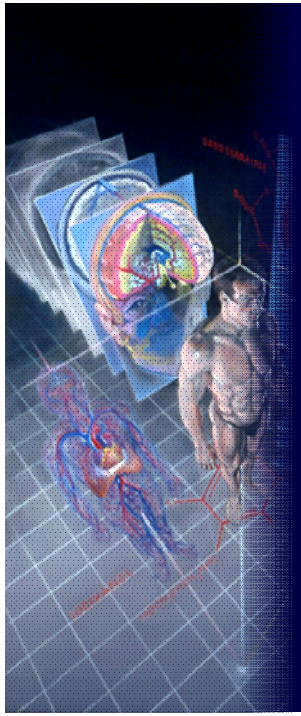

DEGENERATIVE DISORDERS & DEMENTIA

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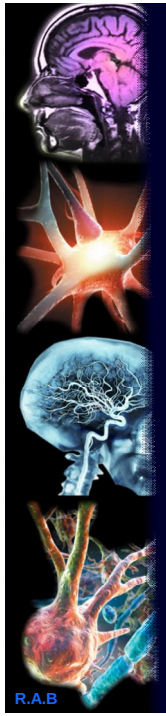
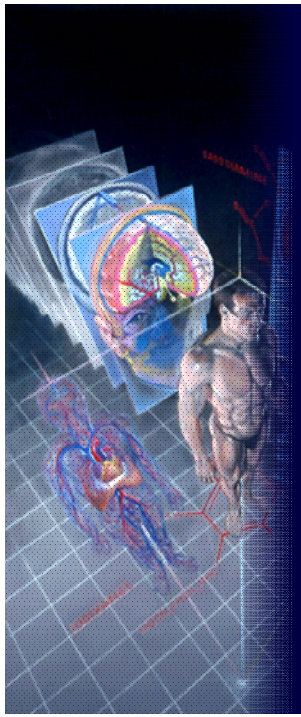


Manifestation

- Increase in time required to retrieve information
- Less able to register and retain new information
- Decrease in attention and concentration
- Minimal memory impairment
- Little or no progression of impairment
- No functional consequences
- Subjective memory complaints
- Objective memory impairments
- No or minor functional impairment
- No diagnosis of AD

R.A.B



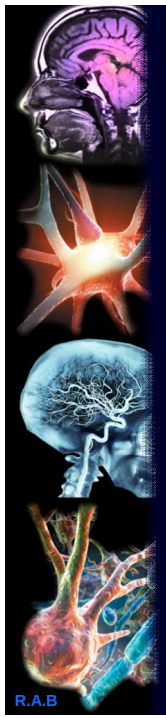
Dementia syndrome

1

Reasons of demencia

- **Neuro-degenerative diseases**
- **Infectious diseases**
- **Metabolic diseases**
- **Traumatic diseases**
- **Toxic diseases**
- **Cerebro-vascular diseases**
- **Other rare causes of dementia**

R.A.B

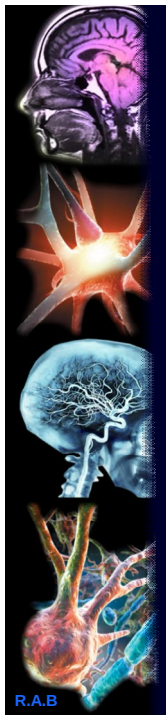


Reasons of demencia

1. Neurodegenerative diseases

- Familial Alzheimer diasease
- Lewy Body Diseases
  - Dementia with Lewy Bodies (DLB)
  - Dementia in Parkinson's disease (PDD)
- Fronto-temporal degeneration
  - Fronto-temporal dementia (FTD)
  - Primary Progressive Aphasia (PPA)
  - Semantic dementia (SD)
  - FTD with Parkinsonism linked to chromosome 17 (FTDP-17)
  - Pick's disease (PiD)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Argyrophilic grain disease
- Multiple system atrophy
- Amyotrophic Lateral Sclerosis (ALS)
- Ataxias
- Huntington's disease (HD)
- Postencephalitic Parkinsonism
- Down syndrome

