hyperreactive to neuroleptic drugs. Fluctuation of dementia (sometimes described as "chronic delirium"), visual hallucinations and unexplained losses of consciousness are signs which are helpful in differentiating DLB from Alzheimer's disease.
4. **Pathogenesis:** unknown
5. **Gross Pathology:** cortical atrophy
6. **Microscopic Pathology:** In addition to characteristic intraneuronal **Lewy bodies** in the substantia nigra, less well-defined Lewy bodies are present in the neurons of the hippocampus, entorhinal cortex, anterior cingulate gyrus and subcortical structures. **Lewy bodies contain alpha-synuclein and ubiquitin.** There may be a combination of Alzheimer's disease pathology with cortical Lewy bodies.

C. Frontotemporal Dementia (e.g. Pick Disease) – tauopathy

1. **Age of Onset:** late middle age; most cases are sporadic
2. **Location of Lesions:** cortex
3. **Clinical Presentation:** similar to Alzheimer's disease
4. **Pathogenesis:** unknown; associated with the misprocessing of tau
5. **Gross Pathology:** decreased brain weight; greater degree of atrophy than Alzheimer's disease (blade-like gyri); in many cases atrophy occurs mainly in the **frontal and temporal lobes**
6. **Microscopic Pathology:** tau positive lesions, neuron loss and gliosis, mainly in frontal and temporal lobes of cerebral cortex; Pick bodies (intraneuronal collections of partially degraded tau fibrils) are found in about 15% of patients with frontotemporal dementia -- these cases are referred to as Pick's disease



DEG 04

Frontotemporal dementia (e.g. Pick disease) – Gross pathology

This gross brain shows severe atrophy in frontal and temporal lobes. Note that occipital and parietal lobes show little atrophy.

D. Huntington Disease - expanded polyglutamine repeat

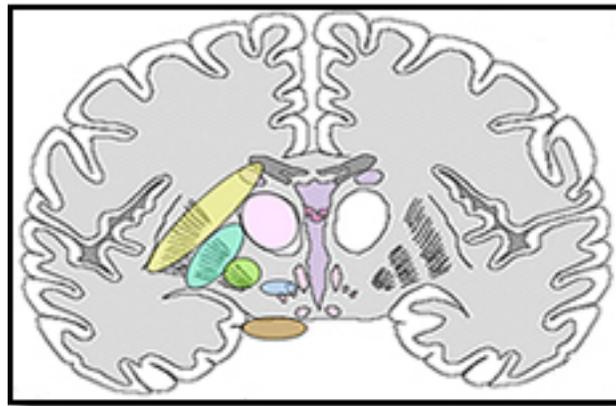
Huntington's disease is covered in the section III on Degenerative Diseases
Primarily Affecting Basal Ganglia, but it should be noted as a possible diagnosis for a patient who presents with dementia.

III. Diseases primarily affecting the basal ganglia

A. Huntington Disease - expanded polyglutamine repeat

1. **Age of Onset:** usually occurs between the ages of 30 and 50; death in 5-25 years.

2. **Location of Lesions:** caudate, putamen, globus pallidus and cerebral cortex.
3. **Clinical Presentation:** may begin with some combination of mood and personality changes, cognitive decline, clumsiness, extrapyramidal motor abnormalities, especially chorea (bursts of movement). Thus two types of symptoms occur:
 - a. Behavioral and cognitive changes, leading to dementia
 - b. Increasingly severe movement disorder
4. **Pathogenesis:** loss of projection neurons in basal ganglia with resulting deficiency of GABA, enkephalin, and substance P. One theory proposes that an excitotoxic mechanism may be involved in the pathogenesis of cell death.

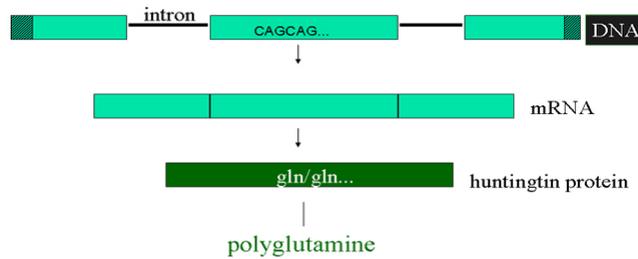


DEG 05

Illustration of basal ganglia anatomy. The striatum consists of the caudate and putamen. The lenticular nucleus consists of putamen and globus pallidus. Connections with the subthalamic nucleus and substantia nigra are important in control of movement.

