DEMENTIA

Oleh :
dr. Risma Karlina Prabwati, SpS

Mild Cognitive Impairment (MCI)

Mild Cognitive Impairment (MCI)

- **Individu yang menderita ggn kognitif tetapi tidak memenuhi kriteria demensia atau penyakit Alzheimer (Petersen et al,1999)**

- **Epidemiologi**
  - **Meningkat dengan bertambahnya usia**
    8,6% usia 60 - 65 th → 16,8% usia 85 th

  - **Flicker C dkk, 1991, Bowen J dkk, 1997, periode 5 – 7 th, 50 – 80% MCI mempunyai resiko demensia**

  - **MCI potensial menjadi Demensia**

Karakteristik MCI

- Penurunan kognitif ringan yang dikeluhkan /dilaporkan/dikonfirmasi secara objektif, tidak termasuk ktriteria demensia
- Skor CDR 0,5, GDS tingkat 3, tidak demensia

  (CDR : Clinical Demensia Rating, GDS : Global Deterioration Scale, IADL : Instrumental Activities of Daily Living)
- Aktifitas sehari hari baik, dapat terganggu ringan pada aktifitas kompleks pada penilaian ADL

Dementia

Definisi

Progressive deterioration of intellect, behaviour and personality as a consequence of diffuse disease of the cerebral hemispheres, maximally affecting the cerebral cortex and hippocampus.

Dibedakan dengan **DELIRIUM**

Kriteria DEMENSIA

A .Ada bukti gangg. MEMORI pendek & panjang

B . Setidaknya SATU:

1. Gangg. Daya pemikiran abstrak
2. Gangg. Daya Nilai
3. Gangg. Fungsi Luhur : Afasia , Agnosia Apraksia , Konstruksional

C. TIDAK ADA gangg. Kesadaran (delirium)

D. A dan B mengganggu Kerja , ADL & sosial

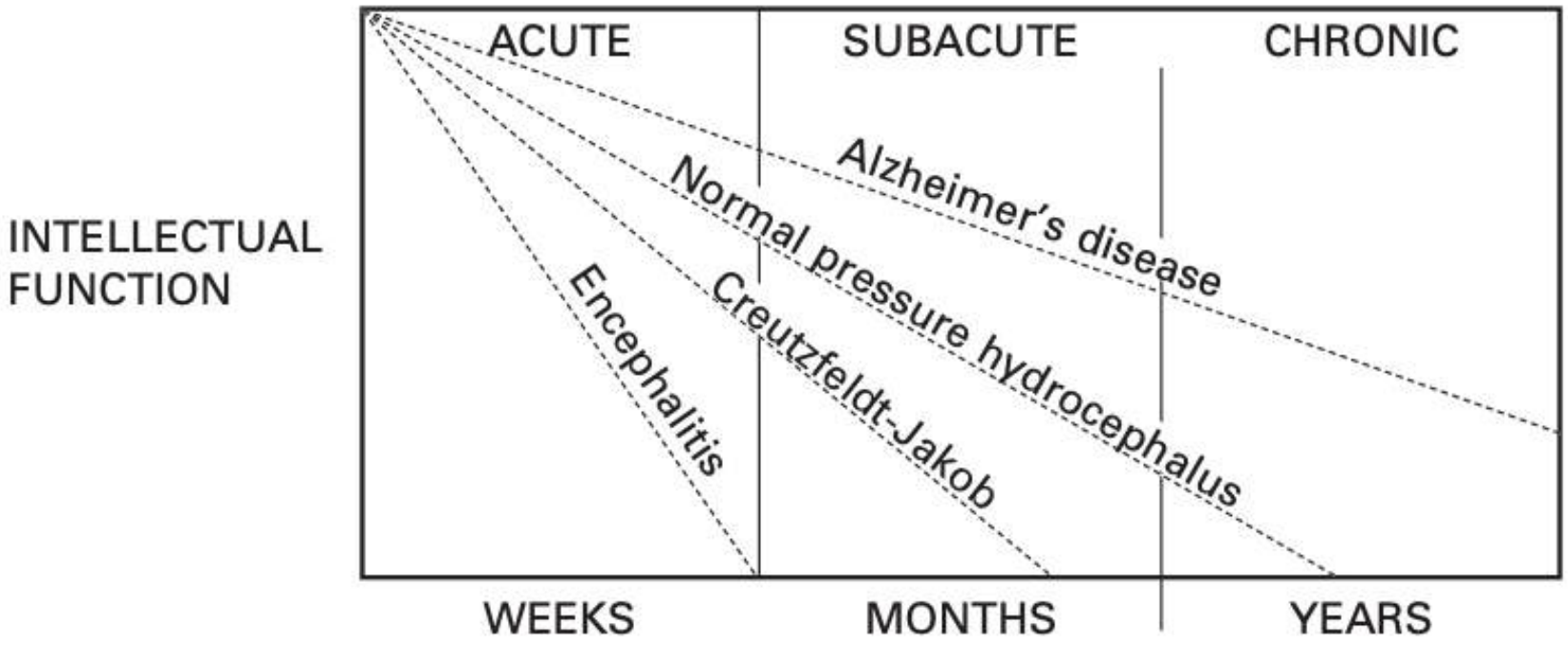
E. Ditemukan / dicurigai penyebab (Ax Px Lab), bila tak ada dianggap Non Organik

