Neuro-degenerative disorders:
- Dementia: Alzheimer’s Disease
- Akinesia: Parkinson’s Disease
- Hyperkinesia: Huntington’s Disease
- Ataxia: Spinocerebellar Degeneration
- Others

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Neurodegenerative Disorders

- Progressive dysfunction and death of neurons
- Affecting specific systems
  (selective neuronal vulnerability)
- Manifesting with
  - cognitive disturbance
  - movement disorder
  - mixture

Pathogenesis of Neurodegeneration

- Protein accumulations
  - cellular inclusion bodies:
    - neurofibrillary tangles, Lewy bodies
  - extracellular proteins:
    - amyloids (antiparallel β-pleated sheet)
- Excitotoxicity (excessive glutamatergic stimulation)
  - expression of certain combinations of glutamate receptors that render neurons vulnerable to excitotoxic damage

Neuronal Inclusion Bodies in Degenerative Diseases

Neuronal cytoplasmic inclusion bodies are the distinguishing features of several important neurodegenerative diseases. Some are identified in hematoxylin-eosin (HE)–stained sections, others only in silver-stained sections, and still others with immunohistologic stains.

The molecular components of these inclusions are identified using immunohistochemical stains. Some inclusions immunoreact for tau, a microtubule associated protein (MAP), others for α-synuclein, a synaptic protein, and still others for ubiquitin, a stress protein.

Intranuclear inclusions derived from the proteins of polyglutamate tracts characterize trinucleotide repeat diseases.

Neurofibrillary tangles, a histologic hallmark of Alzheimer’s disease, are argyrophilic torch and basketshaped or globous filamentous cytoplasmic structures that immunoreact for tau protein. They also are found in normal aging and in a variety of diseases.

Pick bodies, histologic hallmarks of Pick’s disease, are argyrophilic, round, homogenous structures in the swollen pyknotic disrupting the lateral sclerosis. They immunoreact for tau protein.

Lewy bodies are eosinophilic, round inclusions in the melanin containing neurons of the substantia nigra and locus ceruleus in idiopathic Parkinson’s disease and in the cortical neurons of the diffuse Lewy body dementia. They immunoreact for α-synuclein and ubiquitin.

Hirano bodies are rod shaped or ovoid eosinophilic structures within or adjacent to the pyramidal neurons of the hippocampus in Alzheimer’s disease, and they also found in normal aging. They immunoreact for actin.

Bunina bodies are small, eosinophilic granules in the cytoplasm of motor neurons in amyotrophic lateral sclerosis (ALS). They immunoreact for cystatin C.

Skein-like inclusions in ALS immunoreact for ubiquitin.

Lafora bodies in Lafora disease with myoclonus epilepsy are round, basophilic cytoplasmic inclusions containing polyglucosans that stain strongly with PAS reagent.
Neuronal inclusions. A. Neurofibrillary tangles in Alzheimer's disease (silver nitrate stain), showing NFT present immunostaining for tau protein. B. NFT bodies in pyramidal neurons of hippocampus (arrows). C. Lewy body in substantia nigra in Parkinson's disease (SP stain). D. Riken body in a subcortical area in Pick's disease (SP stain), and E. Hirano bodies in both subcortical areas of corticaneurosis (SP stain).

**TABLE 2.1.**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Protein(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibrillary tangle</td>
<td>Tau, microtubule</td>
</tr>
<tr>
<td>Bulb body</td>
<td>Tubulin, microtubule</td>
</tr>
<tr>
<td>Lewy body</td>
<td>Alpha-synuclein</td>
</tr>
<tr>
<td>Hirano body</td>
<td>C, N, M</td>
</tr>
<tr>
<td>Microtubule inclusion</td>
<td>Tubulin, microtubule</td>
</tr>
</tbody>
</table>

in the cortical neurons of the diffuse Lewy body dementia. They immunostain for neurofilament and alpha-synuclein. Hirano bodies are rounded or oval shaped metachromatic structures within or adjacent to the pyramidal neurons of the hippocampus in Alzheimer's disease, and they are also found in normal aging. They immunostain for alpha-synuclein.

Riken bodies are small, metachromatic granules in the cytoplasm of motor neurons in amyotrophic lateral sclerosis (ALS). They immunostain for synaptophysin.

**TABLE 2.2.**

<table>
<thead>
<tr>
<th>Disease with NFTs</th>
<th>Inclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Tau, alpha-synuclein</td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>Alpha-synuclein</td>
</tr>
<tr>
<td>Pick's Disease</td>
<td>Alpha-synuclein</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Tau, alpha-synuclein</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Tau, alpha-synuclein</td>
</tr>
<tr>
<td>Rosellar dementia</td>
<td>Tau, alpha-synuclein</td>
</tr>
<tr>
<td>Niemann-Pick disease, type C</td>
<td>Tau, alpha-synuclein</td>
</tr>
</tbody>
</table>

**FIGURE 3.4.**


**TABLE 2.5.**

**Pathology of Glial Cells**

<table>
<thead>
<tr>
<th>Astrocytes</th>
<th>Oligodendrocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>Swelling</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Gemistocytic astrocyte</td>
<td>Inclusions</td>
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<tr>
<td>Fibroblastic gliosis</td>
<td>Neoplastic transformation</td>
</tr>
<tr>
<td>Alzheimer type 1 and 2 glia</td>
<td>Viral</td>
</tr>
<tr>
<td>Rosenthal fibers</td>
<td>Viral</td>
</tr>
<tr>
<td>Corpora amylacea</td>
<td>Viral</td>
</tr>
<tr>
<td>Inclusions</td>
<td>Neoplastic transformation</td>
</tr>
<tr>
<td>Argophilic</td>
<td>Neoplastic transformation</td>
</tr>
<tr>
<td>Viral</td>
<td>Microglia</td>
</tr>
<tr>
<td>Neoplastic transformation</td>
<td>Macrophage</td>
</tr>
</tbody>
</table>

**FIGURE 3.5.**

Pathogenesis of Neurodegeneration

• Induction of programmed cell death - Apoptosis
• Role of cytokines
  - reactions of microglia and astrocytes (IL-1β, TNF-α)
• Genetic factors
  - single gene mutations
  - expansion of tandem nucleotide triplet repeats

อาการที่เกิดขึ้นอย่างแรกเมื่อเริ่มมีอาการโรคสมองเสื่อม (Dementia) คือ??

อาการความจำเสื่อมในผู้สูงอายุ (Senile Dementia: DSM-IV RT)
1. มีความบกพร่องในความจำในระยะสั้นและระยะยาว
2. มีความบกพร่องในความคิดเชิงนามธรรม
3. มีความบกพร่องในการตัดสินใจ
4. มีความบกพร่องในการทำงานของสมองระดับสูงในเรื่อง การพูด การเคลื่อนไหว การรับรู้ ความคิดสร้างสรรค์
5. มีการเปลี่ยนแปลงในบุคลิกภาพ
6. มีปัจจัยทางกายภาพ (โรคของเนื้อสมอง)
7. ไม่มีโรคซึมเศร้า หรือความบกพร่องของสติสัมปชัญญะ

DEFINITION OF DEMENTIA: (DSM-III-R)
I. Impairment of short- and long-term memory
II. Impairment of Abstract Thinking
III. Impairment of Judgement
IV. Disturbances of higher cortical functions:
   -- aphasia
   -- apraxia
   -- agnosia
   -- constructive difficulties
V. Personality changes
VI. Organic factors involved
VII. No evidence of depression (Pseudo-Dementia) or impaired state of consciousness
ความรุนแรงของการความถี่

1. ระยะแรก ไม่รุนแรง หลงลืมบ้างแต่ยังช่วยตัวเองได้
2. ระยะปานกลาง ต้องมีผู้ดูแล ไม่สามารถดูแลตัวเองได้
3. ระยะรุนแรง ความจำเสียมาก ต้องมีคนดูแล

จำนวนผู้มีอาการความจำเสียมากขึ้นตามอายุ เมื่อมีอายุ 90 ปี มากถึง 50% ของประชากร

การกระจายของกลุ่มอาการความจำเสียตามสาเหตุ

1. ความจำเสียจากโรคอัลไซเมอร์ 40-60%
2. ความจำเสียจากการตายของเนื้อสมองหลายจุด 12-20%
3. ความจำเสียแบบผสมผสาน 10-13%
4. จากสาเหตุอื่นๆ 10-20%

In 1907, ALOIS ALZHEIMER read a paper to the Society of Alienists at Tubingen. Using the Bielschowsky's silver impregnation stain for neurofibrils, he demonstrated the neuritic plaques and neurofibrillary tangles in the brain of a demented woman of 51, establishing the structural basis of the most common type of presenile and senile dementia.
Alzheimer’s Disease -- Neuropathologic findings:

I. Neuronal degeneration
II. Cortical Atrophy
III. Neurofibrillary tangles
IV. Neuritic plaques
V. Amyloid Accumulation

Cerebral atrophy. External surface of the brain with widened sulci and narrowed gyri

Characteristic hydrocephalus ex vacuo or ventricular dilation resulting from loss of cortex

Histology of Alzheimer’s Disease

Neuritic plaques
Neuronal changes
Neurofibrillary tangles
Granulovacuolar degeneration
Hirano bodies
Synaptic losses
Neuronal losses
Amyloid angiopathy

FIGURE 1.1: Alzheimer’s disease. Onset of intellectual decline at 65 years of age, clinical course 1 year. A. The left hemisphere shows prominent atrophy of the frontal lobe. B. The brain shows severe atrophy of the hippocampus, cornu Ammonis, and entorhinal cortex.

FIGURE 1.2: Alzheimer’s disease. Onset of memory decline at 55 years of age. A. The left hemisphere shows severe generalized atrophy. B. The width of the corpus is reduced to 1.5 to 2 mm. The white matter is atrophic, and the ventricles are dilated.

FIGURE 1.3: Alzheimer’s disease. A. Neuritic plaques in the frontal cortex are demonstrated in silver-stained sections (H&E stained sections). B. Senile plaques in the temporal lobe (H&E stained sections). C. High-power view shows amyloid plaques (H&E).

FIGURE 1.4: Alzheimer’s disease. A. An oligodendrocyte with a neuritic plaque (H&E stained sections). B. A cerebellar astrocyte with neurofilaments (H&E stained sections).
Alzheimer's disease. Amyloid angiopathy. Congo red–positive amyloid deposits around and within the walls of small cortical blood vessels (Congo-red stain).

**Figure 5.9**
Alzheimer's disease. Cortical neuronal lesions A. Severe cortical neuronal degeneration and vacuolar changes. B. Frequent remnants of cerebrovascular amyloid plaques (Kramer stain).