5. **Inheritance pattern: autosomal dominant** transmission - toxic gain-of-function of the mutant protein **huntingtin**. The defect is an **expanded CAG trinucleotide repeat**. The CAG-repeat range of normal chromosomes is 9-39 (most shorter than 30; slightly different numbers for the range may be seen in different sources depending on the study quoted). HD chromosomes show repeat lengths of 36-121, with the vast majority greater than 40. Thus repeat lengths of 40 or more virtually guarantee that individuals will develop HD, and a molecular genetic test to determine the repeat length is available after counseling. The age of onset of the disease is related to the length of the trinucleotide repeat, with an increased probability of early onset correlated with higher repeat numbers. The CAG stretch on the HD chromosome is unstable when transmitted to the next generation, with both expansions and contractions occurring during gamete formation. The sex of the transmitting parent has a significant influence on the magnitude of repeat-length changes. When the chromosome is transmitted from the father, expansions occur much more frequently, and thus HD inherited from the father may have an earlier onset. Therefore, there is a tendency for

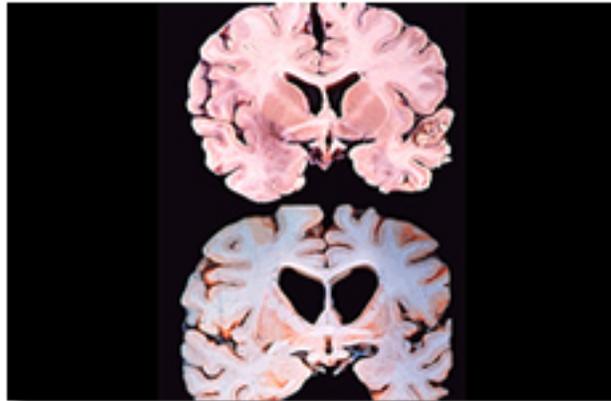
anticipation, earlier onset in paternal descent, and more than 75% of the juvenile onset patients (who have longer repeat lengths) inherit the gene from their father.



DEG 06

CAG repeats in an exon lead to transcription of the CAG repeats into mRNA, with translation resulting in polyglutamine repeats in the huntingtin protein.

- Gross Pathology:** atrophy of the caudate nucleus with ventricular dilatation is the most prominent feature.
- Microscopic Pathology:** loss of neurons in caudate, putamen, globus pallidus and cerebral cortex (other structures may be affected to a lesser extent); massive gliosis

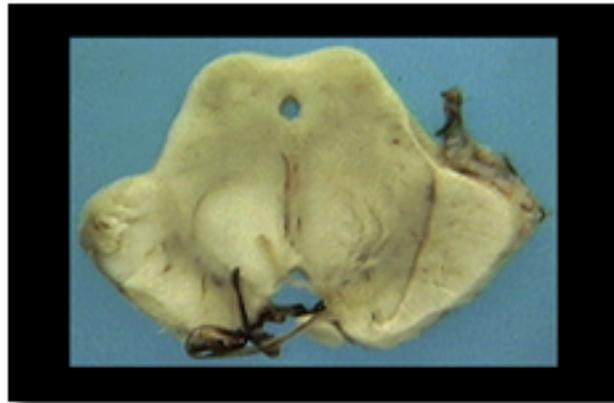


DEG 07

The coronal section at the bottom shows severe atrophy of the caudate nucleus with ventricular dilatation (“boxcar” ventricles”), characteristic of Huntington disease. A normal coronal section (also at the level of the anterior commissure) is shown at the top for comparison.

B. Parkinson Disease - alpha-synucleinopathy

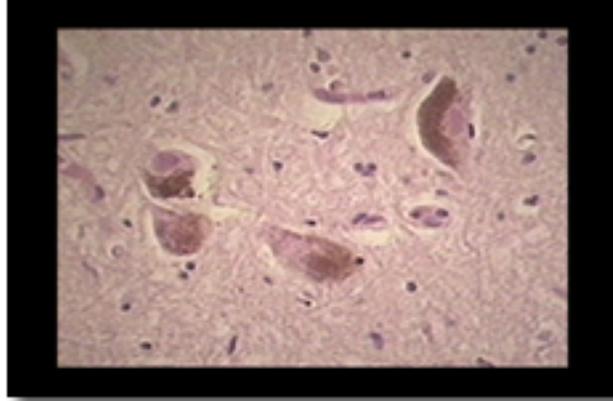
1. **Age of Onset:** middle to old age
2. **Location of Lesions:** substantia nigra mainly; some degeneration may be seen in caudate, putamen, globus pallidus, locus coeruleus and other locations.
3. **Clinical Presentation:** characteristic tremor ("pill-rolling") which is bilateral and symmetrical; hunched over posture; bradykinesia, cogwheel rigidity; instability of posture and gait (rapid shuffle). In some patients, "Parkinson-dementia complex" occurs, with mental changes due to cortical or sub-cortical lesions.
4. **Pathogenesis:** Loss of substantia nigra neurons which use dopamine as a neurotransmitter results in a deficiency of dopamine in caudate, putamen and globus pallidus. L-dopa, a precursor of dopamine that crosses the blood-brain barrier, can be used as replacement therapy to alleviate some symptoms. Grafting of dopamine-containing cells is also a potential therapy.
5. **Gross Pathology:** loss of pigment in substantia nigra.



