

Neurocognitive disorders

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Neurocognitive disorders (NCDs)

- ❧ NCD is the loss of cognitive functioning
- ❧ The loss of the ability to think, remember, or reason, as well as behavioral abilities, to such an extent that it interferes with a person's daily life and activities
- ❧ Is an acquired global impairment of intellect, memory, and personality without impairment of consciousness

NCD.....

- ❧ Signs and symptoms of NCD result when once-healthy neurons (nerve cells) in the brain stop working, lose connections with other brain cells, and die
- ❧ While everyone loses some neurons as they age, people with NCD experience far greater loss
- ❧ While NCD is more common with advanced age, it is not a normal part of aging

NCD....

- Loss of flexibility and adaptability and if you press the patient who lost this flexibility, there will be sudden explosions of anger or grief (catastrophic reaction)
- Self neglect and avoids social engagements
- Disorientation for time and then for place and person

NCD.....

- Aimless behavior
- Slow thinking with perseveration
- False ideas, mostly persecutory
- Speech becomes incoherent or mute

NCD.....

- Behavioral, affective, and psychotic features accompany the cognitive deficits
 - Insight is retained at first but gradually lost
 - Depression, anxiety, distress, irritability and aggression occurs
 - Hallucinations and delusions could appear too
- ** there are special tools to screen for cognitive impairment such as MMSE (Mini-Mental State Examination)

NCD.....

Diagnosis and finding the cause requires the following investigations:

- Full blood count and ESR,
- urea and electrolytes,
- liver function tests,
- calcium and phosphate,
- thyroid function tests,

Cont.....

- Vitamin B12 and Folate,
- MRI and CT brain scan,
- urinalysis,
- syphilis serology,
- HIV status,
- CXR,
- Neuropsychological assessment,
- Genetic testing and
- EEG

NCD.....

Risk assessment includes:

✧ Self neglect, poor judgment, wandering,

✧ abuse, dis-inhibition, aggression,

✧ exploitation by relatives, fitness to drive and aggression toward others

→ NCD is one of the main causes of dependence and disability at older ages

NCD, Types

- ⌘ Various disorders and factors contribute to the development of NCD
- ⌘ Neurodegenerative disorders such as AD, fronto-temporal disorders, and Lewy body disease result in a progressive and irreversible loss of neurons
- ⌘ Currently, there are no cures for these progressive neurodegenerative disorders

Cont...

- ⌘ However, other types of NCD can be halted or even reversed with treatment
- Normal pressure hydrocephalus often resolves when excess cerebrospinal fluid in the brain is drained via a shunt
- Cerebral vasculitis responds to aggressive treatment with immunosuppressive drugs
- ⌘ In rare cases, treatable infectious disorders can cause NCD

Cont...

- ⌘ Some drugs, vitamin deficiencies, alcohol abuse, depression, and brain tumors can cause neurological deficits that resemble NCD
- ⌘ Most of these causes respond to treatment

Types of NCD based on etiology

1. Tauopathies

- In some NCDs, a protein called *tau* clumps together inside nerve cells in the brain, causing the cells to stop functioning properly and die Eg.
 1. Alzheimer's disease (AD)
 2. Corticobasal degeneration (CBD)
 3. Front temporal disorders (FTD)
 4. Progressive supranuclear palsy (PSP)
 5. Argyrophilic brain disease

Cont...

2. **Synucleinopathies**

- In these brain disorders, a protein called alpha-synuclein accumulates inside neurons
- ⌘ One type of Synucleinopathies, Lewy body disease, involves protein aggregates called Lewy bodies, balloon-like structures that form inside of nerve cells

3. Vascular NCD

- Vascular NCD is caused by injuries to the vessels supplying blood to the brain

4. Mixed NCD

- Autopsy studies suggest that a majority of those age 80 and older probably had “mixed NCD,” caused by both AD-related NCD and vascular disease-related processes

Types based on site

1. cortical
2. sub-cortical

Cortical dementia(NCD)

- ❧ Disorder affecting the cortex, the outer portion or layers of the brain.
- ❧ Alzheimer's and Creutzfeldt-Jakob are two forms of cortical dementia
- ❧ Memory and language difficulties(Aphasia) most pronounced symptoms.
- ❧ Aphasia is the inability to recall words and understand common language

Sub-cortical dementia

- ❧ Dysfunction in parts of the brain that are beneath the cortex.
- ❧ Memory loss & language difficulties not present or less severe than cortical.
- ❧ Huntington's disease and AIDS dementia complex.
- ❧ Changes in their personality and attention span.
- ❧ Thinking slows down.

Incidence

- ✧ Suspected that as many as 50% of people over the age of 80 develop Alzheimer's.
- ✧ 5%-8% of all people over 65 have some form of dementia; number doubles every 5 years beyond that age.
- ✧ Alzheimer's causes 50%-70% of all dementia.
- ✧ About 20%-30% of all dementia is believed to be caused by a vascular dysfunction (most common is multi-infarct disease).

Proportion of NCD cases

∞ Alzheimer's Disease (AD): 50-75% of cases


∞ Vascular NCD (VaD): 20-30%

∞ Fronto-temporal NCD: 5-10%

∞ NCD with Lewy Bodies: < 5%

Alzheimer's disease

- ❧ Progressive disorder in which neurons deteriorate resulting in the loss of cognitive functions (memory), judgment and reasoning, movement coordination, and pattern recognition.
- ❧ Predominantly affects the cerebral cortex and hippocampus which atrophy as the disease progresses.