**Figure 5.10**

**Alzheimer's Disease**

Molecular Pathology

- Neuritic Plaques
  - Amyloid β peptide
  - Abnormal Tau-protein
- Neurofibrillary Tangles
- Neuronal Death
FIG. 13. Progression of senile changes in cortical pyramidal cells as seen in Golgi impregnations. A, and in Bielschowsky stains. B, We suggest that the increasing swelling and distortion of the soma—dense-silhouette, and progressive loss of dendrites, first horizontal, then vertical, are closely related to the increased clogging of the cytoplasmic space with abnormal tubular material.
**BIOCHEMISTRY OF THE CLASSICAL BRAIN LESIONS**

- Senile (neuritic) plaques
- Neurofibrillary tangles

Plaques are associated with activated microglia.

---

**Plaques:**

- Extracellular deposits of amyloid-β protein (Aβ):
  - Amyloid fibrils
  - Non-fibrillar forms of amyloid

**Diffuse plaques:**

- Predominantly amorphous form of Aβ
- Mostly Aβ42

**Neurofibrillary tangles:**

- Intraneuronal
- Paired helical filaments (PHF)
- Microtubule associated protein, tau (hyperphosphorylated and insoluble)

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**Genetics of Alzheimer’s Disease**

**APP:** Chromosome 21
- Early onset
- Autosomal dominant

**Presenilin 1:** Chromosome 14
- Early onset
  - Autosomal dominant

**Presenilin 2:** Chromosome 1
- Autosomal dominant

**APOE4:** Chromosome 19
- Susceptibility gene
- Late onset
- Familial and sporadic

**MAP Security:**

- Increases production of total Aβ peptides or of Aβ42 peptides
- Increases density of Aβ plaques and vascular deposits
- Increases production of Aβ42 peptides

**APP:** amyloid precursor protein; APOE4, apolipoprotein E4.
β-Amyloid precursor protein mutations:
Genotype-to-phenotype conversions

<table>
<thead>
<tr>
<th>Codon</th>
<th>Mutation</th>
<th>Name</th>
<th>Effects on Aβ in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>670/671</td>
<td>KM → NL</td>
<td>Swedish</td>
<td>Increase Aβ production</td>
</tr>
<tr>
<td>692</td>
<td>A → G</td>
<td>Flemish</td>
<td>Increase Aβ / p3, increase alternative Aβ N-termini</td>
</tr>
<tr>
<td>693</td>
<td>E → G</td>
<td>Dutch</td>
<td>Increase Aβ / p3, increase Aβ fibrilogenesis (Synthetic peptide)</td>
</tr>
<tr>
<td>717</td>
<td>V → I</td>
<td>London</td>
<td>Increase long Aβ (42 residues)</td>
</tr>
<tr>
<td></td>
<td>V → G</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>V → F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease

Cytosol

Lumen
THE GENETICS OF AD

- Gene encoding the precursor of \( A\beta \), the \( \beta \)-amyloid precursor protein (APP)

- Less than 0.1% of AD cases

- ApoE4: a risk factor

- Presenilin-1 (PS1)

- Presenilin-2 (PS2)

Missense mutations in the presenilins result in an aggressive early-onset form of AD

"A\beta ACCUMULATION IS AN EARLY, INVARIANT AND NECESSARY EVENT IN THE GENESIS OF FAMILIAL AD" 
(A\beta domain in red)

CELL BIOLOGY OF AD

- Both during and after its transport through the secretory pathway to the cell surface, a subset of APP molecules undergoes cleavage

- \( \alpha \)-secretase: principal secretory cleavage (metalloprotease disintegrins)

- \( \beta \) - and \( \gamma \)-secretase: responsible for alternative cleavage that leads to \( A\beta \) formation

Selkoe, Nature 399, A23-A31, 1999

CELL BIOLOGY OF AD

\( A\beta \) IS HETEROGENEOUS

- The C-terminal heterogeneity has special importance for its aggregation

- The first \( A\beta \) form deposited as diffuse plaques in AD ends at residue 42; \( A\beta42 \) is detected later

\( A\beta42 \) with its two additional hydrophobic residues aggregates more rapidly than does \( A\beta40 \)

Selkoe, Nature 399, A23-A31, 1999
**CELL BIOLOGY OF AD**

Where is Aβ generated and located?

Data from a canine model using antibodies to Aβ42 (Norp, Head, Milgram, Hahn, Ottersen, Cotman, Neuroscience 96:495-506, 2000)

Immunolabelled senile plaques in prefrontal cortex

Individual Aβ42 deposit associated with glial processes

**CELL BIOLOGY OF AD**

Aβ42 is expressed along dendritic plasma membranes

This can be confirmed at high resolution by EM immunogold

... as shown at higher magnification

**GENOTYPE TO PHENOTYPE**

Modelling the effects of AD genes in cultured cells or transgenic mice:

- "Aβ ACCUMULATION IS AN EARLY, INVARIANT AND NECESSARY EVENT IN THE GENESIS OF FAMILIAL AD"

- APP missense mutations linked to AD enhance β- and γ-secretase cleavage of APP resulting in elevated β42

- ApoE4: enhanced aggregation of β42

- Presenilin mutations enhance β42 deposition

**GENOTYPE TO PHENOTYPE**

Presenilin

- There are numerous mutations in the presenilins (PSs)

- These result in gain of function

- Presenilin mutations enhance β42 deposition

Selkoe, Nature 399, A23-A31, 1999

Saxl, 1998
Genotype to Phenotype

Presenilin mutations enhance $\beta_42$ deposition.

Hypothesis 1: PS promotes interaction between $\gamma$-secretase and APP.

Hypothesis 2: PS1 and PS2 could themselves be the $\gamma$-secretases.

This would be consistent with EM immunogold studies.

Cloning of Human $\beta$-Secretase

Here we describe a membrane-bound enzyme activity that cleaves full-length APP at the $\beta$-secretase cleavage site, and find it to be the predominant beta-secretase activity in human brain. We have purified this enzyme activity to homogeneity from human brain using a new substrate analogue inhibitor of the enzyme activity, and show that the purified enzyme has all the properties predicted for beta-secretase. Cloning and expression of the enzyme reveals that human brain - secretase is a new membrane-bound aspartic proteinase.

Downstream Effects of $\alpha_42$ Accumulation

$\alpha_42$ — Diffuse $\alpha_42$ plaques — $\alpha_40$ aggregation

Inflammatory response — Oxidative injury

PHF formation — Neuronal death with transmitter deficits (including acetylcholine)

Dementia

Predictions for New Strategies for Pharmacological Intervention

Possible targets:

- $\beta$- or $\gamma$-secretase inhibitors
- Inhibitors of $\alpha_4$ oligomerization or fibrillation
- Anti-inflammatory drugs
- Antioxidants
- Neurorestorative factors (e.g., neurotrophins)
SELECTIVE CELL LOSS

DIBUTURYL ARICEPT

INFLAMMATION, NEUROTOXICITY AND APOPTOSIS IN AD

42 Aβ accumulation leads to local microglial activation, cytokine release, and reactive astrocytosis

42 Aβ initiated inflammatory and neurotoxic process lead to the generation of free radicals

42 Aβ APOPTOSIS
Classical Alzheimer features and cholinergic dysfunction: towards a unifying hypothesis?


Department of Anatomy, University of Köln, Germany.

CONCLUSION: These findings provide first evidence for a direct impact of classical Alzheimer pathology features on nicotinic receptor expression in brain. This study may provide a model to test whether down-regulation of nicotinic receptors could be used for testing the potential of drugs to stop or reverse these effects.
THE GENETICS OF AD

Classical Alzheimer features and cholinergic dysfunction: towards a unifying hypothesis?


Department of Anatomy, University of Kiel, Germany.

CONCLUSION: These findings provide first evidence for a direct impact of classical Alzheimer pathology features on nicotinic receptor expression in vitro. Our model will be useful for testing the potential of drugs to stop or reverse these effects.
The PET studies reveal deficits in nAChRs as an early phenomena in AD, stressing the importance of nAChRs as a potential target for drug intervention. Treatment with cholinergic drugs in AD patients indicate improvement of the nAChRs in the brain, as visualized by PET. Further studies on neuroprotective mechanisms mediated via nAChR subtypes are exciting new avenues.
Dynamics of Gray Matter Loss in Alzheimer’s Disease

Paul M. Thompson, Kristin M. Harrell, Greg De Zelting, Andrew L. Jenkins, Stephen L. Ross, James Samji, Brian Leow, Michael E. Moseley, Andreas Delis, Daniel N. Oktay, and Arthur W. Toga

Laboratory of Brain Imaging, Brain Research Institute, University of California, Los Angeles, California 90095, and Center for Medical Image Science and Visualization, Linköping University, Linköping, Sweden.

We detected and mapped axiologically precise trajectories of gray matter loss in a cohort of patients with Alzheimer’s disease (AD). The loss patterns were measured in lateral directions at 1.5-year intervals from temporally and spatially distinct label and control regions, mapping white matter volume. The white matter loss patterns were highly consistent with the progression of the disease, with the most pronounced changes in the parietal and occipital lobes. Overall, the results suggest that the progression of the disease is accompanied by a decrease in white matter volume, with the most pronounced changes occurring in the parietal and occipital lobes.

Figure 1. Initial deficit in lateral directions at 1.5-year intervals. The deficit is located in the left hemisphere, with a greater effect in the left parietal and occipital lobes.

Figure 2. Significance map for the initial deficit in lateral directions at 1.5-year intervals. The significance is greater in the left hemisphere, with a greater effect in the left parietal and occipital lobes.

Figure 3. Leftward reduction at 1.5-year intervals. The leftward reduction is greater in the left hemisphere, with a greater effect in the left parietal and occipital lobes.

Figure 4. Percent deficit at 1.5-year intervals. The percent deficit is greater in the left hemisphere, with a greater effect in the left parietal and occipital lobes.

Breakthrough Brain Imaging-agent Enables Researchers to See Amyloid Plaques in People with Alzheimer’s Disease

STOCKHOLM, Sweden, July 23, 2002 (U.S. Newswire) - The first human studies of a promising compound used with Positron Emission Tomography (PET) Imaging indicate that researchers now can, for the first time, successfully highlight amyloid plaques in the brains of individuals in the early stages of Alzheimer’s disease.

Having the ability to quantify amyloid deposition in the brain will have a profound impact on our ability to monitor the progression of Alzheimer’s as well as gauge the effectiveness of medical treatments,” said William Thies, Ph.D., vice president of medical and scientific affairs for the Alzheimer’s Association.
Better Scanning for Alzheimer’s
New Technique Allows Viewing of Brain Lesions in Living Patients
By Melinda T. Wall

Jan. 10 – A new imaging technique may make it possible to diagnose and treat Alzheimer’s disease at an earlier stage.