Jenis Dementia

Treatable Dementia

Dementia Irreversible

- Demensia vaskuler
- Alzheimer Demensia
- Demensia akibat Parkinson Disease
- Demensia akibat penyakit Pick


INTELLECTUAL FUNCTION
ACUTE
SUBACUTE
CHRONIC
Alzheimer's disease
Normal pressure hydrocephalus
Creutzfeldt-Jakob
Encephalitis
WEEKS
MONTHS
YEARS

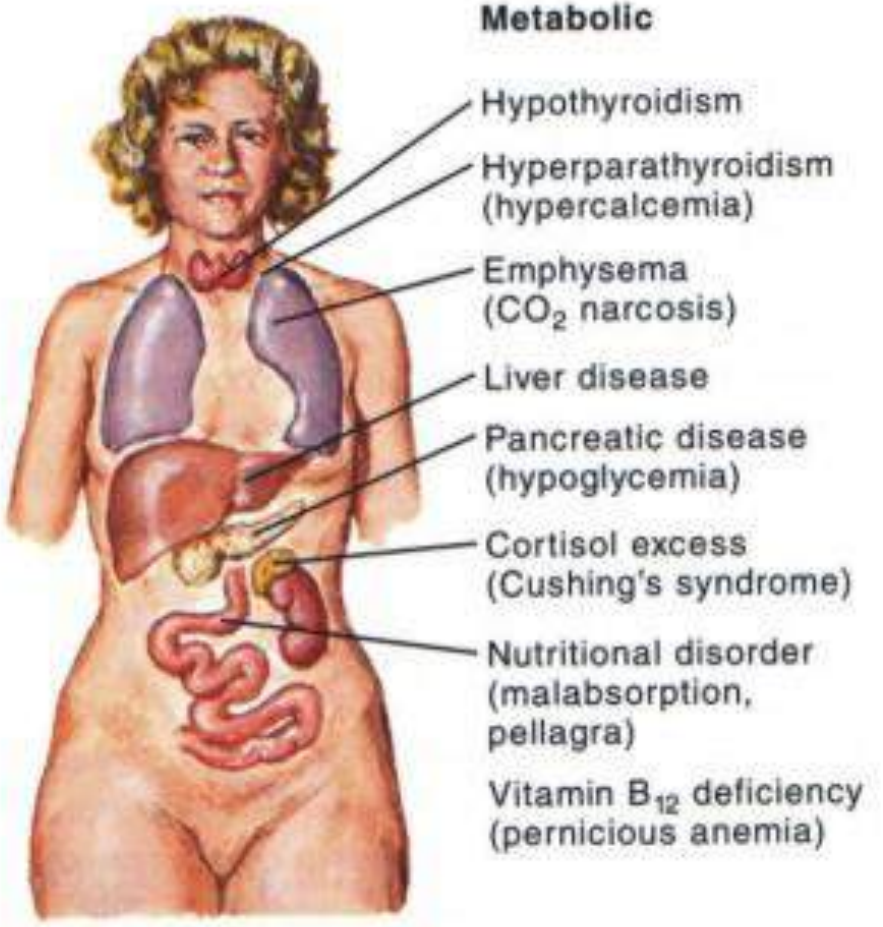
Treatable Dementia

D rug Toxicity
E motional disorders
M etabolit and Endocrine dis
E yes & Ear
N utritionals disorders
T rauma & **T** umors
I nfection
A rteriosclerosis