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- ❧ In 1906, a German physician, Dr Alois Alzheimer first described an agglomeration of pathologic abnormalities in the autopsied brain of a woman who was affected for years by memory problems, confusion and language dysfunction
 - ❧ He reported the presence of a collection of dense deposits or plaques outside the neurons and bands of fibres or tangles within the brain cells

AD....

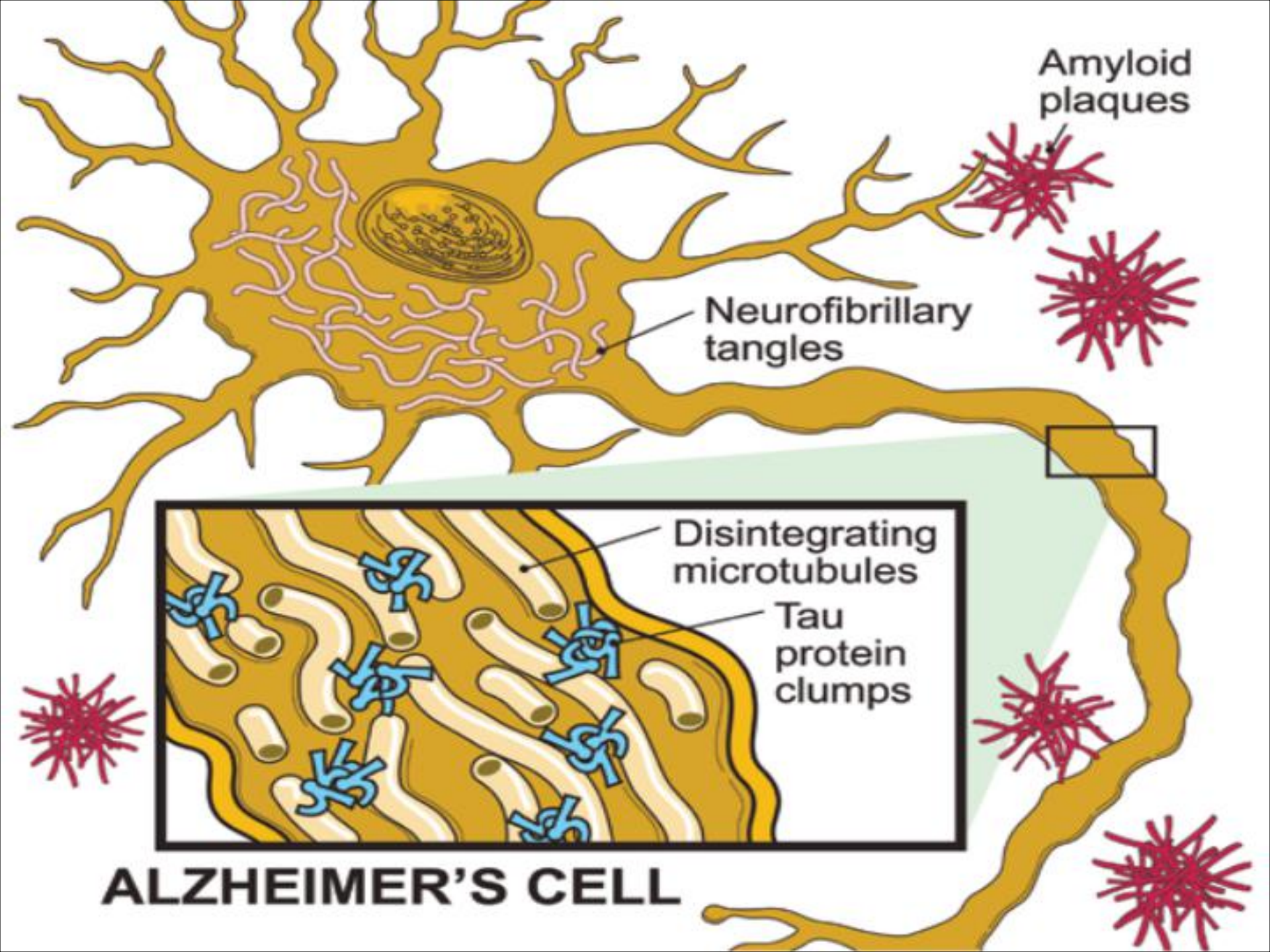
- ❧ These senile plaques and neurofibrillary tangles have been recognised to be the two core pathological hallmarks of Alzheimer's disease
- ❧ Plaques are composed of amyloid beta ($A\beta$) and are called amyloid plaques, and the tangles consist of hyperphosphorylated tau protein

Neuritic Plaques

- ❧ Commonly found in brains of elderly people but appear in excessive numbers in the cortex of AD pt.'s
- ❧ Surrounded by deteriorating neurons that produce acetylcholine (neurotransmitter essential for processing memory and learning)

Neurofibrillary Tangles

- ❧ Twisted remains of a protein which is essential for maintaining proper cell structure.
- ❧ It is not known whether the plaques and tangles are the cause of AD or part of the results of the disorder.



Amyloid
plaques

Neurofibrillary
tangles

Disintegrating
microtubules

Tau
protein
clumps

ALZHEIMER'S CELL

AD....

Both senile plaques and neuro-fibrillary tangles are associated with the progressive loss of neurons and synapses, brain atrophy and dilatation of the lateral ventricles due to loss of brain tissue, which are the broad features of brain damage in NCD

AD....

- ❧ A further important cause of the brain damage in AD is ischemia, which may be caused by cerebral amyloid angiopathy
- ❧ Brain changes underlying AD probably develop over a period of at least 20-30 years before the onset of symptoms.

AD.....