New Technique Detects Early Onset of Alzheimer’s Disease
UCLA scientists have created the first technique to image the onset of Alzheimer’s disease in the living brain, before the disorder attacks brain cells.

March 4, 2002

UCLA scientists have created the first technique to image the onset of Alzheimer’s disease in the living brain—before the disorder attacks brain cells. The method will allow doctors to monitor the disease as it unrolls, speeding diagnosis and new treatments, according to a report in the January 2002 issue of the American Journal of Pathology. The technique will allow doctors to monitor the disease as it progresses, speeding diagnosis, intervention, and new therapies for the disorder that affects 10 percent of people older than 65.

PET Imaging of Plaques and Tangles in Alzheimer’s Disease, Other Dementias, and in Normal Persons
This project uses PET to image the actual underlying lesions that define Alzheimer’s: the amyloid plaques and neurofibrillary tangles. Volunteers receive two PET scans (a standard scan and a second amyloid imaging scan), an MRI, and memory assessments. Different forms of mild memory loss, and dementia (e.g., Alzheimer’s, Lewy Body, etc.) are studied.

Pathology Detection
Dementia Patient Elderly Normal Subject

Longitudinal quantitative proton magnetic resonance spectroscopy of the hippocampus in Alzheimer’s disease
R. M. Jones, K. M. H. McHale, N. W. Bagby, M. W. Bagby, P. E. Welsh, and A. D. Zafar

MR Imaging and Alzheimer’s Disease: A Novel Noninvasive Technique for Detecting Alzheimer’s Disease Early in the Course of the Disorder
R. M. Jones, K. M. H. McHale, N. W. Bagby, M. W. Bagby, P. E. Welsh, and A. D. Zafar

Summary

Neuroimaging techniques, particularly magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT), have become important tools for the early detection of Alzheimer’s disease in recent years. These techniques can detect changes in the brain that are characteristic of Alzheimer’s disease, such as reduced brain volume and increased glucose metabolism in the hippocampus. However, these techniques are not always able to detect these changes in the early stages of the disease, when intervention might be the most effective. Therefore, there is a need for new methods to detect Alzheimer’s disease early in its course.

In this study, we evaluated the use of longitudinal quantitative proton magnetic resonance spectroscopy (1H MRS) to detect changes in the hippocampus that are characteristic of Alzheimer’s disease. The hippocampus is a brain region that is particularly vulnerable to the effects of Alzheimer’s disease, and changes in its metabolism can be detected early in the disease process. We used 1H MRS to measure the levels of neurotransmitter-related metabolites in the hippocampus of patients with Alzheimer’s disease and of healthy controls.

The results of this study show that there are significant changes in the levels of neurotransmitter-related metabolites in the hippocampus of patients with Alzheimer’s disease compared to healthy controls. These changes are most pronounced in patients with mild cognitive impairment, the earliest stage of the disease, and are consistent with the hypothesis that changes in the hippocampus are an early marker of Alzheimer’s disease.

These results suggest that longitudinal quantitative proton magnetic resonance spectroscopy of the hippocampus may be a useful tool for the early detection of Alzheimer’s disease. Further research is needed to confirm these findings and to develop a standardized protocol for using 1H MRS in the clinical setting.
Definition of Aging

- Progressive, unfavorable loss of adaptation resulting in decreasing expectation of life with the passage of time
  "The older you get, the closer you are to death"

- Normal aging process:
  - Universal
  - Intrinsic
  - Progressive
  - Undesirable

Aging Brain

- Neuronal shrinkage and loss
- Dendritic and synaptic loss
- Lipofuscin accumulation within neurons
- Reactive astrogliosis, microglial activation
- Small number of neuritic plaques (deeper cortex)
- Large number of non-neuritic β-amyloid plaques
- Neurofibrillary tangles (anteromedial temporal region)
- Neuropil threads (entorhinal, hippocampus, amygdala)

Definition of Dementia

- Impairment of previously attained occupational or social functioning due to acquired persistent impairments of memory and of one or more of the following intellectual functional domains:
  - language
  - visuospatial skills
  - personality and social skills
  - abstract reasoning and judgment,
  in the presence of normal consciousness

Clinical Patterns of Dementia

- Cortical Dementia
  - cerebral cortex involved
  - aphasia, agnosia, apraxia, aacalculia
  - difficulty in learning new material

- Subcortical Dementia
  - basal ganglia, thalamus, mesencephalon involved
  - impaired problem-solving produced by slowness of thought process and forgetfulness
  - difficulty in retrieving learned material
  - dysarthria, rigidity, tremor, chorea
Cortical Dementia

- Temporoparietal Dementia
  - Initially, memory impairment (temporal lobe)
  - Later, impairment of visuospatial skills and integration of sensory inputs, leading to aphasia, agnosia, and apraxia (parietal lobe)
- Frontotemporal Dementia
  - Initially, behavioral disturbances - impairment of judgment, abstract reasoning, strategic planning, emotional restraint, appetite control, and continence (frontal lobe)
  - Later, memory impairment (temporal lobe)

Etiologies of Dementia

- Neurodegenerative Disorders
  - Alzheimer’s disease (50-75%)
  - Dementia with Lewy bodies (10-25%)
  - Frontotemporal dementias (12-20%)
  - Tangle-only dementia
  - Argyrophilic grain dementia
- Cerebrovascular Disorders
  - Vascular dementias
- Infective Disorders
  - HIV-associated dementia
  - Progressive multifocal leukoencephalopathy

Etiologies of Dementia

- Prion Diseases
- Disorders of Myelination
  - Multiple sclerosis
  - Leukodystrophies
- Mitochondrial Disorders
- Intermittently Raised Pressure Hydrocephalus
- Head Injury
  - Dementia pugilistica (punch-drunk syndrome)
  - Subdural hematoma
- Toxic Disorders
  - Chronic alcoholism

Pathogenesis of Neurodegeneration

- Protein accumulations
  - Cellular inclusion bodies:
    - Neurofibrillary tangles, Lewy bodies
  - Extracellular proteins:
    - Amyloids (antiparallel β-pleated sheet)
- Excitotoxicity (excessive glutamatergic stimulation)
  - Expression of certain combinations of glutamate receptors that render neurons vulnerable to excitotoxic damage

Neurodegenerative Disorders

- Progressive dysfunction and death of neurons
- Affecting specific systems
  - Selective neuronal vulnerability
- Manifesting with
  - Cognitive disturbance
  - Movement disorder
  - Mixture

Pathogenesis of Neurodegeneration

- Induction of programmed cell death - Apoptosis
- Role of cytokines
  - Reactions of microglia and astrocytes (IL-1β, TNF-α)
- Genetic factors
  - Single gene mutations
  - Expansion of tandem nucleotide triplet repeats
Alzheimer's Disease

- Alois Alzheimer
  - Anatomical Lab, Royal Psychiatric Hospital, Munich
  - Auguste D. (1907) and Johann F. (1911)
- Remarkable rise in prevalence with age after 75 years
  - 2% of population in the U.S.
  - 50-60% of population over age 85 years

Molecular Genetics of AD

- AD1: APP (amyloid precursor protein)
  - normal transmembrane glycoprotein
  - APP gene mutations 21: 10% of familial early-onset AD
  - AD associated with Down's syndrome (trisomy 21)

Molecular Genetics of AD

- AD2: ApoE (apolipoprotein E)
  - distributing membrane cholesterol and phospholipids
  - ε2, ε3, ε4 alleles 19 encoding E2, E3, E4 isoforms
  - binds Aβ peptide (E4 does so most strongly)
  - promotes Aβ polymerization (amyloid)
  - ε4 allele increases risk of late-onset AD
  - ε2 allele reduces risk of late-onset AD

Molecular Genetics of AD

- AD3: PS1 (presenilin-1) gene mutations
  - 50% of familial early-onset AD
  - alter APP proteolytic processing, enhancing amyloidogenic Aβ42/43 production

- AD4: PS2 (presenilin-2) gene mutations
  - familial late-onset AD
  - mechanism similar to PS1

Molecular Genetics of AD

- Cortical atrophy and reduced white matter volume of temporal (hippocampus), frontal, parietal regions; sparing of occipital and motor cortex
- Microscopic features:
  - Neurofibrillary tangles and neuropil threads
    - paired helical filaments => hyperphosphorylated microtubule-associated protein tau (τ) of 55, 64, 69 kD
  - Neuritic plaques
    - β-amyloid (Aβ42/43 peptide) core associated with tau+ dystrophic neurites, reactive astrocytes, microglia
Pathologic Features

- Microscopic features:
  - Loss of synapses and, later of neurons from cerebral cortex, nucleus basalis of Meynert (cholinergic projection to cerebral cortex)
  - Cerebral amyloid angiopathy (Aβ39/40 peptide)
    - cortical arterioles (media) => lobar hemorrhage
    - leptomeningeal arteries (adventitia)
  - Granulovacuolar degeneration in hippocampal pyramidal neurons
  - Hirano bodies in hippocampal CA1 and subiculum

AD Brain

Neuritic Plaque

Neuritic Plaque

Neurofibrillary Tangles

β-Amyloid Plaque
Neuritic Plaque

Hirano Body
Granulovacuolar Degeneration

Cerebral Amyloid Angiopathy

Giant Cell Angiitis
Diagnosis of Alzheimer's Disease

- Clinical Diagnosis (Neurology 1984;34:939-944)
  - NINCDS-ADRDA: Probable AD
  - Possible AD

- Clinical-Pathologic Diagnosis (Neurology 1991;41:479-486)
  => Age-related Neuritic plaque score + Clinical dementia
  - Definite AD
  - CERAD NP probable AD
  - CERAD NP possible AD
  - Normal

Diagnosis of Alzheimer’s Disease

  => Neurofibrillary tangles and Neurofibril threads
  - Transentorhinal stages I-II
  - Limbic stages III-IV
  - Isocortical stages V-VI


Diagnosis of Alzheimer’s Disease

- Pathologic Diagnosis (Neurobiol Aging 1997;18(S4):S1-S2)
  The National Institute of Aging
  The Ronald and Nancy Reagan Research Institute of the Alzheimer’s Association
  => CERAD + Braak and Braak
  - High likelihood
  - Intermediate likelihood
  - Low likelihood

Diagnosis of Alzheimer’s Disease

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  => CERAD + Braak and Braak
  - High likelihood
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  - Low likelihood

Dementia with Lewy Bodies

- Pathologic features:
  - neuronal loss and Lewy bodies (ubiquitin+) in cerebral cortex (limbic > insular > temporal > parietal > frontal), amygdala, nucleus basalis of Meynert, substantia nigra, locus ceruleus
  - neurites (ubiquitin+, tau-) in hippocampal CA2-3
  - numerous diffuse plaques and smaller numbers of neuritic plaques in neocortex (Alzheimer’s disease changes)
  - neurofibrillary tangles in entorhinal cortex
  - cholinergic deficit in cerebral cortex
  - dopaminergic deficit in cortical and subcortical regions

Dementia with Lewy Bodies

- Clinical features:
  - progressive cognitive decline, fluctuating cognition with pronounced variations in attention and alertness
  - recurrent visual hallucinations (well-formed, detailed)
  - parkinsonism
  - repeated falls, syncope, neuroleptic sensitivity, systematized delusions, non-visual hallucinations

![Image of brain sections showing different stages of Alzheimer's disease and Lewy bodies.](image)

**FIGURE 5.11**
Differential diagnosis. A man diagnosed with dementia and Parkinson’s disease at age 55 years; steadily deteriorated, at times reporting visual and auditory hallucinations. After an approximate 3.5-year clinical course, he died at age 66. A. Amyloid plaques in the frontal lobes. B. Lewy body in a cortical neuron (blue). C. Intranuclearity of cortical Lewy bodies for α-synuclein (immunostain).