DEG 08

This section of the midbrain shows depigmentation of substantia nigra, characteristic of Parkinson disease. The arrow indicates the location of the substantia nigra, adjacent to the cerebral peduncle.

6. **Microscopic Pathology:** loss of melanin-containing neurons in substantia nigra with pigment taken up by macrophages; gliosis; **Lewy (inclusion) bodies** in substantia nigra neurons; Lewy bodies contain alpha-synuclein



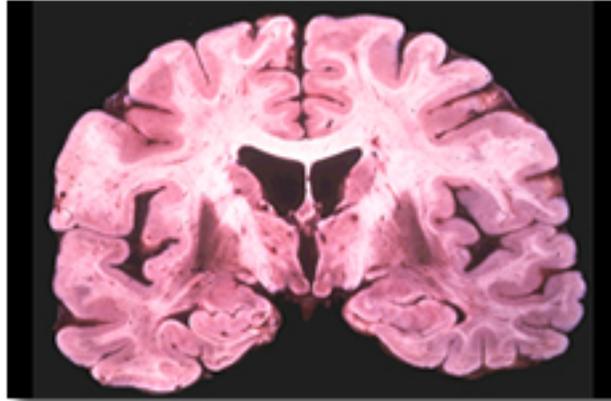
DEG 09

This H&E-stained section of the substantia nigra shows two Lewy bodies – intracellular inclusions in neurons. The Lewy body, which contains alpha-synuclein, is characterized by a dark center with a lighter halo.

C. Wilson Disease (Hepatolenticular Degeneration)

1. **Age of Onset:** adolescence
2. **Location of Lesions:** liver (cirrhosis), putamen and globus pallidus (lenticular nucleus), copper deposition in the limbus of eye (Kayser-Fleischer ring).
3. **Clinical Presentation:** onset marked by liver cirrhosis, even in the young; signs and symptoms of basal ganglia pathology, mainly movement disorders such as dystonia; some behavioral manifestations. In some patients, symptoms can mimic those of schizophrenia and other neurological disorders. **Kayser-Fleischer rings** (due to deposits of copper) can be seen in the eye.
4. **Pathogenesis:** an inborn error of copper metabolism marked by decreased plasma binding of copper and deposition of copper in tissues with the production of cirrhosis and progressive brain involvement
5. **Inheritance pattern:** autosomal recessive; the defective gene is on chromosome 13. A large variety of mutations in a single gene makes carrier detection difficult.
6. **Gross Pathology:** atrophy and discoloration of putamen and globus pallidus.

7. **Microscopic Pathology:** neuronal loss and gliosis in putamen, and to a lesser extent, globus pallidus, thalamus, cerebral cortex.



DEG 10

This coronal section shows atrophy and discoloration of putamen & globus pallidus (lenticular nucleus). The arrow indicates the putamen.

IV. Diseases with spinal cord and/or cerebellum involvement

A. **Amyotrophic lateral sclerosis (ALS):** one type of motor neuron disease

1. **Age of Onset:** middle-aged and elderly (usually older than 50 years)
2. **Location of Lesions:** **degeneration of both upper and lower motor neurons**, i.e., cortical pyramidal cells, neurons in cranial nerve nuclei, anterior horn cells are all involved. Degeneration of the corticospinal tract axons and peripheral nerves occurs in association with the neuronal degeneration.
3. **Pathogenesis:** unknown; approximately 10% of cases appear to be familial, with an autosomal dominant inheritance pattern.
4. **Clinical Presentation:** symptoms expected of upper motor neuron dysfunction (hyperactive reflexes, Babinski signs) and/or lower motor neuron dysfunction of either cranial nerves or spinal nerves (weakness, dysphagia, dysphonia, muscular wasting and fasciculations, pulmonary insufficiency).
5. **Gross Pathology:** atrophy of anterior horns and ventral nerve roots; cortical atrophy.
6. **Microscopic Pathology:** loss of anterior horn cells in spinal cord and motor neurons in the motor strip; Wallerian degeneration.
7. **Effect on Muscle:** causes denervation atrophy of affected muscles.