Treatable Dementia

Plate 12

Treatable Dementias



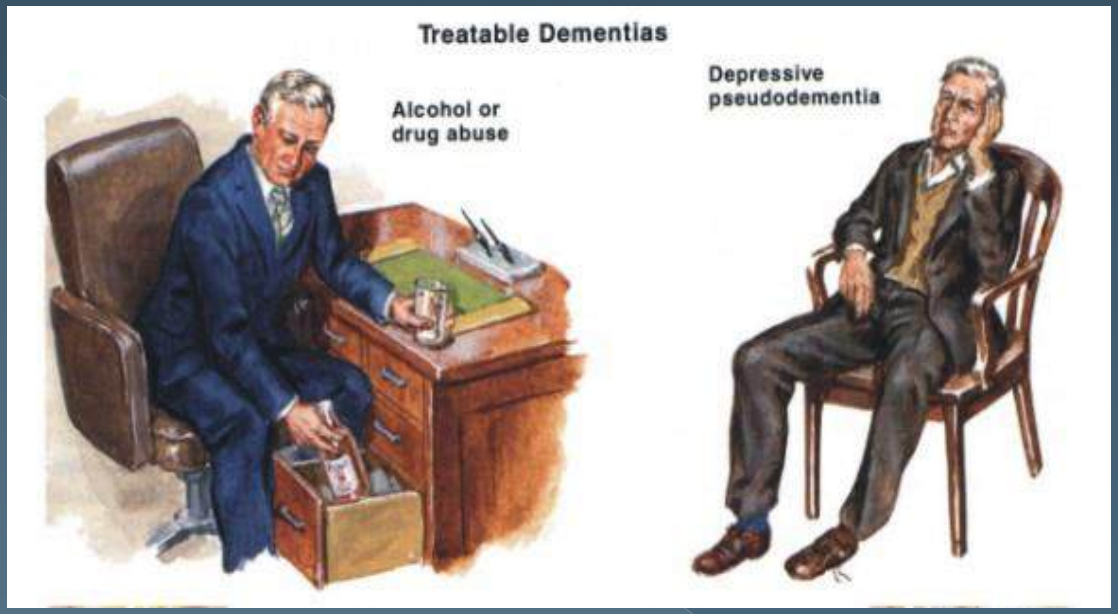
Metabolic

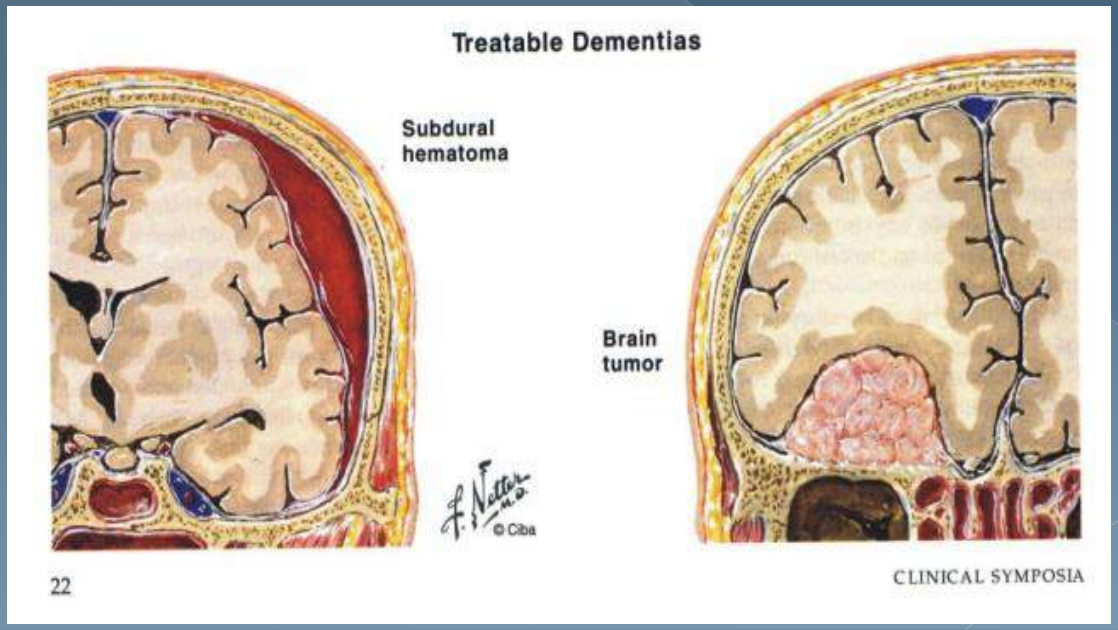
- Hypothyroidism
- Hyperparathyroidism (hypercalcemia)
- Emphysema (CO_2 narcosis)
- Liver disease
- Pancreatic disease (hypoglycemia)
- Cortisol excess (Cushing's syndrome)
- Nutritional disorder (malabsorption, pellagra)
- Vitamin B_{12} deficiency (pernicious anemia)