<table>
<thead>
<tr>
<th>Diffuse Cortical Dementias</th>
<th>Molecular Pathology</th>
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<td>Dementia with Lewy Bodies</td>
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<tr>
<td>Neurofibrillary tangles</td>
<td>Lewy bodies</td>
</tr>
<tr>
<td>Amyrophobic</td>
<td>Enzymophagic</td>
</tr>
<tr>
<td>Tau-Positive</td>
<td>α-Synuclein-positive</td>
</tr>
</tbody>
</table>
Frontotemporal Dementias

- Selective neurodegeneration of frontal and temporal lobes:
  - Pick’s disease
  - Dementia with motor neuron disease inclusions (MND-inclusion dementia)
  - Dementia with changes of corticobasal degeneration (CBD)
  - Dementia of frontal type
  - Chromosome 17-linked neurodegenerative disorders
  - Frontal Alzheimer’s disease
  - Primary progressive aphasia

Pick’s Disease

- Pathologic features:
  - Severe atrophy of frontal and anterior temporal lobes;
  - sparing of posterior 2/3 of superior temporal gyrus
  - Asymmetrical atrophy with predilection for left hemisphere in 2/3 of cases
  - Atrophy of amygdala and caudate
  - Transcortical neuronal loss with status spongiosus, and astrocytosis
  - Ballooned neurons (Pick’s cells, argyrophilic, αB-crystallin+, phosphorylated neurofilament+)

Fronto-Temporal Dementia Brain

Pick’s Disease

- Pathologic features:
  - Pick’s bodies
  - Argyrophilic spherical inclusions in neuronal soma
  - Phosphorylated neurofilament+, tau+, ubiquitin+, tubulin+, chromogranin+
  - Hyperphosphorylated tau protein of 55 and 64 kD
  - EM: intermediate filaments, 15 nm straight filaments, some paired helical filaments, no limiting membranes
  - In dentate granule cells, pyramidal cells of subiculum and hippocampal CA1, neocortex, subcortical nuclei
  - Not remain behind after death of affected neurons
### Frontotemporal Lobar Dementias

**Molecular Pathology**

<table>
<thead>
<tr>
<th>Neuronal/Glia Inclusions</th>
<th>Neuronal Inclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau positive</td>
<td>Ubiquitin-positive</td>
</tr>
<tr>
<td>Pick's disease</td>
<td>Dementia with motor neuron disease</td>
</tr>
<tr>
<td>Dementia with Parkinsonism linked to chromosome 17</td>
<td>Dementia with ubiquitin-only immunoreaction</td>
</tr>
</tbody>
</table>

### Criteria of Pick's Disease

1. Clinical: some or several of following:
   - Personality changes: hyperactivity, outbursts of rage, abnormal social behavior
   - Language disorders: dysphasia, compulsive repetition of a word, echolalia
   - Memory disorders: later, poor concentration, progressive oversights

2. Fronto-temporal atrophy disclosed by structural neuroimaging: MRI, TC

3. Exclusion of frontal infarcts or multi-infarction disclosed by MRI, TC

4. Massive neuronal loss disclosed by decreased levels of N-acetylaspartate, disclosed by SMR.

5. Frontal bilateral hypometabolism disclosed by functional neuroimaging: PET, SPECT

6. Pick's body: argyrophilic neuronal inclusions, disclosed by biopsy or necropsy
Pick’s Disease

MND-Inclusion Dementia

- Pathologic features:
  - atrophy of frontal and temporal lobes, and basal ganglia
  - transcortical neuronal loss with status spongiosus, and astrocytosis
  - ballooned neurons in neocortex
  - neuronal loss from basal ganglia, substantia nigra
  - MND inclusions (ubiquitin+, tau-) in dentate granule cells, amygdala, neocortical layer 2

- Clinically, frontotemporal dementia without motor neuron disease; in contrast to amyotrophic lateral sclerosis with dementia of frontal type

Dementia with Changes of CBD

- Pathologic features:
  - atrophy of frontal and temporal lobes, and basal ganglia
  - neuronal loss from superficial neocortex with microvacuolation, and astrocytosis
  - ballooned neurons in neocortex
  - neuronal loss from basal ganglia, substantia nigra
  - tau+ neuronal inclusions in neocortical layer 2
  - tau+ glial cells in neocortex and substantia nigra

- Clinically, frontotemporal dementia without akinesic-rigid movement disorder (of corticobasal degeneration)

Dementia of Frontal Type

- Pathologic features:
  - atrophy of frontal and temporal lobes, and basal ganglia

Dementia Lacking Distinctive Histologic Features

- Sporadic and familial (possibly X- or Y-linked)
- Pathologic features:
  - atrophy of frontal and temporal lobes, and basal ganglia
  - neuronal loss from superficial to transcortical neocortex with microvacuolation to status spongiosus, and astrocytosis
  - ballooned neurons in neocortex
  - neuronal loss from basal ganglia, substantia nigra
  - no inclusions demonstrable on immunohistochemistry for ubiquitin and tau
Dementia of Frontal Type

- Clinically, frontal dementia

**Progressive Subcortical Gliosis**
- pronounced subcortical white matter gliosis of frontal and temporal lobes
- relatively mild laminar microvacuolation of neocortex
- gliosis of basal ganglia, thalamus, brain stem, and spinal anterior horns
- no inclusions, argyrophilic plaques, or ballooned neurons

Chromosome 17-Linked Neurodegenerative Disorders

- **Chromosome 17-linked autosomal dominant parkinsonism and dementia (PallidoPontoNigral Degeneration)**
  - Hyperphosphorylated tau protein of 64 and 69 kD
  - Pathologic features overlap with sporadic CBD and PSP
    - argyrophilic neuronal and glial inclusions
      (tau+, ubiquitin+, phosphorylated neurofilament-)
  - Clinical features:
    - initially, parkinsonism, personality changes, or both
    - later, frontal dementia and supranuclear gaze palsy, followed by dystonia and pyramidal signs

Chromosome 17-Linked Neurodegenerative Disorders

- **Chromosome 17-linked dementia**
  - Pathologic features:
    - argyrophilic neuronal inclusions (tau+, ubiquitin+, phosphorylated neurofilament+)
    - glial inclusions (tau+, ubiquitin+)
    - ballooned neurons (tau+)
  - Clinically, frontotemporal dementia with prominent parkinsonism and amyotrophy

Primary Progressive Aphasia

- Pathologic features:
  - restricted cortical atrophy in dominant cerebral hemisphere around Sylvian fissure
  - neuronal loss, microvacuolation, ballooned neurons, Alzheimer's disease changes, changes of CBD
- Clinical features:
  - isolated progressive non-fluent aphasia
  - in some, frontotemporal dementia eventually develops

Tangle-Only Dementia

- Pathologic features:
  - argyrophilic tau+ neurofibrillary tangles and neuropil threads in hippocampus, entorhinal cortex, and amygdala (Braak stage III)
  - neuronal loss and neurofibrillary tangles in substantia nigra
  - no neuritic plaques
- Clinical features:
  - mostly female, age at onset 80 years
  - clinical Alzheimer's disease; some with parkinsonism

Argyrophilic Grain Dementia

- Pathologic features:
  - small spindle-shaped argyrophilic grains and coiled bodies or filaments (tau+, EM: straight filaments with 9 nm diameter) in hippocampus, entorhinal cortex, and some subcortical nuclei
- Clinical Alzheimer's disease
Vascular Dementia

• **Small Vessel Disease**
  - hyaline arteriosclerosis and arteriolosclerosis
  - strongly associated with systemic arterial hypertension and diabetes mellitus

• **Large Vessel Disease**
  - atherosclerosis, thrombosis, embolism, vasculitides

• **Global Cerebral Hypoperfusion**
  - episodes of systemic arterial hypotension complicating cerebrovascular disease

⇒ **Leukoaraiosis**: rarefaction of white matter in neuroimaging

---

Small Vessel Disease

• **Ischemic White Matter Degeneration**
  - bilateral patchy myelin pallor, axonal loss, astrocytosis
  - most pronounced in deep frontal and temporal white matter
  - moderate dilatation of lateral and third ventricles
  - co-existent lacunar infarcts

• **Cribriform Atrophy of White Matter**
  - hyalinized vessels with greatly widened perivascular spaces surrounded by myelin pallor and astrocytosis
  - most numerous in anterior temporal and frontal white matter

---

Small Vessel Disease

• **Lacunar Infarction**
  - basal ganglia, thalamus, pons, and cerebral white matter

• **Granular Atrophy of Cortex**
  - numerous cortical micro-infarcts
  - hyaline arteriosclerosis and microvascular thrombosis
  - associated with Antiphospholipid Antibody Syndrome

---

Small Vessel Disease

• **Binswanger’s Subcortical Arteriosclerotic Leukoencephalopathy**
  - controversial nosology
  - hypertensive elderly, 6th or 7th decade
  - cerebral atherosclerosis, arteriolosclerosis
  - symmetrical white matter damage
  - bilateral ventricular enlargement