B. **Spinocerebellar Degenerations (spinocerebellar ataxias)** – This group of diseases affects the cerebellar cortex, spinal cord, peripheral nerves, and other regions, to variable extents. Degeneration of neurons occurs in the affected areas.

There is a group (at least 7) of genetically distinct **spinocerebellar ataxias** characterized by an autosomal dominant inheritance pattern. Some of these are caused by unstable expansions of CAG repeats, which encode polyglutamine regions in different proteins. **Friedreich ataxia**, the most common autosomal recessive form of spinocerebellar ataxia, is caused by a GAA trinucleotide repeat expansion and is discussed below.

Friedreich Ataxia: one type of spinocerebellar ataxia

1. **Age of Onset:** childhood/adolescence (average 11 years)
2. **Location of Lesions:** dorsal root ganglion spinal cord (especially sensory and spinocerebellar systems) and cerebellum
3. **Pathogenesis:** unknown; mitochondrial enzyme abnormalities may play a role
4. **Clinical Presentation:** Symptoms include ataxia of gait, hand clumsiness, weakness, sensory loss in limbs; chronic disease involving cardiac and skeletal abnormalities, with death in the 3rd-4th decade, usually from myocardial degeneration.
5. **Inheritance Pattern:** autosomal recessive; in most cases there is a GAA trinucleotide repeat expansion in the first intron of a gene encoding a protein named frataxin.
6. **Gross Pathology:** atrophy of spinal cord.
7. **Microscopic Pathology:** loss of axons and myelin in **posterior columns, spinocerebellar tracts** and **corticospinal tracts**, with secondary gliosis; loss of dorsal root ganglion cells and **cerebellar Purkinje cells**; and degeneration of the cerebellar **dentate nucleus**.

V. Prion Diseases (Transmissible Spongiform Encephalopathies-TSE)

A. Introductory concepts:

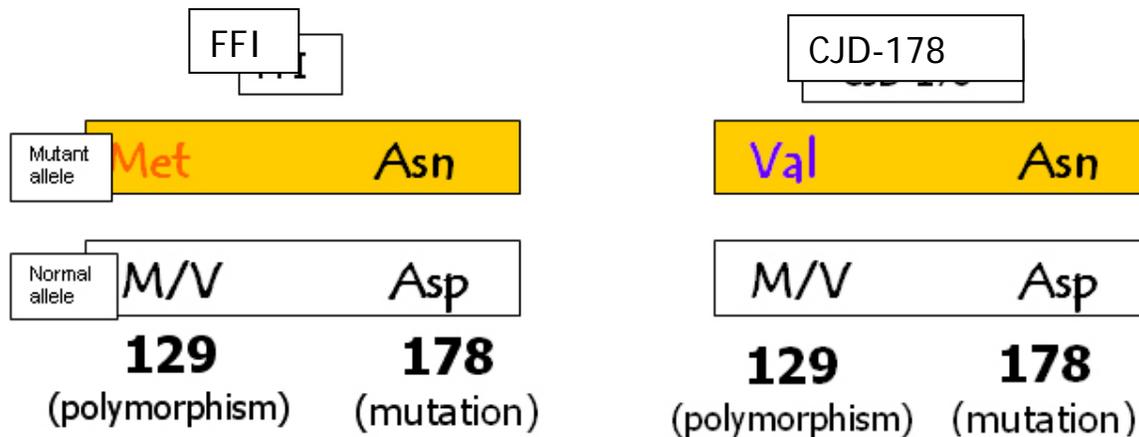
Human prion diseases (transmissible spongiform encephalopathies, including Creutzfeldt-Jakob disease (CJD) are all associated with abnormal forms of a specific protein, called prion protein (PrP); the diseases may be sporadic, inherited, and/or infectious. Several of these diseases have been transmitted to primates and to other animals through injections of infected brain tissue. The first prion disease to be transmitted to animals in this way was **kuru**, which was transmitted in the human population of the Fore tribe in New Guinea through cannibalism rituals. Prion diseases also occur in several mammalian species. **Scrapie** has existed for hundreds of years in sheep. Bovine spongiform encephalopathy ("mad cow" disease identified in Great Britain and Europe) occurs in cattle, and is thought to be the source of infection causing the 'new variant' form of CJD (nvCJD or vCJD) identified recently in young adults in Great Britain. Genetically transmitted human prion diseases include Gerstmann-Straussler-Schenker syndrome, fatal familial insomnia, and a small percentage of CJD cases.