R.A.B



Reasons of demencia

4. Traumatic diseases

- Repeated head trauma

5. Toxic diseases

- Warnicke-Korsakoff Syndrome

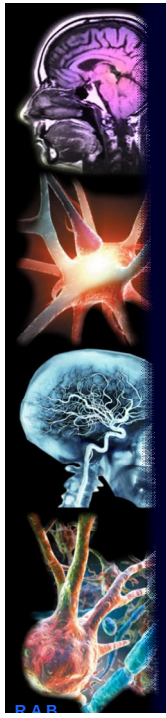
6. Cerebro-vascular diseases

- Binswanger disease
- Amyloid angiopathy

7. Other rare causes of dementia

- Multiple Sclerosis
- Normal Pressure Hydrocephalus

R.A.B



Reasons of demencia

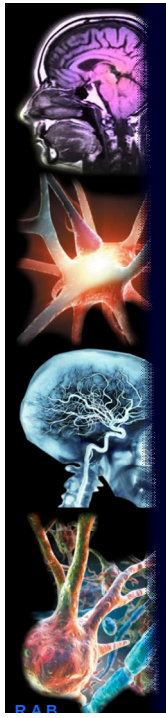
2. Infections

- Human Prion Disease
  - Sporadic,
  - Iatrogenic CJD
  - Variant CJD,
  - Familial CJD
  - GSS , FFI
- HIV
- Syphilis
- Postencephalitic parkinsonism
- Herpes Encephalitis

3. Metabolic diseases

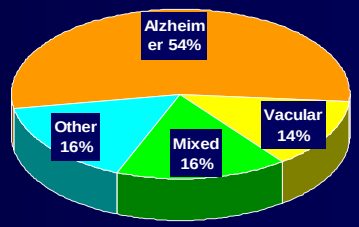
- Thyroid disorders
- Hallervorden-Spatz
- Hepatic and renal failure
- Chronic hypovitaminoses
- Cerebral lipoidosis
- Metachromatic leukodystrophy
- Adrenoleukodystrophy

R.A.B



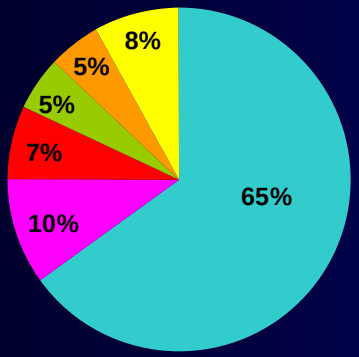
Classifications of dementia

1. Alzheimer type
2. Vascular type
3. Mixed type
4. Uncategorized type



R.A.B

Causes of dementia



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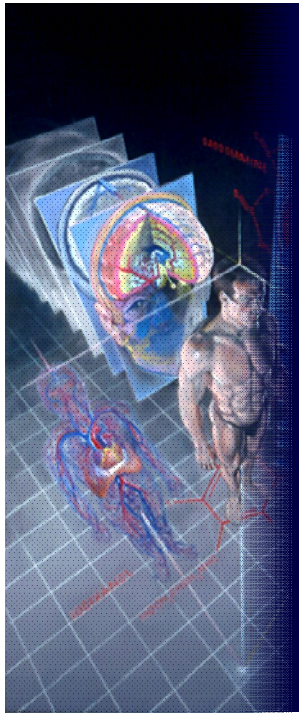


Degenerative diseases

2

Mild Cognitive Impairment (MCI)

- Subjective memory complaints
- Objective memory impairments
- No or minor functional impairment
- No diagnosis of AD

R.A.B

Accumulations diseases

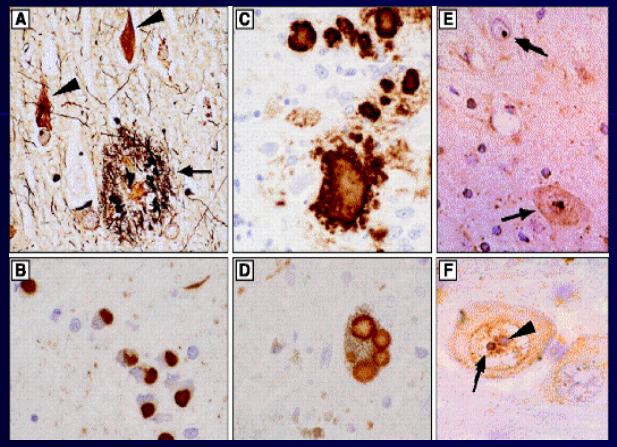
- Amyloid-beta protein
- Alpha-synuclein protein
- Hyperphosphorylated tau protein
- Prion protein
- Superoxide dismutase
- Huntingtin
- Atrophin
- Ataxin
- Laforin
- Glial fibrillary acidic protein
- Proteolipid protein
- Polyglucosan
- Neuroserpin