---

Small Vessel Disease

• **CADASIL** (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
  - missense mutations of Notch 3 gene [19p13.1]
  - small arteries with PAS+ hyalinization, basophilic granularity, smooth muscle degeneration of media
  - EM: dense granular deposits indenting cell membrane and intimately associated with basal lamina of smooth muscle cells
  - lacunar infarcts of subcortical white matter
  - onset in 5th or 6th decade with systemic vasculopathy
  - Skin biopsy for EM of dermal arterioles

---
Large Vessel Disease

- Multi-Infarct Dementia
  - multiple bilateral cerebral infarcts affecting cortex, white matter, basal ganglia, and thalamus
  - common in middle and posterior cerebral territory
- Bilateral infarcts in critical sites
  - in medial thalamus, hippocampus

Global Cerebral Hypoperfusion

- Hippocampal sclerosis
- Watershed-boundary zone infarcts
  - in frontal and parietal cortex
- Laminar cortical necrosis

Intermittently Raised Pressure Hydrocephalus

- Clinical features:
  - onset after 70 years of age
  - triad of memory disturbance, early gait disturbance, and early urinary incontinence
  - CT scan: ventricular dilatation and low density in periventricular white matter
  - CSF pressure:
    - within normal limits at isolated measurement
    - intermittently raised on monitoring

Intermittently Raised Pressure Hydrocephalus

- Pathologic features:
  - symmetric dilatation of lateral and third ventricles
  - cerebral cortex preserved
  - rarefaction and gliosis of periventricular white matter

Dementia Pugilistica

**Punch-Drunk Syndrome**

- Becoming clinically obvious years after the last fight
- Present in 20% of older professional boxers > 50 years
- More likely to develop in boxers with long careers who have been dazed or knocked out on many occasions
- Progression through 3 stages:
  1) affective disorder and mild incoordination
  2) dysplasia, apraxia, agnosia, apathy, blunting of affect
  3) global cognitive decline and Parkinsonism

Dementia Pugilistica

- Pathologic features
  - fenestrated septum pellucidum
  - neuronal loss from substantia nigra cerebral cortex, cerebellum
  - neurofibrillary tangle formation in cerebral cortex
  - diffuse β-amyloid plaques in cerebral cortex
Akinetic-Rigid Disorders

Parkinson's Disease

The main psychiatric complications in Parkinson's disease are depression, anxiety, dementia, psychosis, confusion, and subtle neuropsychological deficits. About 40% of parkinsonian patients develop depression. About half of these have a major depressive disorder and the other half have symptoms of chronic low-grade depression or dysthymia. (Dysthymia is less severe in intensity than major depression and is present for at least 2 years without prolonged remission.)

The masked facies of PD causes the appearance of a constricted affect that can make patients appear depressed, when they are not. Dopamine deficiency can also cause apathy and psychomotor retardation mimicking depression, and it is important to ask patients directly about their mood.

Akinetic-Rigid Disorders

- Parkinsonism: rigidity, bradykinesia, resting tremor
- Causes of Parkinsonism:
  - Parkinson's Disease
  - Drug-Induced Parkinsonism
  - Progressive Supranuclear Palsy (PSP)
  - Corticobasal Degeneration (CBD)
  - Postencephalitic Parkinsonism (PEP)
  - Multiple System Atrophy (MSA)
  - Arteriosclerotic Pseudoparkinsonism
  - Alzheimer's Disease
  - Dementia Pugilistica

Neurodegenerative Diseases with Parkinsonism: Delineating Parkinson's Features
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Primary LB Pathology</th>
<th>Clinical Effect</th>
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</thead>
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<td>Parkinson’s disease</td>
<td>Substantia nigra</td>
<td>Akineti-rigid syndrome</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Cerebral cortex</td>
<td>Dementia</td>
</tr>
<tr>
<td>Autonomic failure</td>
<td>Sympathetic neurons</td>
<td>Autonomic failure</td>
</tr>
<tr>
<td>Lewy body dysphagia</td>
<td>Dorsal motor nucleus of vagus</td>
<td>Dysphagia</td>
</tr>
</tbody>
</table>

Lewy Bodies
- Maybe structural manifestation of cytoprotective response designed to eliminate damaged cytoskeletal proteins
- Constituent proteins:
  - α-synuclein, phosphorylated neurofilaments, ubiquitin, ubiquitin carboxy-terminal hydrolase (PGP9.5), multicatalytic protease, β-crystallin, protein kinases
  - tubulin, microtubule-associated proteins, β-amyloid precursor protein, synaptophysin, chromogranin-A
- Classical (brain stem) Lewy bodies
- Cortical Lewy bodies
- Pale bodies

Parkinson's Disease
- Genetic susceptibility to environmental agents predisposing to oxidative stress and free radical-mediated damage in neuronal population already under oxidative stress as part of normal metabolic requirements in producing dopamine
- Pathologic features:
  - neuronal loss from
    - dopaminergic substantia nigra-pars compacta [ventrolateral tier > ventromedial tier > dorsal tier (aging)]
    - noradrenergic locus ceruleus
    - serotonergic raphe nuclei

Parkinson's Disease
- Pathologic features:
  - classical Lewy bodies in substantia nigra, locus ceruleus, raphe nuclei, dorsal motor nucleus of vagus, pedunculo-pontine nucleus, Edinger-Westphal nucleus, thalamus, hypothalamus, nucleus basalis of Meynert, intermediolateral column of spinal cord, sympathetic and parasympathetic neurons (enteric)
  - cortical Lewy bodies (in small numbers in limbic cortex)
  - neurites (ubiquitin+, tau-) in substantia nigra, hippocampal CA2-3, nucleus basalis of Meynert, dorsal motor nucleus of vagus, amygdala

Parkinson's Disease
- Pathologic features:
  - Lewy bodies in substantia nigra, locus ceruleus, raphe nuclei, dorsal motor nucleus of vagus, pedunculo-pontine nucleus, Edinger-Westphal nucleus, thalamus, hypothalamus, nucleus basalis of Meynert, intermediolateral column of spinal cord, sympathetic and parasympathetic neurons (enteric)
  - cortical Lewy bodies (in small numbers in limbic cortex)
  - neurites (ubiquitin+, tau-) in substantia nigra, hippocampal CA2-3, nucleus basalis of Meynert, dorsal motor nucleus of vagus, amygdala
Loss of Nigral Neurons

Classical Lewy Body

Parkinson’s Disease

- Reduced dopaminergic input into striatum
  => net effect of increased activity in substantia nigra-
pars reticulata and globus pallidus-interna, inhibiting
generation of movement in motor thalamus
  => reduced movement (akinetic-rigid syndrome)
- Clinical features:
  - mean age of onset 61 years, mean disease duration 13 years
  - parkinsonism
  - cognitive disturbance, gut dysmotility, dysphagia, autonomic dysfunction

Progressive Supranuclear Palsy

- Dysfunction of nigrostriatal dopaminergic system
- Pathologic features:
  - neuronal loss and astrocytosis
  - neuronal accumulation of abnormal tau protein
    - diffusely distributed
    - aggregated into argyrophilic globose neurofibrillary tangles (EM: straight filaments of 15 nm diameter)
  - glial (astrocytic) accumulation of abnormal tau protein

Progressive Supranuclear Palsy

- Pathologic features:
  - neuropil threads (argyrophilic aggregates of abnormal tau protein in both neuronal and glial processes)
  - abnormal tau protein of 64 and 69 kD
  - tauopathy usually severely affecting substantia nigra (ventromedial tier), locus ceruleus, globus pallidus, subthalamic nucleus, peri-aqueductal gray, red nucleus, dorsal and medial raphe nuclei, nuclei of CN III, IV, X (dorsal), and XII, cerebellar dentate nucleus (grumose degeneration: granular eosinophilic material, swollen Purkinje cell axon terminals, around neurons)

Progressive Supranuclear Palsy

- Pathologic features:
  - tauopathy commonly but variably affecting nucleus basalis of Meynert, nuclei of CN V, VI, and VII, striatum, pontine tegmentum, pontine nuclei, inferior olivary nuclei (neuronal hypertrophy and vacuolation), hippocampus and entorhinal cortex, motor cortex
- Clinical features:
  - symmetrical akinesia and rigidity, most marked axially
  - early dysequilibrium, resulting in frequent falls
  - supranuclear ophthalmoplegia
  - variable dysarthria, dysphagia, cognitive decline
  - death after 6-7 years from aspiration pneumonia
Progressive Supranuclear Palsy

- Clinical syndrome of PSP may be caused by other pathologic processes, e.g., Lewy body disorders, corticobasal degeneration, cerebrovascular disease, Creutzfeldt-Jakob disease
- Pathologic features of PSP may be found in patients who have not had typical clinical features of PSP
- Differential pathologic diagnosis:
  - Postencephalitic parkinsonism
  - Corticobasal degeneration
  - Alzheimer’s disease

Corticobasal Degeneration

- Sporadic, very rarely familial
- Pathologic features:
  - Neuronal loss, cortical microvacuolation, astrocytosis, and loss of myelinated fibers from cerebral white matter
  - Ballooned neurons (phosphorylated neurofilament+, αB-crystallin+) in asymmetrically atrophic posterior frontal, parietal, and peri-Rolandic cortex
  - Argyrophilic tau+ filamentous inclusions (corticobasal inclusions) in basal neurons (substantia nigra lateral tier, locus ceruleus,pons) and rare cortical neurons

Corticobasal Degeneration

- Pathologic features:
  - Argyrophilic tau+ glial cells in peri-Rolandic cortex and underlying white matter, and other affected regions
  - Argyrophilic tau+ neuropil threads and star-like tufts (neuronal and glial processes) in cortex and white matter
  - Abnormal tau protein of 64 and 69 kD
  - Varying affecting globus pallidus, striatum, subthalamic nucleus, thalamus, red nucleus, brain stem nuclei
### Corticobasal Degeneration

- Clinical features
  - Early (years 1-3): asymmetric clumsiness, stiffness, jerking of arms or legs
  - Middle (years 3-5): dystonic rigidity and akinesia of limbs with rhythmic myoclonus, ‘alien limb’ phenomenon, lower limb apraxia, pyramidal deficits, cortical sensory disturbance
  - Late (years 5-8): frontotemporal dementia
- Death from bronchopneumonia, with limb contractures

### Postencephalitic Parkinsonism

- PEP followed 1915-1927 world pandemic of encephalitis lethargica (von Economo’s), latent period 9 years
- Pathologic features:
  - neuronal loss and astrocytosis
  - neuronal accumulation of abnormal tau protein as argyrophilic neurofibrillary tangles (identical to tangles in Alzheimer’s disease)
- tau+ glial cells
- usually affecting substantia nigra, locus ceruleus, hippocampus, entorhinal cortex, nucleus basalis of Meynert