B. Characteristics of the prion protein and prions

Prion protein (PrP) is a 30 kD normal cellular protein present in neurons. Disease occurs when the prion protein undergoes a conformational change from its normal alpha-helix configuration to an abnormal beta-pleated sheet configuration (PrP-Sc). The conformational change may occur spontaneously at an extremely low rate or at a higher rate if there is a defect in the gene. The agent can "replicate" when the abnormal form PrP-Sc interacts with the normal, cellular prion protein and the abnormal prion induces the normal form to adopt a similar abnormal form. The mechanism that initiates conversion is unknown. PrP-Sc is resistant to degradation and accumulates in cells that undergo vacuolation. The infectious potential of prions is not destroyed when subjected to ultraviolet radiation, formalin, or typical sterilization procedures; thus care must be taken by health care professionals in surgical or pathological procedures.

C. Role of codon 129 in determining disease severity

A polymorphism at codon 129 in the PrP gene is important in determining disease characteristics.



For example, the normal PrP sequence has Asp (D) at codon 178 and a polymorphism with either Met (M) or Val (V) at codon 129. One form of inherited prion diseases is associated with a mutation (Asp → Asn) at codon 178. When the allele containing the D178N mutation also has a Val at codon 129, the patient develops CJD, with lesions mainly in the cortex. In contrast, when the D178N allele has Met at codon 129, the clinical disorder is fatal familial insomnia (FFI) with lesions mainly in the thalamus and brainstem. Also, homozygosity at codon 129 leads to more severe disease course, and the amino acid at codon 129 plays a role in determining susceptibility to disease after infection.

D. Creutzfeldt-Jakob Disease (CJD)

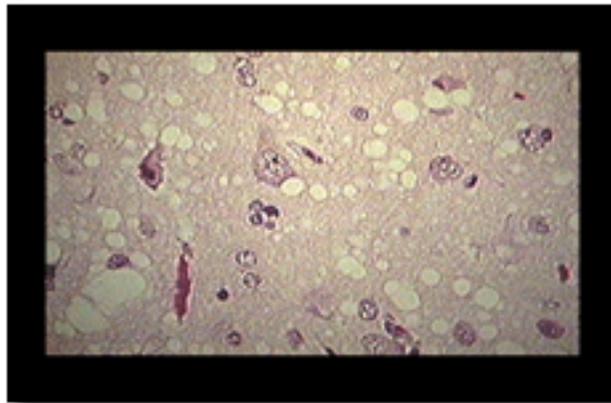
1. Clinical Features

- a) Onset: between 40 and 80 years of age

- b) Clinical presentation: The major features are dementia and myoclonus. Other symptoms, less consistently seen, include motor disorders and cerebellar incoordination.
- c) Duration: death usually in 3-12 months
- d) Transmission: A small percentage of cases are familial, but most are sporadic. In a few cases, transmission has occurred by corneal transplant or administration of contaminated growth hormone.
- e) CSF findings: usually normal; possible slight increase in protein

2. Pathological changes

- a) Gross pathology: Cortical atrophy and ventricular dilatation may be present; these changes are usually mild and are not diagnostic.
- b) Microscopic pathology: The major diagnostic change is spongiform encephalopathy in gray matter throughout brain and spinal cord. The tissue appears "spongy", i.e. containing holes. Severe neuronal loss and gliosis also are present and mild demyelination may occur. Ultrastructural changes include intracytoplasmic vacuoles as the basis for the spongy change.



DEG 11

Spongiform encephalopathy (neuronal vacuoles) are characteristic of CJD. The pathology is variable in location and extent. Patterns of PrP-Sc deposition correlate with vacuolation profiles.

C. Variant Creutzfeldt-Jakob Disease (vCJD)

Since 1995, over 100 individuals in the United Kingdom have been diagnosed with vCJD. The clinical presentation was different from typical CJD: young adults were affected, behavioral disorders were prominent in the early stages of the disease, and the symptoms progressed more slowly. However, neuropathologic findings and molecular features were similar to CJD. Evidence indicates that these cases are a result of eating tissue from cows with bovine spongiform encephalopathy (BSE).