Prevalence of AD

- 50-75% of NCD is due to Alzheimer disease
- 2-7% of the population aged over 65years
- 20% of the population over 85 years
- The prevalence increases with increasing age
- It mainly affects older people but 2 to 10% of all cases are estimated to start before the age of 65 years
- After this, the prevalence doubles with every five year increment in age

AD....

- ❧ Insidious onset & gradual progression
- ❧ Major NCD: 2 or more cognitive domains impaired
(unlike other Major NCDs) + impaired instrumental
activities of daily living (IADLs)
- ❧ Mild NCD: 1 or more cognitive domains impaired,
IADLs intact

AD....

“Probable” vs. “Possible”:

- “Probable” vs. “Possible” are differentiated in part by presence of Alzheimer’s disease gene
- This can be from family history or formal genetic testing

AD...

➤ Major NCD due to AD

Probable AD: either one must be present:

- Evidence of AD genetic mutation, or
- All 3 of the following:
 - Impairment in memory + 1 other domain
 - Progressive, gradual decline
 - No other possible etiology
- Otherwise, *Possible AD is diagnosed*




- **AD...**

- **Mild NCD due to AD**

- **Probable AD:** requires evidence of Alzheimer's gene
- **Possible AD:** no evidence of AD gene, but all 3 of these factors exist:
 - Decline in memory & learning
 - Progressive, gradual decline
 - No evidence of other etiologies

Clinical features

- ✓ Amnesia, gradual and progressive
- ✓ Aphasia
- ✓ Apraxia
- ✓ Agnosia
- ✓ Disturbance in executive functioning e.g. planning and reasoning

- 
- ✓ Depression
 - ✓ Psychosis (delusions and hallucinations)
 - ✓ Behavioural symptoms e.g. agitation and wandering
 - ✓ Personality change (reduction in drive, aggression, sexual disinhibition)

Median survival from diagnosis is 5-7 years.

AD....

Pathophysiology:

1. Senile Plaques and Neurofibrillary Tangles

- ✓ A definite diagnosis of Alzheimer disease can be made only by autopsy examination of a patient's brain
- ✓ This neuro-pathological evaluation reveals gross cerebral atrophy, signifying loss of neurons
- ∞ The diagnostic lesions are found on microscopic evaluation of the most affected areas of the brain, which reveal the presence of extracellular neuritic plaques and intracellular neuro-fibrillary tangles