### Multiple System Atrophy

- Pathologic features:
  - Glial cytoplasmic inclusions
    - argyrophilic flame- or sickle-shaped structures
    - tau+, ubiquitin+, tubulin+, αB-crystallin+
    - in oligodendroglia in gray and white matter
  - high density and wide distribution in CNS with MSA
  - Neuronal cytoplasmic inclusions
    - argyrophilic rounded filamentous structures
    - ubiquitin+
    - numerous in basis pontis and putamen

### Multiple System Atrophy

- Pathologic features:
  - Neuronal nuclear inclusions
    - argyrophilic web of fine fibrils beneath nuclear membrane
    - sparse in most cases, in basis pontis and putamen
  - Glial nuclear inclusions
    - argyrophilic rods
    - sparse in most cases, in basis pontis and putamen
  - Neuropil threads
    - argyrophilic, ubiquitin+, tau-
    - numerous in basis pontis and putamen
Multiple System Atrophy

- Pathologic features:
  - Very variable distribution of neuronal loss and astrocytosis in dorsolateral putamen (gray-green color), substantia nigra, locus ceruleus, Purkinje cell layer of cerebellum, basis pontis, inferior olivary nucleus, dorsal motor nucleus of vagus, intermediolateral column of spinal cord, Onufrowicz's nucleus
  - Corresponding loss of myelinated fibers from external capsule, striatopallidal fibers, cerebellar white matter, middle cerebellar peduncle, transverse pontine fibers

Arteriosclerotic Pseudoparkinsonism

- Lacunar infarction in basal ganglia, white matter of frontal lobe, or rarely infarction of substantia nigra
- Clinically, lower body parkinsonism (bradykinesia and rigidity)
  - Hypertension or diabetes mellitus as risk factor for arteriosclerosis

Hyperkinetic Movement Disorders
Hyperkinetic Movement Disorders

- Chorea
  - Huntington’s Disease
  - Neuroacanthocytosis
  - Benign Hereditary Chorea
  - Sydenham’s Chorea
- Myoclonus
- Ballismus and Hemiballismus
- Dystonia
- Tic Disorders

CAG Repeat Disorders

- Mid-life onset (25-45 years) with considerable variability
- Progression with fatal outcome
- Characteristic selective neuronal degeneration
- Anticipation: later generations are affected at an earlier age and more severely than earlier generations in the same family
- Expansions of repeats correlate with severity and earlier onset
- Genetic screening possible (simple blood test, genetic discrimination)

Huntington’s Disease

- CAG repeat expansion in HD gene (4p16.3 resulting in polyglutamine stretch in huntingtin protein, autosomal dominant
- mutant huntingtin (abnormal conformation) is cleaved at higher efficiency by caspases than normal form => increased vulnerability to apoptosis
- Pathologic features:
  - progressive loss of striatal medium spiny neurons (projecting to globus pallidus and substantia nigra)
  - medial to lateral progression in caudate
  - dorsal to ventral progression in putamen

- lesser loss of striatal small and large aspiny interneurons in late stages
- loss of large pyramidal neurons in layers 5 and 6 of cerebral neocortex, and hippocampus, in the absence of astrocytosis
- neuronal loss from globus pallidus, hypothalamus, substantia nigra, cerebellar Purkinje cell layer
- abnormal ubiquitin+ neurites in deep neocortical layers

Huntington’s Disease

Pathologic features:
- progressive loss of striatal medium spiny neurons (projecting to globus pallidus and substantia nigra)
- medial to lateral progression in caudate
- dorsal to ventral progression in putamen

- lesser loss of striatal small and large aspiny interneurons in late stages
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- neuronal loss from globus pallidus, hypothalamus, substantia nigra, cerebellar Purkinje cell layer
- abnormal ubiquitin+ neurites in deep neocortical layers

![Image of brain scan](image)

**FIGURE 8.34**
Huntington’s Disease. A 43-year-old man that is mildly impaired by Huntington’s disease. He was diagnosed with the disease at age 35 years and had 11 years prior to death. A: Coronal section of the brain stained with cresyl violet showing progressive neuronal loss from the putamen, caudate, and globus pallidus. B: Coronal section of the brain stained with ubiquitin showing abnormal ubiquitin+ neurites in deep neocortical layers. C: CT scan of the brain from a different patient with Huntington’s disease showing atrophy of the lateral ventricular walls.
Huntington’s Disease

- Reduced inhibitory GABAergic input to globus pallidus-externa
  => increased inhibitory GABAergic input to subthalamic nucleus
- reduced excitatory glutamatergic input to globus pallidus-interna and substantia nigra-pars reticulata
- reduced inhibitory GABAergic input to motor thalamus
- increased excitatory glutamatergic input to cerebral cortex
=> chorea

Huntington’s Disease

- Clinical features:
  - Hyperkinetic HD in mid-life or late onset
    - Late onset (25%, maternal transmission):
      => chorea, dystonia, rigidity, cognitive dysfunction
  - Akinetic-rigid HD in juvenile or early onset
    - Juvenile onset (10%, paternal transmission):
      => akinesia, rigidity, dystonia, seizures, ataxia

Neuroacanthocytosis

- Multisystem neurodegeneration, genetically heterogeneous, with acanthocytes in blood, associated with
  - abetalipoproteinemia
  - McLeod syndrome: X-linked, striatal degeneration, myopathy, absent Kx protein and reduced Kell blood group antigen expression
- Pathologic features:
  - dilatation of frontal lateral ventricle
  - consistent neuronal loss and astrocytosis in caudate, putamen, globus pallidus

Neuroacanthocytosis

- Pathologic features:
  - less consistent neuronal loss from thalamus, substantia nigra, spinal anterior horns
- Marked phenotypic variation:
  - chorea, dystonia, tics, parkinsonism
  - cognitive impairment, psychiatric disturbance
  - dysphagia, dysarthria, seizures

Myoclonus

- Focal Myoclonus (Rhythmic Myoclonus)
  - Epilepsy Partialis Continua (cerebral cortex)
  - Palatal Myoclonus (or Tremor)
    (central tegmental tract or dentate nucleus)
  - Brain Stem Myoclonus (ocular myoclonus)
    (oposcodons) in children with neuroblastoma
  - Segmental Myoclonus (spinal cord)
- Arrhythmic Myoclonus
  (Stimulus-Sensitive or Action Myoclonus)
- Myoclonus with other clinical features

Myoclonus

- Myoclonus with other clinical features, e.g.
  - dementia
    - Creutzfeldt-Jakob disease
    - dementia with Lewy bodies
    - dentatorubropallidoluysian atrophy
  (DRPLA)
  - delirium
    - hepatic failure
    - renal failure
    - carbon dioxide retention
  - ataxia
    - myoclonic ataxia
  - epilepsy
    - mitochondrial disorders, Battée’s disease, sialidosis, Lafora body disease, DRPLA, Baltic myoclonus
**Ballismus and Hemiballismus**

- Severe forms of chorea
- Damage to subthalamic nucleus or its efferent tracts, e.g. - infarct, hemorrhage, infection, metastatic tumor, demyelination
- Reduced excitatory glutamatergic input to globus pallidus-interna and substantia nigra-pars reticulata
  \( \Rightarrow \) reduced inhibitory GABAergic input to motor thalamus
  \( \Rightarrow \) increased excitatory glutamatergic input to cerebral cortex
  \( \Rightarrow \) ballism

**Dystonia**

- Primary (idiopathic)
  - Inherited
    - Primary Torsion Dystonia
    - DOPA-Responsive Dystonia (Segawa Syndrome)
    - X-Linked Primary Torsion Dystonia
  - Sporadic
- Secondary (Symptomatic)
  - Wilson’s Disease, Hallervorden–Spatz Disease, Lewy Body Disorders, Neuroacanthocytosis, Perinatal Brain Injury, Phenothiazine Toxicity
  - focal damage to basal ganglia (Hemidystonia)
  - psychogenic

- Also classified into focal, segmental, generalized, multifocal, and hemidystonia
- Commonest are adult-onset primary focal dystonias:
  - torticollis, blepharospasm, oromandibular dystonia, spastic dysphonia, writer’s cramp
  - Craniofacial dystonia (Meige’s syndrome)
  - segmental dystonia affecting eye lids, face and mouth
- Primary torsion dystonia (autosomal dominant)
  - gene \( 9q34 \) encoding gelsolin, in Ashkenazi Jews
  - affecting neck or trunk in childhood or adolescence, becoming generalized by 3 years

- Dopa-responsive dystonia (autosomal dominant)
  - gene encoding GTP cyclohydrolase I (in synthesis of tetrahydrobiopterin, co-factor for tyrosine hydroxylase) mutation resulting in reduced dopamine synthesis
  - severe nigral degeneration
  - dystonia affecting gait before other limb movements, fluctuating in severity through the day
  - parkinsonism and later generalized dystonia
  - prolonged and dramatic responsiveness to L-dopa, free from side-effects (occurring in Parkinson’s)

- X-linked primary torsion dystonia
  - gene \( Xq12-q13.1 \), in Filipino population
  - striatal neuronal loss and astrocytosis
  - onset 35 years of spasmodic eye blinking and parkinsonism
Ataxic Disorders

Spinocerebellar Ataxias (SCA)
- Primary
  - Inherited
  - Sporadic
    - Multiple System Atrophy
    - Idiopathic Cerebellar Degeneration
- Secondary
  - Paraneoplastic, Toxic-Nutritional, Metabolic, Mitochondrial, Vascular, Infective-Inflammatory, Prion Disease

Classification of Inherited SCA
- Autosomal Recessive Cerebellar Ataxias
  - Friedreich’s Ataxia
  - SCA with Retained Tendon Reflexes
  - SCA with Isolated Vitamin E Deficiency
  - Ataxia-Telangiectasia
  - Others
- X-Linked Cerebellar Ataxias
- Autosomal Dominant Cerebellar Ataxias (ADCA)
  - ADCA I (SCA 1-6, 8)
  - ADCA II (SCA 7)
  - ADCA III
  - ADCA IV
  - DentatoRubroPallidoLysial Atrophy (DRPLA)
  - Episodic Ataxias (EA)

Friedreich’s Ataxia
- GAA repeat expansion (normal 10-21, mutant 200-900) in 1st intron of gene \(9q\) encoding frataxin, autosomal recessive
- frataxin involved in control of oxidative phosphorylation in mitochondria, potentially via effect on mitochondrial DNA stability
- marked reduction in frataxin mRNA in cerebellum and spinal cord