R.A.B

Accumulation disorders

Principal Protein	Disease
Amyloid-beta protein	Alzheimer's disease Down's syndrome Dementia with Lewy bodies
Alpha-synuclein protein	Parkinson's disease Dementia with Lewy bodies Cortical Lewy body disease Multiple system atrophy Neurodegeneration with brain iron accumulation
Prion protein	Creutzfeldt-Jakob disease, Kuru Fatal familial insomnia Gerstmann-Straussler-Scheinker disease

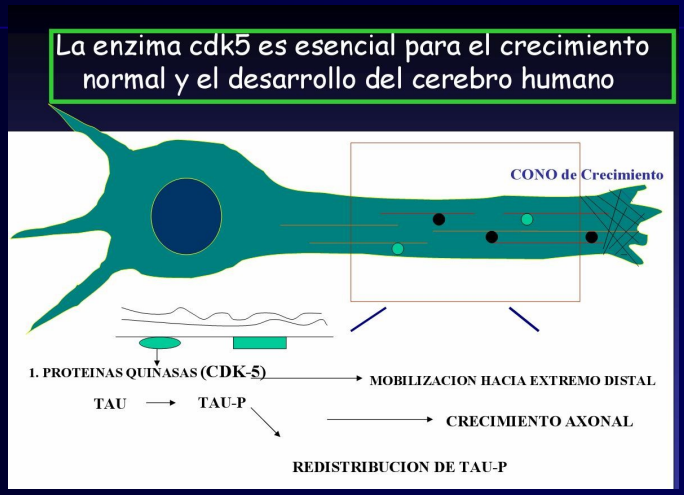
R.A.B



(A) **Alzheimer's disease.** neurofibrillary tangles + extracellular amyloid plaque(arr)
(B) **Pick's disease** - Fibrillar tau inclusions
(C) **Prion disease** PrPSc amyloid deposition in
(D) **Parkinson's disease** - multiple Lewy bodies in a nigral neuron
(E) **Machado-Joseph's disease** - neuronal intranuclear inclusions **ataxin-3** in.
(F) Mutant **ataxin-3**, demonstrating that it is distinct from the nucleolus.

R.A.B

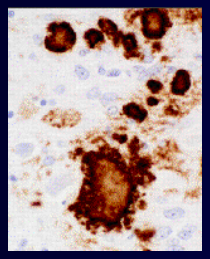
La enzima cdk5 es esencial para el crecimiento normal y el desarrollo del cerebro humano



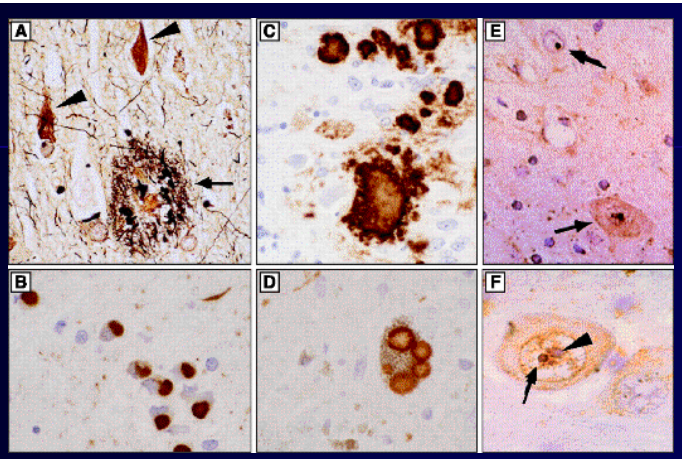
R.A.B

tauopatie

Principal Protein	Disease
Hyperphosphorylated tau protein	Alzheimer's disease Down's syndrome Frontotemporal lobar degeneration, m.pick Frontotemporal demencia u pakinsonizmu s väzbou na ch 17 Progressive supranuclear palsy Sy. Guam (parkinson-dementia complex) Corticobasal degeneration Pallidopontonigral degeneration Niemann-Pick Type C disease