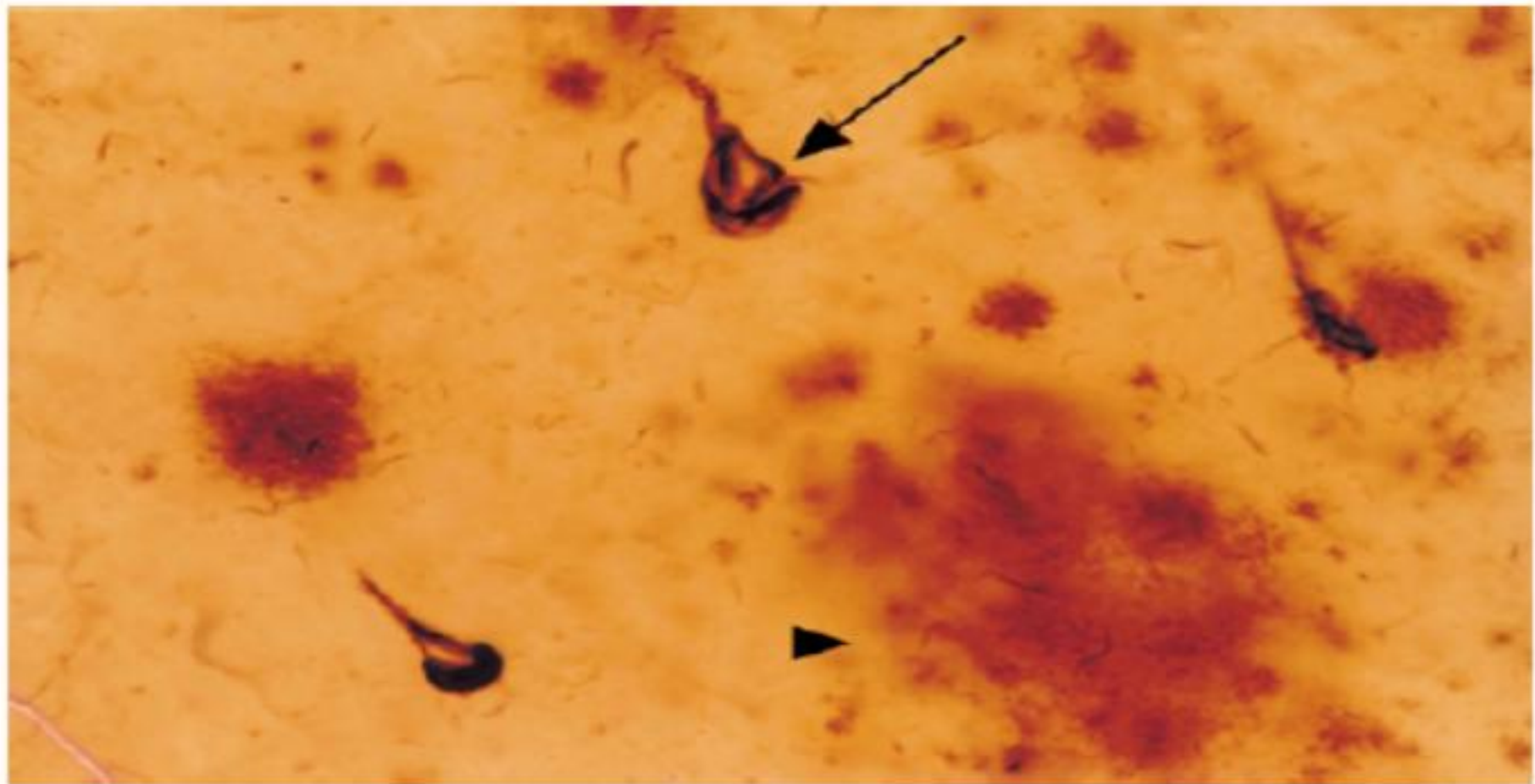
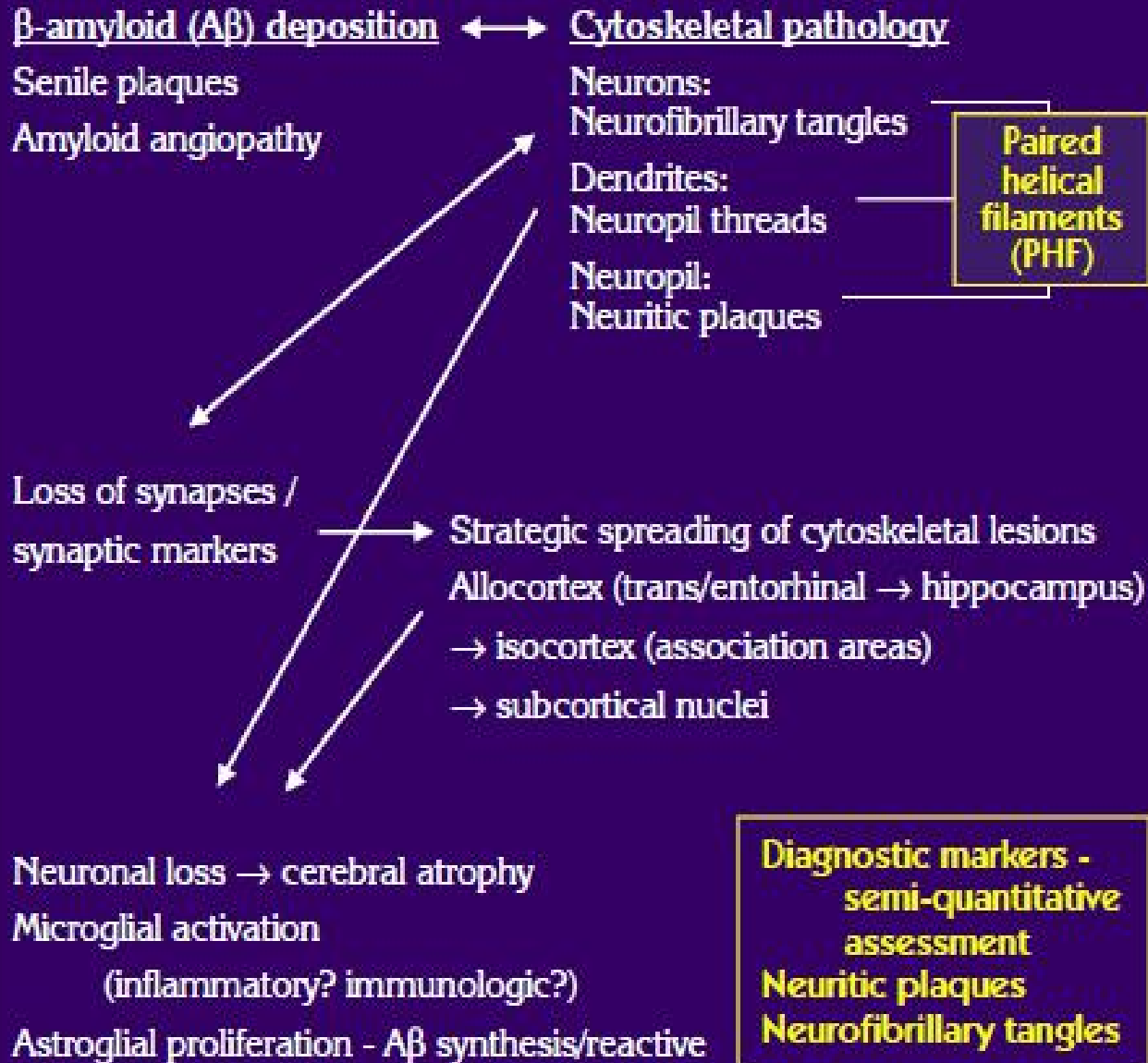


Figure 2 Light micrograph of Alzheimer disease neuropathology. Section from the cortex of a patient with Alzheimer disease showing tangles and plaques. The intraneuronal tangle (arrow) is stained dark brown with an antibody that specifically targets paired helical filaments. These filaments are also seen as the dense brown material (dystrophic processes) embedded in the extracellular plaque (arrowhead). The lighter reddish staining of the plaque is from another antibody directed specifically against β -amyloid.

Cont.....