Friedreich’s Ataxia
- Pathologic features:
  - spinal cord with degeneration of posterior columns ( gracile > cuneate), distal degeneration of pyramidal and spinocerebellar tracts, severe neuronal loss from Clarke’s column
  - medulla with neuronal loss from accessory cuneate and gracile nuclei, from vestibular and cochlear nuclei and superior olivary nuclei; normal inferior olives
  - cerebellum with severe neuronal loss from dentate nuclei with atrophy of superior cerebellar peduncles; normal cerebellar cortex (hypoxic-ischemic)
Friedreich’s Ataxia

- Pathologic features:
  - cerebral cortex maybe with hypoxic-ischemic change
  - globus pallidus and subthalamic nuclei maybe with neuronal loss
  - optic nerves and tracts with slight fiber loss
  - peripheral nerves with neuronal loss from dorsal root ganglia, severe depletion of large myelinated axons from dorsal roots and sensory nerves

- Clinical features:
  - onset usually before 15 years of age
  - gait ataxia and later limb ataxia, dysarthria, loss of joint position and vibration sense in lower limbs, generalized areflexia, pyramidal lower limb weakness, extensor plantar responses
  - ataxia due to combination of sensory neuropathy and degeneration of cerebellar afferent and efferent fibers
  - scoliosis and pes cavus
  - cardiomyopathy in over 60% and diabetes mellitus in 10%
  - death by end of 4th decade

Spinocerebellar Ataxia with Isolated Vitamin E Deficiency

- Mutations of gene encoding α-tocopherol transfer protein, needed for absorption of dietary vitamin E
- Clinically indistinguishable from Friedreich’s ataxia
- Progression can be prevented by vitamin E supplements

Ataxia-Telangiectasia

- Inactivation of ATM protein (similar to signal transduction mediator phosphatidylinositol-3’ kinase), ATM gene 11q22.3, autosomal recessive
- ATM protein involved in cell cycle control and DNA damage surveillance
- AT cells hypersensitive to radiation, exhibiting chromosomal breakage, telomere shortening, increased intrachromosomal recombination
- AT cells with bizarre large hyperchromatic nuclei

- Cerebellar cortex with extensive loss of Purkinje and granule cells, retrograde neuronal loss from inferior olives
- substantia nigra with neuronal inclusions resembling Lewy bodies
- spinal cord with degeneration of posterior columns (gracile fasciculi), and sometimes loss of anterior horn neurons
- dorsal root ganglia with loss of satellite cells, small ganglion cells, interstitial cells having bizarre nuclei
- sometimes neurofibrillary tangles in basal ganglia, hippocampus, cerebral cortex
- clinically, early ataxia as soon as beginning to walk; later dysarthria, chorea, abnormal eye movements
**Ataxia-Telangiectasia**

- Telangiectasia in sclera and sun-exposed skin
- Progeric changes of hair and skin
- Generalized hypoplasia of lymphoid tissue (lymph nodes, thymus) and gonads
- Impaired humoral and cell-mediated immunity
- Increased liability to cancer, e.g. T cell prolymphocytic leukemia with t(7;14), T cell lymphoma, mammary carcinoma in mothers
- Elevated α-fetoprotein levels

**ADCA**

- Olivopontocerebellar atrophy (OPCA) pattern
- Atrophy of cerebellar cortex, with retrograde atrophy of inferior olivary nuclei
- Atrophy of pontine nuclei and their efferent tracts in middle cerebellar peduncles
- Milder degeneration of cerebral cortex, striatum, substantia nigra, spinocerebellar tracts, corticospinal tracts, Clarke’s columns, anterior horn cells of spinal cord, and sensory ganglia
- Either pattern of degeneration can result from several genetically distinct diseases
- Tend to present in adult life

<table>
<thead>
<tr>
<th>Type</th>
<th>Protein</th>
<th>Gene Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA 1-OPCA I</td>
<td>Ataxin 1</td>
<td>6p, CAG repeat</td>
</tr>
<tr>
<td>SCA 2-OPCA II</td>
<td>Ataxin 2</td>
<td>12q23-24.1, CAG repeat</td>
</tr>
<tr>
<td>SCA 3-MJD</td>
<td>Ataxin 3</td>
<td>14q, CAG repeat</td>
</tr>
<tr>
<td>SCA 4</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>SCA 5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>SCA 6-Infantile SCA Ca channel</td>
<td>19p13, CAG repeat</td>
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</tr>
<tr>
<td>SCA 8</td>
<td>10q24</td>
<td></td>
</tr>
</tbody>
</table>

- Cerebellar ataxia with variable ophthalmoplegia, optic atrophy, cognitive impairment, parkinsonism, pyramidal signs, chorea, dystonia, and peripheral neuropathy

**ADCA II**

- Gene }
- SCA 7-OPCA III
  - A form of ADCA II
  - Gene }
  - Ataxin 7 protein
- Cerebellocortical atrophy, severe olivary atrophy, and variable loss of pontine nuclei
- Cerebellar ataxia, variable supranuclear ophthalmoplegia, pigmentary macular degeneration (blindness), pyramidal signs

**ADCA III**

- Cerebellocortical atrophy and dentate nucleus atrophy
- Cerebellar ataxia and some pyramidal signs
  - Onset after 50 years of age

**ADCA IV**

- Mitochondrial DNA mutations
- Neuronal loss from dentate nuclei and inferior olives, milder atrophy of cerebellar cortex, red nuclei, and dorsal columns
- Cerebellar ataxia with additional features, e.g. myoclonus, deafness, dementia, optic atrophy, myopathy, and neuropathy
DRPLA
• CAG repeat expansion in gene 12p encoding atrophin 1, autosomal dominant
• Pathology in cerebellar and pallidal efferent pathways:
  - severe neuronal loss from dentate nucleus, globus pallidus-externa, subthalamic nucleus
  - moderate neuronal loss from red nucleus
  - mild neuronal loss from caudate, putamen, thalamus, substantia nigra, inferior olives
  - atrophy of superior cerebellar peduncles, spinocerebellar tracts, posterior spinal columns
• Clinically, ataxia, chorea, myoclonus epilepsy, dementia

Trinucleotide Tandem Repeat Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Repeat</th>
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<tbody>
<tr>
<td>Fragile X Syndrome</td>
<td>CGG</td>
</tr>
<tr>
<td>Myotonic Dystrophy</td>
<td>CTG</td>
</tr>
<tr>
<td>Friedreich’s Ataxia</td>
<td>GAA</td>
</tr>
<tr>
<td>Spinobulbar Muscular Atrophy (SBMA)</td>
<td>CAG</td>
</tr>
<tr>
<td>Huntington’s Disease (HD)</td>
<td>CAG</td>
</tr>
<tr>
<td>DentatoRubroPallidoLuisial Atrophy (DRPLA)</td>
<td>CAG</td>
</tr>
<tr>
<td>Spinocerebellar Atrophy (SCA) 1, 2, 3, 6, 7</td>
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CAG Repeat Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Protein</th>
<th>Aggregation</th>
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<tbody>
<tr>
<td>SBMA</td>
<td>Androgen receptor</td>
<td>NINI</td>
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<tr>
<td>HD</td>
<td>Huntingtin</td>
<td>NINI, Neuropil</td>
</tr>
<tr>
<td>DRPLA</td>
<td>Atrophin</td>
<td>NINI</td>
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<tr>
<td>SCA 1</td>
<td>Ataxin 1</td>
<td>NINI</td>
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<tr>
<td>SCA 2</td>
<td>Ataxin 2</td>
<td>Cytoplasm</td>
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<tr>
<td>SCA 3-MJD</td>
<td>Ataxin 3</td>
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<td>SCA 6</td>
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<tr>
<td>SCA 7</td>
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<td>NINI</td>
</tr>
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</table>

NINI = Neuronal IntraNuclear Inclusion

CAG Repeat Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Repeat Normal</th>
<th>Repeat Mutant</th>
<th>Transmission</th>
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<tbody>
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<tr>
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<td>11-34</td>
<td>38-180</td>
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<tr>
<td>DRPLA</td>
<td>7-25</td>
<td>49-88</td>
<td>12p dominant</td>
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<tr>
<td>SCA 1</td>
<td>25-36</td>
<td>39-83</td>
<td>6p dominant</td>
</tr>
<tr>
<td>SCA 2</td>
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<td>34-59</td>
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<tr>
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<td>55-84</td>
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<tr>
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Genetic Features of Trinucleotide Repeat Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene Product</th>
<th>Chromosome</th>
<th>Repeats</th>
<th>Abnormal Length</th>
<th>Normal Length</th>
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<tbody>
<tr>
<td>HD</td>
<td>Huntingtin</td>
<td>4p</td>
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<td>SBMA</td>
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<td>SCA 2</td>
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<td>CAG</td>
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<td>SCA 7</td>
<td>Ataxin 7</td>
<td>12q</td>
<td>CAG</td>
<td>38-180</td>
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</table>

CAG, CAG Repeat Disorders; DRPLA, DentatoRubroPallidoLuisial Atrophy; SCA, Spinocerebellar Atrophy; SBMA, Spinobulbar Muscular Atrophy; HD, Huntington’s Disease; MJD, Myoclonus Epilepsy, Dementia; NINI, Neuronal IntraNuclear Inclusion.
Motor Neuron Disorders

- Primary
  - Idiopathic
  - Inherited
    - Autosomal Recessive
    - X-Linked
      - Bulbospinal Neuropathy (Kennedy's)
    - Autosomal Dominant
      - Familial ALS
      - Familial ALS with Frontal Lobe Dementia

- Secondary
  - Infective
    - Acute Poliomyelitis
  - Metabolic
  - Immune
  - Toxic
  - Vascular
  - Paraneoplastic
Motor Neuron Diseases

- Amyotrophic Lateral Sclerosis (ALS)
- Progressive Bulbar Palsy (PBP)
- Progressive Muscular Atrophy (PMA)
- Primary Lateral Sclerosis (PLS)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Spinal-LMN</th>
<th>Bulbar-LMN</th>
<th>Cortical-UMN</th>
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<tbody>
<tr>
<td>ALS</td>
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<tr>
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<td>-</td>
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<tr>
<td>PMA</td>
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<tr>
<td>PLS</td>
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<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Amyotrophic Lateral Sclerosis

- Neurodegenerative disorder affecting upper motor neurons (motor cortex) and lower motor neurons (brain stem, spinal cord) +/- non-motor systems
- Sporadic ALS
- Familial ALS (10%), e.g., mutations in Cu-Zn superoxide dismutase (SOD1) gene 21q
- Excitotoxic damage by neurotransmitter glutamate