R.A.B



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R.A.B

Parkinson's disease

- Definition: Progressive degenerative brain disease characterized by decline in cognitive functions sufficient to cause impairment in social and occupational performance
  - Increasing memory loss (declarative -> implicit)
  - Cognitive decline (reasoning,
  - Changes in behavior, personality, judgment
- Most common cause of dementia among people > 65y
  - Typical late onset - 65+ yrs (< 10% of cases earlier, mostly caused by a specific gene mutation)
- Incidence: 4 millions in US; underdiagnosed elsewhere ?
  - Either sex affected - **women 2-3 x often**; when diagnosed they are in more progressive state (? longer life span) ;
  - Women live longer with symptoms until diagnosis (they live alone lacking social and instrumental support triggering diagnosis)
- Prognosis: terminal illness with survival ~ 8 yrs post-diagnosis (women live longer)
- AD can't be diagnosed for certain until death
- Currently linked to several genes (transgenic mouse models)

R.A.B

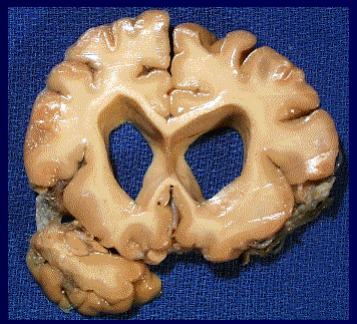
Accumulation disorders

Principal Protein	Disease
Superoxide dismutase	Familial amyotrophic lateral sclerosis
Huntingtin	Huntington's disease
Atrophin	Dentatorubral-pallidoluysian atrophy
Ataxin	Spinocerebellar atrophies
Laforin	Lafora's progressive myoclonus epilepsy
Glial fibrillary acidic protein	Adult Alexander disease
Proteolipid protein	Pelizaeus-Merzbacher disease
Polyglucosan	Polyglucosan body disease

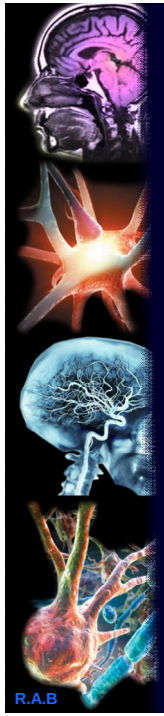
R.A.B

Huntington disease

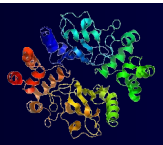
- AD – inherited neurodegenerative disorder
- Etiology: expanded polyglutamine (CAG) repetes at the amino terminus of the protein huntingtin
- PA:
  - cortical, striatal degeneration;
  - neuronal intranuclear inclusions of mutant **huntingtin**
  - specific aggregate-interacting proteins - huntingtin-associated proteins:
    - ubiquitin
    - huntingtin interacting protein 2 (HIP2) - contributes to the ubiquitination of huntingtin
- Manifestations:
  - Motor disorder –chorea
  - Cognitive disorder

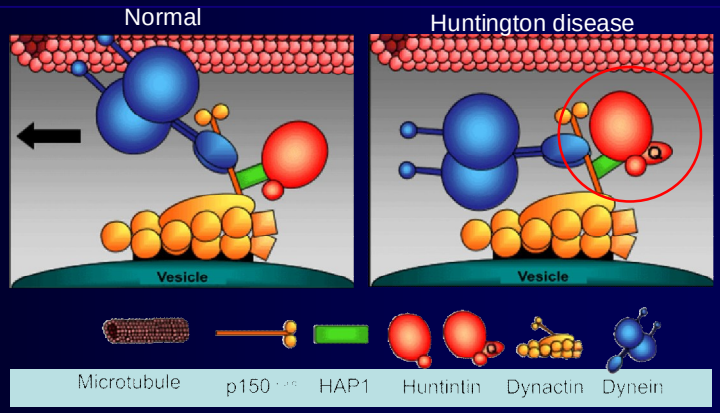


R.A.B



Huntingtin



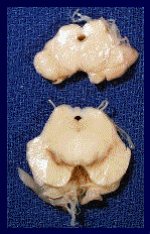


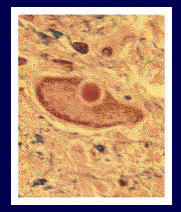
- Interruption of axonal transport causes axonal and somatic death
- Huntingtin gene (IT15) - contains a polymorphic trinucleotide (CAG)n repeat longer than the normal - expanded and unstable. IThe severity of symptoms and early onset of the disease enhances with the increasing length of CAG repeats.
- HAP1, apopain and GAPD