- ❧ Plaques and tangles are found predominantly in the frontal and temporal lobes, including the hippocampus
- ❧ In more advanced cases, the pathology extends to other regions of the cortex, including the parietal and occipital lobes

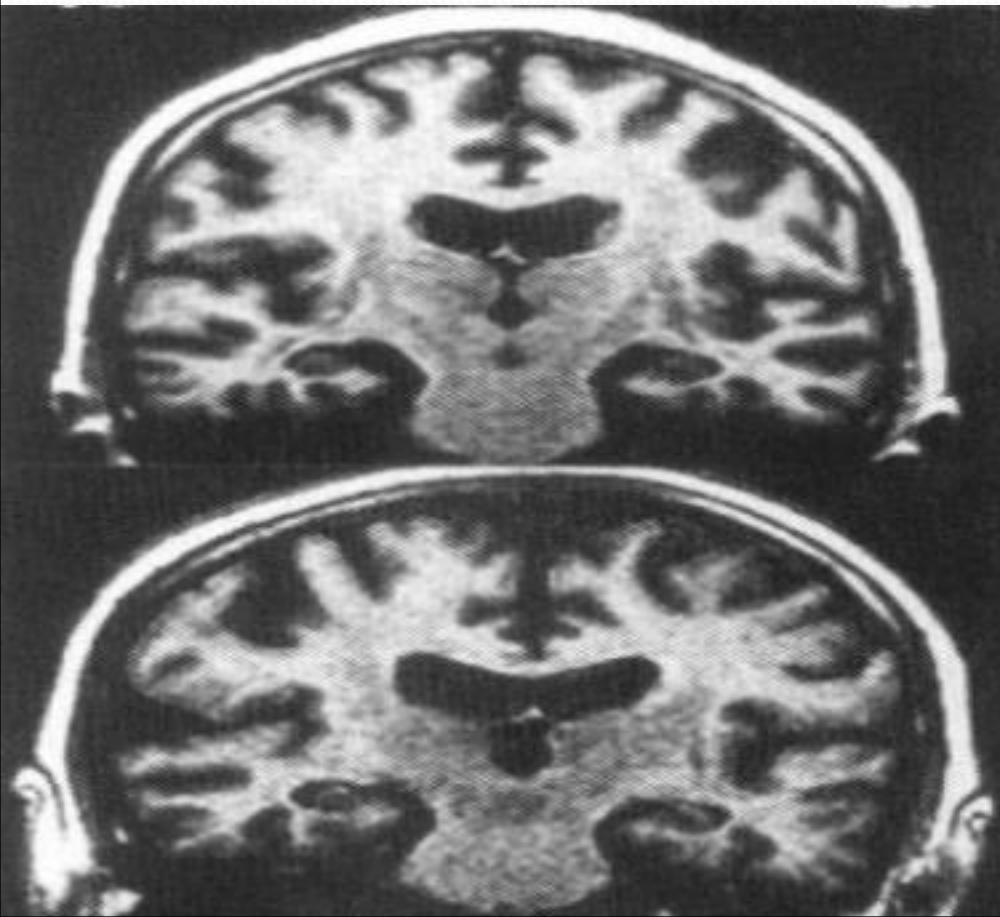
Histopathology of Alzheimer's disease - diagnostic markers



AD.....

Neuropathology

- ❖ The brain is shrunken, widened sulci, enlarged ventricles, brain weight is reduced



AD.....

Etiology

- The major risk factor is age
- Genes
- ✓ Most of the cases are not genetically inherited but in rare cases it is familial and causative mutations were identified in three genes, APP (amyloid precursor protein), presenilin 1 and presenilin 2
- **Environment**
- ✓ Environmental factors include past history of depression, diabetes mellitus, obesity, aluminum exposure and head injury

AD...

- NSAIDs, hormone replacement, and statins are protective
- Other theories include cholinergic hypothesis based on the loss of acetylcholine in the cerebral cortex
- The role of oxidative stress, inflammation, and apoptosis (programmed cell death)

Summary of Risk factors for AD

- ⌘ Family History - a clear inherited pattern exists in approximately 10% of cases
- ⌘ Down's Syndrome - Nearly 100% of people who live into their 40's
- ⌘ Chronic Hypertension - Treatment reduces the risk
- ⌘ Head Injuries - Three times more likely to develop AD
- ⌘ Gender - inclusive data. Some studies show a greater risk for females while others show an increased risk for males.

Types of Alzheimer Disease:

1. Early-onset Familial

- Alzheimer disease is generally diagnosed after the age of 65 years, when it is referred to as late-onset Alzheimer disease
- Early-onset Alzheimer disease has onset before age 65, and approximately 10% of these early-onset cases have a familial form of the condition, which is transmitted as an autosomal dominant trait

AD....

❧ Mutations in three genes – amyloid precursor protein, presenilin-1 and presenilin-2 – cause the majority of cases of familial Alzheimer disease

2. **Late-onset Sporadic**

❧ Other than the difference in the age of onset, early-onset familial Alzheimer disease and the late-onset sporadic type are difficult to distinguish clinically and pathologically

AD...

Genetics of Alzheimer Disease

- ❧ There are three genes known to be important in the aetiology of the early-onset familial condition: the APP on chromosome 21, the presenilin-1 (PS1) gene on chromosome 14, and the presenilin-2 (PS2) gene on chromosome 1
- ❧ Apolipoprotein E on chromosome 19 is an important risk factor for sporadic Alzheimer disease.

Stages of AD

Early stage

Middle stage

Late stage

Symptoms at early stage AD

- ⌘ Begins with forgetfulness
- ⌘ Progresses to disorientation and confusion
- ⌘ Personality changes
- ⌘ Symptoms of depression/manic behaviors

Symptoms of middle stage

- ⌘ Need assistance with ADLs
- ⌘ Unable to remember names
- ⌘ Loss of short-term recall
- ⌘ May display anxious, agitated, delusional, or obsessive behavior
- ⌘ May be physically or verbally aggressive

Symptoms at late stage

- ✧ Loss of verbal articulation
- ✧ Loss of ambulation
- ✧ Bowel and bladder incontinence
- ✧ Extended sleep patterns
- ✧ Unresponsive to most stimuli

Treatment and Prevention of AD

- ❧ The most important class of drugs used in the specific treatment of Alzheimer disease was developed for the ability to increase acetylcholine levels in the central nervous system
- ❧ Acetylcholine levels are reduced in Alzheimer disease brains

Cont.....