Amyotrophic Lateral Sclerosis

- Pathologic features:
  - motor neuronal loss from spinal anterior horns, brain stem nuclei (hypoglossal, ambiguus, facial, trigeminal), and motor cortex (Betz cells)
  - 3 types of motor neuron disease (MND) inclusions in surviving motor neurons seen on H&E and ubiquitin immunoreactivity in both sporadic and familial forms of ALS:
    - Bunina bodies, small eosinophilic, in beaded chain, cystatin C-immunoreactive
    - large hyaline inclusions resembling Lewy bodies

Amyotrophic Lateral Sclerosis

- Pathologic features:
  - large irregular inclusions, lightly basophilic
  - dying back degeneration of axons in corticospinal tracts
  - atrophy of anterior nerve roots; axonal degeneration and loss of large myelinated fibers from peripheral nerves
  - no neuronal loss from CN III, IV, VI nuclei and sacral Onufrowicz’s nuclei, but ubiquitin+ inclusions present

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Amyotrophic Lateral Sclerosis

- Clinical features:
  - weakness of distal limbs, chewing and swallowing muscles, to all muscles, except extra-ocular muscles and bowel and bladder sphincteric muscles
  - death from respiratory failure or aspiration pneumonia within 5 years
- ALS with frontal lobe dementia
  - ubiquitin+ MND inclusions in non-motor cortex (frontal, anterior temporal, insular) and dentate granule cells
  - not MND-inclusion dementia (of frontotemporal type)

Spinal Muscular Atrophy

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
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<tbody>
<tr>
<td>Proximal SMA</td>
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<tr>
<td>1a Infantile, acute</td>
<td>AR</td>
</tr>
<tr>
<td>1b Infantile, chronic</td>
<td>AR</td>
</tr>
<tr>
<td>2 Onset 1-6 years, chronic</td>
<td>AR, AD</td>
</tr>
<tr>
<td>3 Onset 2-18 years, chronic</td>
<td>AR (AD rare)</td>
</tr>
<tr>
<td>4 Adult, chronic</td>
<td>AR</td>
</tr>
<tr>
<td>5 Adult, chronic</td>
<td>AD</td>
</tr>
<tr>
<td>Distal SMA</td>
<td></td>
</tr>
<tr>
<td>Complex Distribution SMA</td>
<td></td>
</tr>
</tbody>
</table>

Spinal Muscular Atrophy

- Progressive lower motor neuron degeneration
  - AR-SMA 1, 2, 3 - mutations in 2 adjacent genes 5q13:
    - survival motor neuron-telomeric (SMNT)
    - neuronal apoptosis inhibitory protein (NAIP)
  - apparent genetic homogeneity in AR-SMA (95%, SMNT deletions) with phenotypic heterogeneity
    - the higher the copy number of SMN-centromeric (SMNC), the milder the SMA phenotype
    - NAIP gene deletion => severe phenotype
Spinal Muscular Atrophy

• SMA 1 pathologic features:
  - motor neuronal loss from spinal anterior horns (most in cervical and lumbar), hypoglossal nuclei, and other motor nuclei of brain stem
  - sparing of thoracolumbar autonomic nuclei and of sacral Onufrowicz’s nuclei
  - remaining motor neurons are swollen, containing abnormally phosphorylated neurofilaments and showing peripheral granular immunoreactivity for ubiquitin (no distinct inclusions)

• SMA 3 (chronic proximal, Kugelberg-Welander disease)
  - onset 2-17 years of age
  - atrophy and weakness of proximal limb muscles (legs), and later of distal and respiratory muscles
  - D/Dx: dystrophin myopathy
  - metabolic myopathy
  - limb girdle dystrophy
  - contractures and scoliosis
  - survival beyond late adolescence

Spinal Muscular Atrophy

• SMA 1 pathologic features:
  - atrophy of anterior spinal nerve roots; loss of large myelinated axons in peripheral nerves
  - neurogenic (group) atrophy of skeletal muscles:
    - sheets of atrophic fibers
    - scattered normal-sized or hypertrophic fibers
  - SMA 1 (acute infantile, Werdnig-Hoffmann disease)
    - neonatal hypotonia (floppy baby)
    - maybe congenital arthrogryposis
    - severe progressive symmetrical muscle weakness affecting limbs and respiratory muscles
    - death at 4-6 weeks of age from respiratory failure

Fazio-Londe Disease

• Severe motor neuronal loss from hypoglossal, vagal, and facial nuclei
• moderate motor neuronal loss from spinal anterior horns and trigeminal and oculomotor nuclei
• neuronal loss from thalamus, striatum, dentate nuclei, and cerebellar cortex
• 3 types: autosomal recessive with early respiratory symptoms and rapid progression
• autosomal recessive with onset in mid-childhood and long clinical course
• autosomal dominant

Brown-Vialetto-van Laere Syndrome

• Autosomal recessive
• Neuronal loss from CN VII to XII nuclei, with dense astrocytosis in ventral cochlear nuclei and axonal loss from cochlear nerves
• variable degeneration of spinocerebellar tracts, Purkinje cells, spinal posterior columns, Clarke’s column, and anterior horn cells
• Onset in 2nd decade with sensorineural deafness, followed by CN VII, IX, XII palsies
Kennedy’s Disease
Spinobulbar Muscular Atrophy (SBMA)
X-Linked Bulbospinal Neuronopathy
- CAG repeat expansion in 1st exon of androgen receptor gene \( Xq \), recessive inheritance
- variable phenotypic expression unrelated to size of expansion
- Pathologic features:
  - motor neuronal loss from facial and hypoglossal nuclei, and from spinal anterior horns
  - neurogenic atrophy of skeletal muscles (tongue)
  - sparing of CN III, IV, VI nuclei

Hereditary Spastic Paraparesis
- Heterogeneous condition with autosomal dominant, autosomal recessive or X-linked recessive inheritance
- Degeneration of corticospinal tracts (lumbar, lower thoracic) and of posterior columns (upper thoracic, cervical)
  - degeneration of Purkinje cells and dentate nuclei
  - preservation of olivary and pontine nuclei

Hereditary Spastic Paraparesis
- Pure spastic paraparesis
  - slowly progressive
  - spasticity > weakness
  - pes cavus
  - later, reduced vibration sense and disturbed micturition
  - mostly, autosomal inheritance
    - commonest, autosomal dominant, \( X \)-q & \( X \)-2
    - autosomal recessive, \( X \)-q

Kennedy’s Disease
- Pathologic features:
  - sparing of thoracolumbar autonomic nuclei, sacral Onufrowicz’s nuclei, Clarke’s columns
  - testicular atrophy with maturation failure of spermatozoa or hyalinized seminiferous tubules
- Clinical features:
  - males in 3rd decade with slowly progressive weakness of facial, bulbar, and proximal limb muscles
  - primary sensory neuronopathy
  - gynecomastia, infertility

Hereditary Spastic Paraparesis
- Complicated spastic paraparesis
  - combined with optic atrophy, amyotrophy, extrapyramidal disturbances, sensory neuropathy, retinal degeneration
  - mostly, X-linked recessive inheritance
    - proteolipid protein (PLP) gene, related to Pelizaeus-Merzbacher disease
    - L1 cell adhesion molecule (L1-CAM) gene, related to X-linked hydrocephalus and MASA syndrome (mental retardation, adducted thumbs, shuffling gait, aphasia)

Neuro-axonal Dystrophy
- Axonal degeneration (from distal to proximal) in CNS and PNS as dystrophic axonal swellings “spheroids”
  - EM: mitochondria, lysosome-related dense bodies, tubulomembranous structures, amorphous matrix material, and few neurofilaments at periphery
  - Histochemistry: non-specific esterase, NADH transferase
  - Immunoreactivity: neurofilament and ubiquitin only in spheroids smaller than 30 \( \mu m \)
### Neuro-axonal Dystrophy

- **Physiologic Neuro-axonal Dystrophy**
- **Primary**
  - Infantile Neuro-axonal Dystrophy (Seitelberger’s)
  - Late Infantile, Juvenile and Adult Neuro-axonal Dystrophy
  - Neuro-axonal Leukodystrophy
  - Hallervorden-Spatz Disease
  - Nasu-Hakola Disease
  - Giant Axonal Neuropathy
- **Secondary Neuro-axonal Dystrophy**

### Physiologic Neuro-axonal Dystrophy

- Normal part of brain aging
- Age-related occurrence from 10 years of age
- Neuro-axonal spheroids in gracile and cuneate nuclei, substantia nigra-pars reticularis, globus pallidus-interna, spinal anterior horns, sympathetic ganglia

### Infantile Neuro-axonal Dystrophy

- Autosomal recessive
- Pathologic features:
  - Cerebral and cerebellar atrophy
  - Spheroids and reactive astrocitosis widely distributed in gray matter of CNS and PNS
  - Degeneration of corticospinal and spinobulbar tracts
- Clinical features:
  - Early (1-2 years of age) weakness, hypotonia, areflexia
  - Later (2-6 years of age) rigidity, spasticity, cerebellar ataxia, deafness, blindness, cognitive decline
  - Mostly, death before 6 years
- In lysosomal α-N-acetylgalactosaminidase deficiency

### Hallervorden-Spatz Disease

- Abnormal cysteine metabolism in pallidum, autosomal recessive
- Bilateral globus pallidus-interna and substantia nigra-pars reticularis with neuronal loss, astrocitosis, pigment (lipofuscin, neuromelanin, iron) deposition, neuro-axonal spheroids
- Maybe, spheroids in cerebral cortex and brain stem nuclei; Lewy bodies; neurofibrillary tangles
- Pigment in renal tubular epithelium
- Sometimes associated with hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa (HARP syndrome)

### Nasu-Hakola Disease

Polycystic Lipomembranous Osteodysplasia with Sclerosing Leukoencephalopathy

- Autosomal recessive
- Pathologic features:
  - Eosinophilic wrinkled thickening of membrane of adipocytes
  - Severe loss of myelinated fibers from cerebral white matter
  - Severe neuronal loss with mineralization in basal ganglia
- Clinical features:
  - Onset in 2nd decade with repeated bone fractures caused by multiple bone cysts (best seen in hands and feet)
  - In 3rd decade, parkinsonism and frontal lobe dementia

### Giant Axonal Neuropathy

- Generalized disorder of cytoplasmic intermediate filaments suggested, autosomal recessive
- Pathologic features:
  - Peripheral nerves with segmental swellings of axons containing closely packed neurofilaments
  - Atrophy of cerebral and cerebellar white matter and spinal long tracts; dystrophic axonal swellings in corticospinal tracts, middle and inferior cerebellar peduncles, and spinal posterior columns; Rosenthal fibers in white matter; occasional multinucleated astrocytes
  - Tightly curled or kinky hair