R.A.B

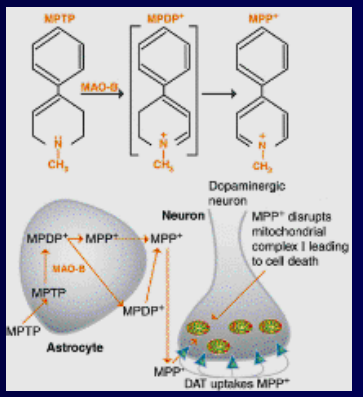
Parkinson's disease

MPTP causes selective death of dopaminergic SN neurons in the brain. MPTP crosses the blood-brain barrier, it is converted into MPDP+, an intermediate product, by the enzyme MAO-B within brain astrocytes. MPDP+ can then spontaneously form MPP+ either within the astrocyte itself or after diffusion into the extracellular space. MPP+ is then specifically taken up into dopaminergic neurons via the dopamine transporter (DAT). Once inside the dopaminergic neuron, MPP+ is taken up into the mitochondria via an energy-dependent transport process, where it acts as a specific inhibitor of mitochondrial complex I.



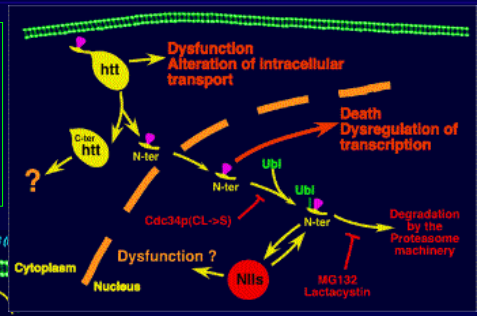


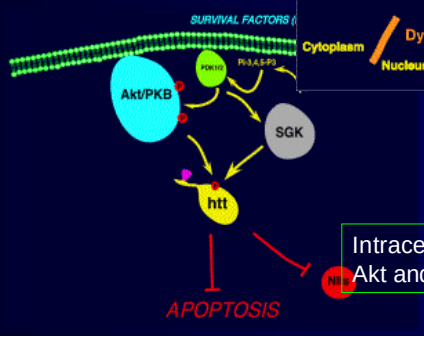
Lewy body in the cytoplasm of a pigmented DA neuron in SN



Huntingtin

Multiple damages by abnormal huntingtin
- transportation block
- abnormal transcription
- preamture apoptosis
- accumulates





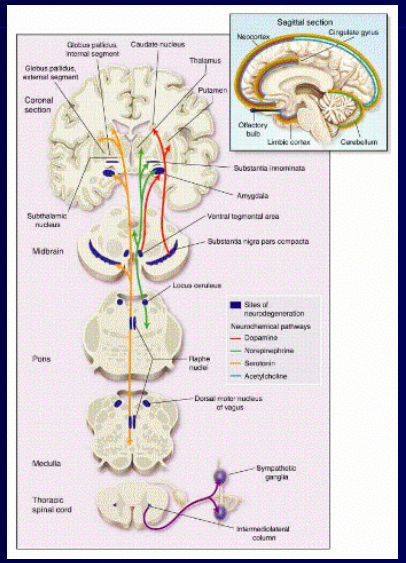
Intracellular signaling induced by Akt and SGK on huntingtin.

R.A.B

Parkinson's disease

- Dopaminergic defect
- Serotoninergic defect
- Noradrenergic defect
- Acetylcholibergic defect

- substantia nigra pars compacta - DA - nigrostriatal pathway - striatum
  ventral tegmental area - DA - entorhinal cortex, olfactory tubercle, cingulate gyrus, and frontal cortex.
- locus ceruleus - NA - spinal cord, cerebellum, central gray matter of the midbrain, amygdala, substantia innominata, thalamus, limbic cortex
- raphe nuclei - SE - spinal cord cerebellum, substantia nigra, amygdala, striatum, and cortex.
- substantia innominata - nucleus basalis of Meynert - Ach
- intermediolateral column - preganglionic sympathetic fibers



R.A.B