- There are now two classes of compounds that can increase brain acetylcholine levels:
 - (1) Acetyl cholinesterase inhibitors (ACEIs), which increase synaptic concentrations of acetylcholine
 - (2) Muscarinic agonists, which mimic acetylcholine by directly stimulating the muscarinic acetylcholine receptor
- While ACEIs modestly decrease the rate of cognitive decline in Alzheimer disease, the dementia remains progressive and the benefits of these medications, while measurable, are small

AD...

- chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the risk of Alzheimer disease, supporting the hypothesis that development of the condition involves inflammation
- Use of NSAIDs could delay the onset of Alzheimer disease by 5–7 years

AD....

- ❧ Other studies have been done using vitamin E or other antioxidants, which can protect the neurons against free radical damage
- ❧ Experiments in cell culture have shown that b-amyloid neurotoxicity may be due to its ability to increase production of hydrogen peroxide in nerve cells

Vascular NCD

- ∞ Is the second commonest cause of NCD
- ∞ More in men than women

Clinical features:

- ∞ It appears in the late sixties or seventies
- ∞ Emotional and personality changes appear first followed by impairment of memory and intellect

VNCD...

- ⌘ Depression, emotional liability and confusion
- ⌘ Behavioral retardation and anxiety
- ⌘ Transient Ischemic attacks or mild strokes are common
- ⌘ The course is stepwise with periods of deterioration and partial recovery
- ⌘ They have shorter survival than Alzheimer patients

VNCD...

- ✧ They have signs of hypertension, arteriosclerosis in the peripheral and retinal vessels and signs of focal neurological deficits
- ✧ Vascular NCDs arise as a result of risk factors that similarly increase the risk for cerebrovascular disease (stroke), including atrial fibrillation, hypertension, diabetes, and high cholesterol
- ✧ It is possible to have both Alzheimer's dementia and vascular dementia in the same patient at the same time

SCADDTC and NINDS-AIREN criteria of vascular-ischemic dementia (VID)

Possible VID:

- 1) Clinical criteria of dementia with one or more cerebral infarcts
 - 2a) History (one infarct with dementia in timely relationship)
 - 2b) Binswanger's syndrome with early urinary incontinence, gait disorders, vascular risk factors, white matter lesions CT / MRI

Probable VID:

- 1) All clinical signs of dementia
- 2) Two or more cerebral infarcts (history, clinical, imaging) or one infarct followed by proven dementia
- 3) Imaging signs of at least one infarct

Proven VID

- a) Clinically proven dementia
- b) Pathological demonstration of multiple cerebrovascular lesions

Mixed type dementia

Combination of degenerative (Alzheimer) and vascular dementia

Hachinski score

Clinical feature	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints.	1
Emotional incontinence.	1
History of hypertension	1
History of stroke	2
Clinical evidence of atherosclerosis	1
Focal neurologic symptoms.	2
Focal neurologic signs	2

from
Hachinski
et al,
Arch Neurol
32; 1975:
632

A total score of 4 or less is suggestive of a degenerative cause of dementia such as Alzheimer's disease

A score of 7 or more is suggestive of vascular dementia

Pathology of vascular NCD

Small vessel disease

- Ischemic white matter degeneration
- Cribriform atrophy of white matter
- Lacunar infarction in subcortical nuclei and white matter
- Granular atrophy of cortex

Large vessel disease

- Very extensive or multifocal infarction (multi-infarct dementia)
- Critically sited infarcts

Hypoperfusion lesions

⌘ Hippocampal sclerosis

- Laminar cortical necrosis

Rare local vascular disorders

CADASIL

- Cerebral amyloidosis
- Cerebral vasculitis
- Antiphospholipid antibody syndrome

Types of vascular NCD include:

a) **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)**

✧ This inherited form of CVD results in a thickening of the walls of small- and medium-sized blood vessels, eventually stemming the flow of blood to the brain

✧ It is associated with mutations of a specific gene called Notch 3

VNCD...

b) Multi-infarct NCD

- ⌘ This type of NCD occurs when a person has had many small strokes that damage brain cells
- ⌘ One side of the body may be disproportionately affected, and multi-infarct dementia may impair language or other functions, depending on the region of the brain that is affected
- ⌘ When the strokes occur on both sides of the brain, however, dementia is more likely than when stroke occurs on one side of the brain

Cont....

- ✧ In some cases, a single stroke can damage the brain enough to cause NCD
- ✧ This so-called single-infarct dementia is more common when stroke affects the left side of the brain—where speech centers are located—and/or when it involves the hippocampus, the part of the brain that is vital for memory


VNCD...

c) Sub-cortical vascular NCD (Binswanger's disease)

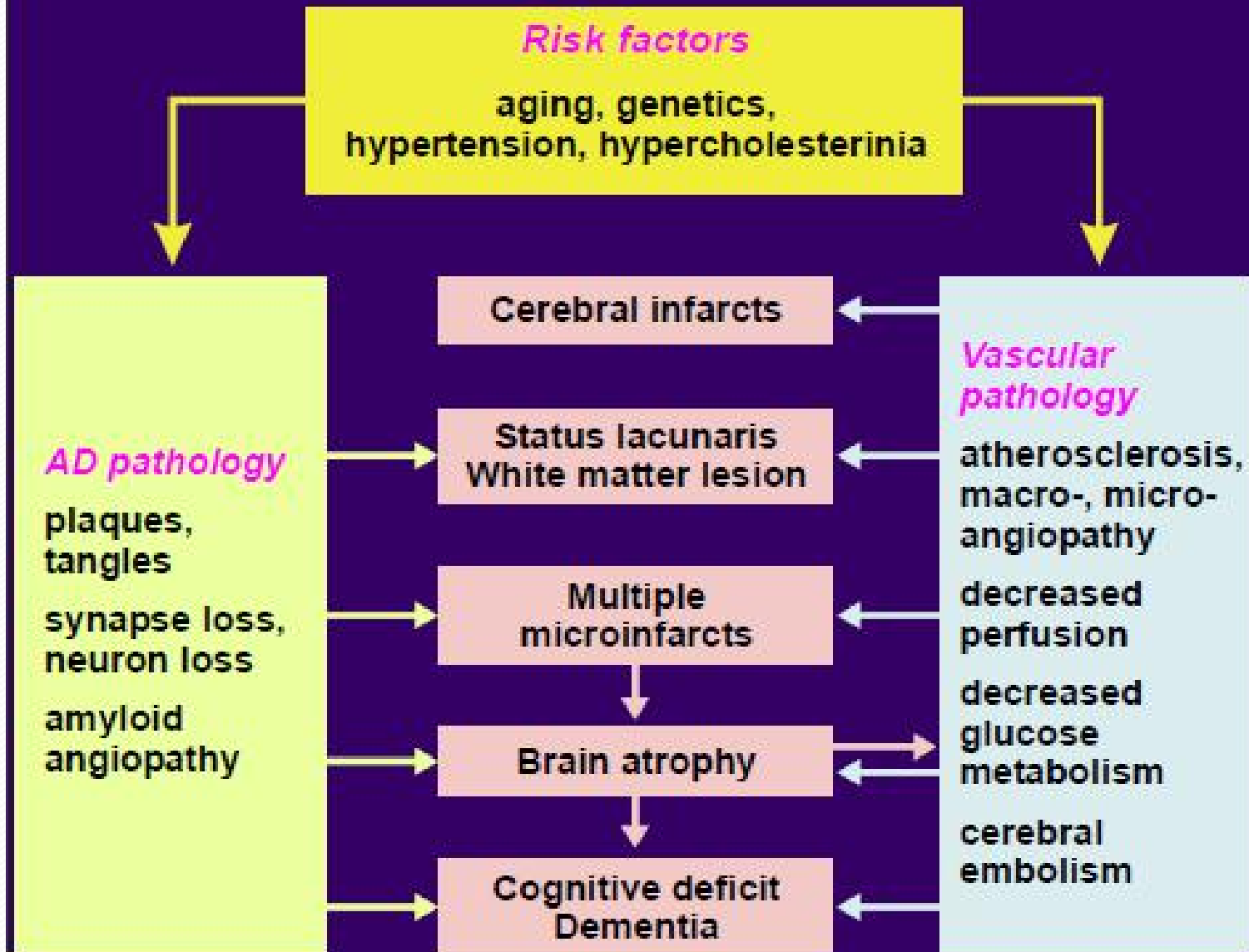
- ❧ A rare form of NCD that involves extensive microscopic damage to the small blood vessels and nerve fibers that make up white matter
- ❧ A characteristic feature of this disease is psychomotor slowness, such as an increase in the time it takes for a person to think of a letter and then write it on a piece of paper

VNCD...

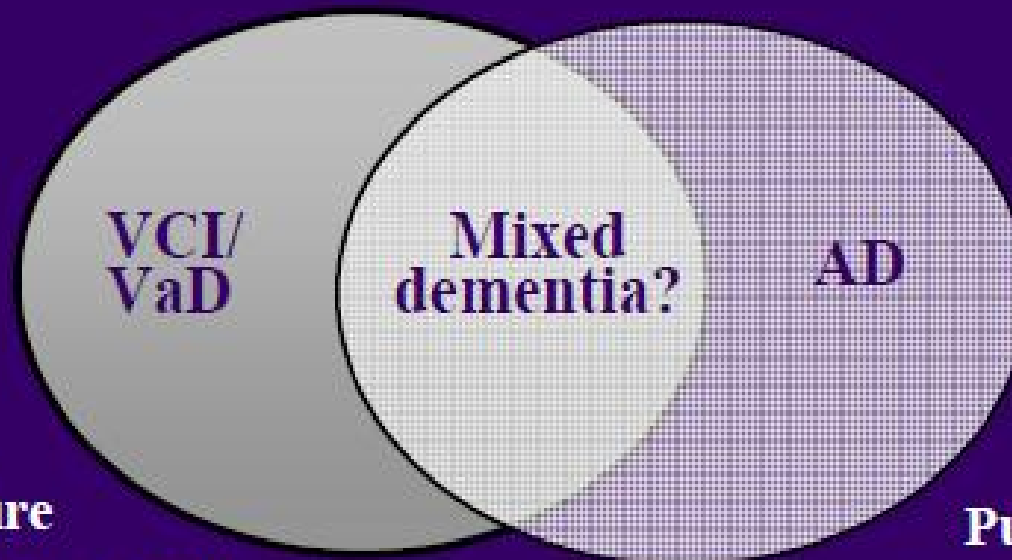
- ❧ People with sub-cortical vascular disease often have high blood pressure, a history of stroke, or evidence of disease of the large blood vessels in the neck or heart valves
- ❧ Treatment is aimed at preventing additional strokes and may include drugs to control blood pressure .

- 
- ❧ Some studies indicate that mixed vascular-degenerative dementia is the most common cause of dementia in the elderly
 - ❧ Several studies have found that many of the major risk factors for vascular disease also may be risk factors for AD

Pathogenic factors in the development of mixed dementia



VaD and AD – Overlap



**Pure
VaD / MID?**

Pure AD?

Even Auguste D exhibited
CBV pathology

“...clinically diagnosed VaD ...87% AD either alone (58%) or with cerebrovascular disease (42%) (mixed- neurodegeneration)...”
(Nolan et al, 1998)

NCD with Lewy Bodies

- ⌘ The cardinal feature is Lewy bodies in the cerebral cortex
- ⌘ Main clinical features include
 - Fluctuating level of dementia
 - Recurrent delirium like phases
 - Parkinsonism
 - Visual hallucinations

NCD with LB..

Neuropathology

- ⌘ Presence of Lewy bodies in the cerebral cortex
- ⌘ They are seen in the substantia nigra
- ⌘ Presence of α -synuclein and ubiquitin proteins

NCD with LB...

Onset: Insidious

Core symptoms

- Fluctuating cognition/attention/alertness
- Visual hallucinations-well formed and detailed
- Parkinsonian movement develops 1 year after cognitive impairment

Suggestive features

- Rapid eye movement (REM) sleep disorder
- Neuroleptic sensitivity: Worsening of movement disorder and impaired consciousness

NCD with LB...

❧ Symptoms such as difficulty sleeping, loss of smell, and visual hallucinations often precede movement and other problems by as long as 10 years, which consequently results in NCD with LB going unrecognized or misdiagnosed as a psychiatric disorder until its later stages

NCD with LB...

- ❧ Neurons in the substantia nigra that produce dopamine die or become impaired, and the brain's outer layer (cortex) degenerates
- ❧ Many neurons that remain contain Lewy bodies
- ❧ Later in the course of LBD, some signs and symptoms are similar to AD and may include memory loss, poor judgment, and confusion
- ❧ Other signs and symptoms of LBD are similar to those of Parkinson's disease

NCD with LB...

- ❧ There is no cure for LBD, but there are drugs that control some symptoms
- ❧ The medications used to control LBD symptoms can make motor function worse or exacerbate hallucinations

Fronto-temporal NCD

- ⌘ Presentation is usually between 45 & 70 years of age
- ⌘ Prominence of behavioral rather than cognitive features
- ⌘ The frontal form presents with behavioral and personality change and the temporal form with language disorder
- ⌘ There are familial and sporadic cases
- ⌘ 10% of the cases are autosomal dominant

Frontotemporal NCD..

- ✧ On neuroimaging there is focal and asymmetrical atrophy of the temporal and frontal poles
- ✧ EEG is usually normal unlike the diffuse slowing in Alzheimer's disease
- ✧ Acetylcholine and dopamine are not affected but serotonin markers are reduced

Fronto-temporal NCD..

- ⌘ Are caused by a family of brain diseases that primarily affect the frontal and temporal lobes of the brain
- ⌘ They account for up to 10 percent of all NCD cases
- ⌘ Some, but not all, forms of FTD are considered Taupathies
- ⌘ In some cases, FTNCD is associated with mutations in the gene for tau (MAPT), and tau aggregates are present.

FTNCD...

- ✧ In FTNCD, changes to nerve cells in the brain's frontal lobes affect the ability to reason and make decisions
- ✧ People can live with fronto-temporal disorders for 2 to 10 years
- ✧ In some cases, FTNCD is associated with progressive neuromuscular weakness otherwise known as amyotrophic lateral sclerosis.

Cont.....

- ❧ The signs and symptoms may vary greatly among individuals as different parts of the brain are affected
- ❧ No treatment that can cure or reverse FTNCD is currently available

FTNCD is classified into two main types of syndromes:

1. Behavioral variant fronto-temporal NCD causes a person to undergo behavior and personality changes

- ❧ People with this disorder may do impulsive things that are out of character, such as steal or be rude to others
- ❧ They may engage in repetitive behavior (such as singing, clapping, or echoing another person's speech)

Cont.....

- ✧ They may overeat compulsively; lose inhibitions, causing them to say or do inappropriate things (sometimes sexual in nature); or become apathetic and experience excessive sleepiness
- ✧ While they may be cognitively impaired, their memory may stay relatively intact

Cont.....

2. **Primary progressive aphasia (PPA)** causes a person to have trouble with expressive and receptive speaking—finding and/or expressing thoughts and/or words
 - ⌘ Sometimes a person with PPA cannot name common objects
 - ⌘ Problems with memory, reasoning, and judgment are not apparent at first but can develop and progress over time

FTNCD....

Other types of FTDs include:

a) Fronto-temporal NCD with parkinsonism linked to chromosome 17 (FTDP-17)

❧ *a rare form of dementia that is believed to be inherited from one parent and is linked to a defect in the gene that makes the tau protein*

❧ *The three core features are*

1. Behavioral and personality changes

2. Cognitive impairment, and

3. Motor symptoms

❧ *People with this type of FTNCD often have delusions, hallucinations, and slowness of movement and tremor as seen in Parkinson's disease*

b) Pick's disease

- A tauopathy subtype of FTNCD characterized by hallmark Pick bodies—masses comprised of tau protein that accumulate inside nerve cells, causing them to appear enlarged or balloon-like
- ∞ Antidepressants and antipsychotics can control some of the behavioral symptoms of Pick's disease, but no treatment is available to stop the disease from progressing

Reading assignment

📖 Read on assessment techniques on screening tests for neuro-cognitive disorders



Thank You