Iatrogenic

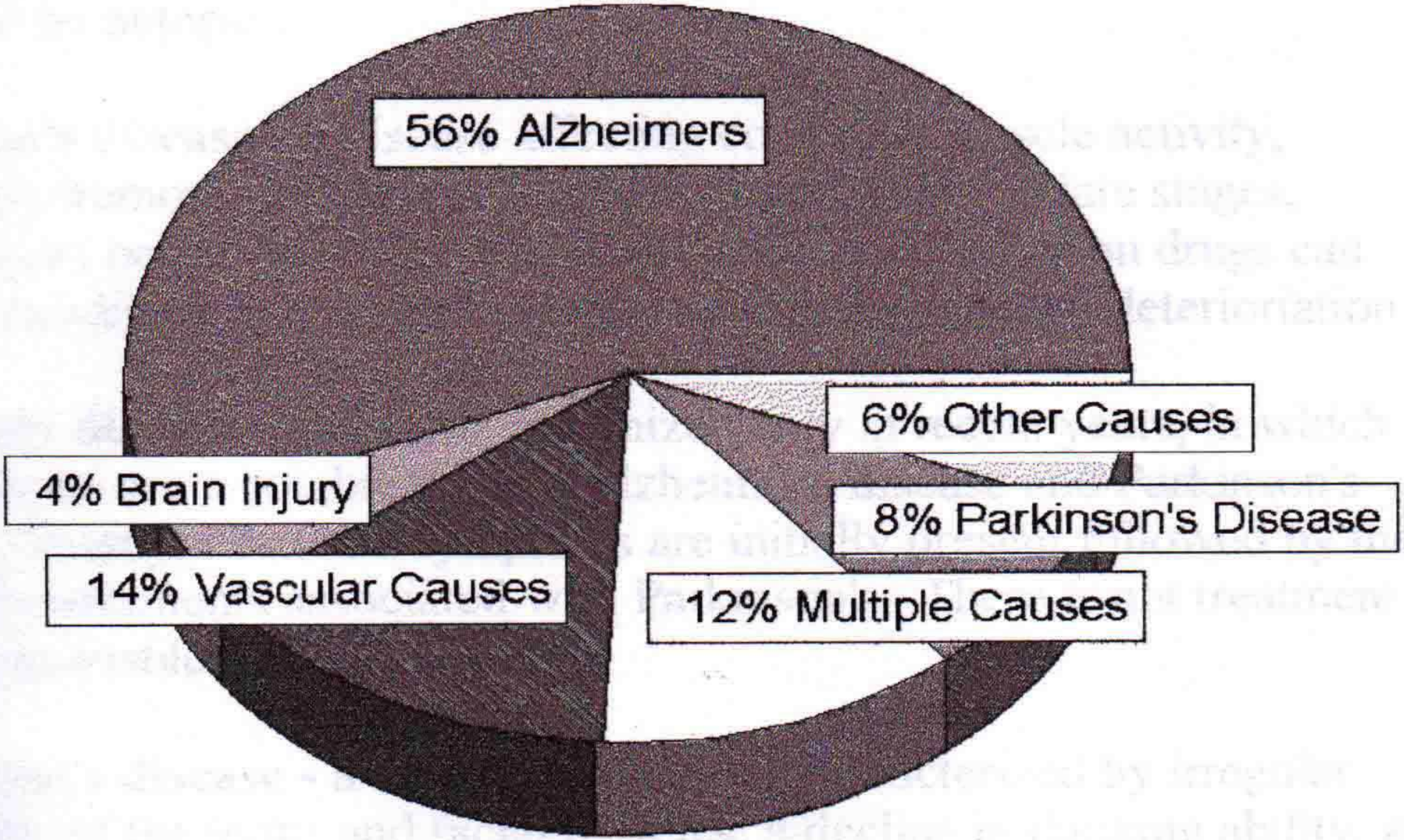
- Overmedication
- Drug side effects

Treatable Dementia





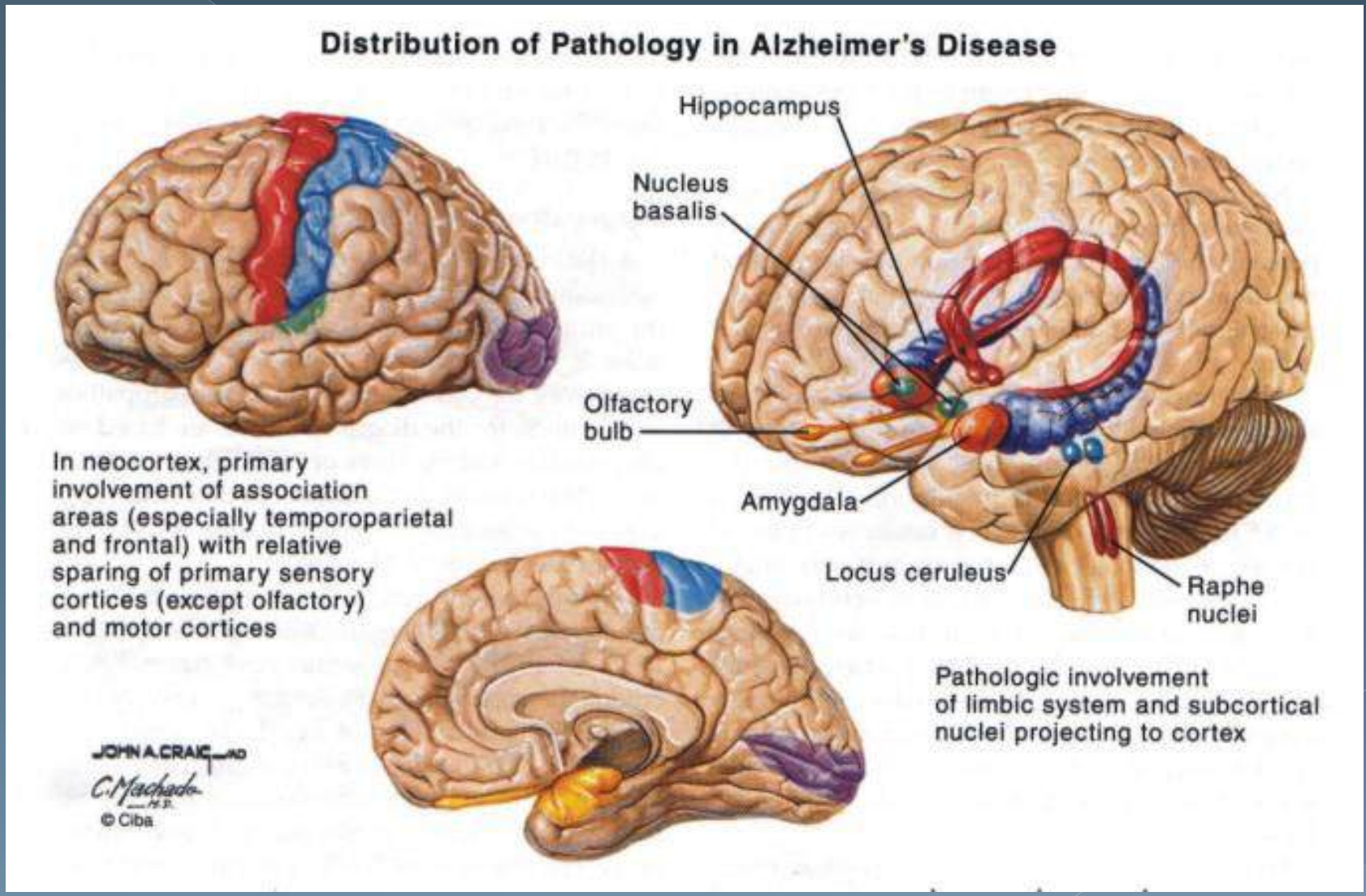
Causes of Dementia



DEMENTIA	Suspected cause	Appropriate investigations
without neurological signs or systemic illness	– *Alzheimer's disease*	CT/MR scan Confirmation: pathology (post mortem)
	– *Frontotemporal dementia/Pick's disease*	CT/MR scan Confirmation: pathology (biopsy)
with neurological signs (gait disturbance and incontinence)	– *Tumour*	CT/MR scan Genetics Confirmation: pathology (biopsy or post mortem)
	– *Degenerative disease,* e.g. Huntington's disease	CT/MR scan Confirmation: CSF pressure monitoring (tumour-biopsy)
	– *Normal pressure hydrocephalus* *Frontal lobe tumour*	
with neurological signs and systemic symptoms and signs	– *Inflammatory disease,* e.g. Demyelinating disease (page ••) Vasculitis & collagen vascular disease	Serum autoantibodies Evoked responses CSF (immunology) CT/MR scan
	– *Infective disease,* e.g. AIDS Syphilis Meningitis	Serum antibodies (viral) VDRL, TPHA HIV status CSF examination CT/MR scan
with 'stroke risk factors' (page 519)	– *Multi-infarct state*	CT/MR scan)
with poor nutrition	– *Nutritional disease*	Serum B_1 (thiamine) Red cell transketolase (thiamine) Serum B_{12} Serum folate
with metabolic and endocrine symptoms and signs	– *Metabolic and endocrine disease*	Function tests: – thyroid – parathyroid – renal – hepatic – adrenal
with history of head trauma	– *Post-traumatic dementia*	CT/MR scan

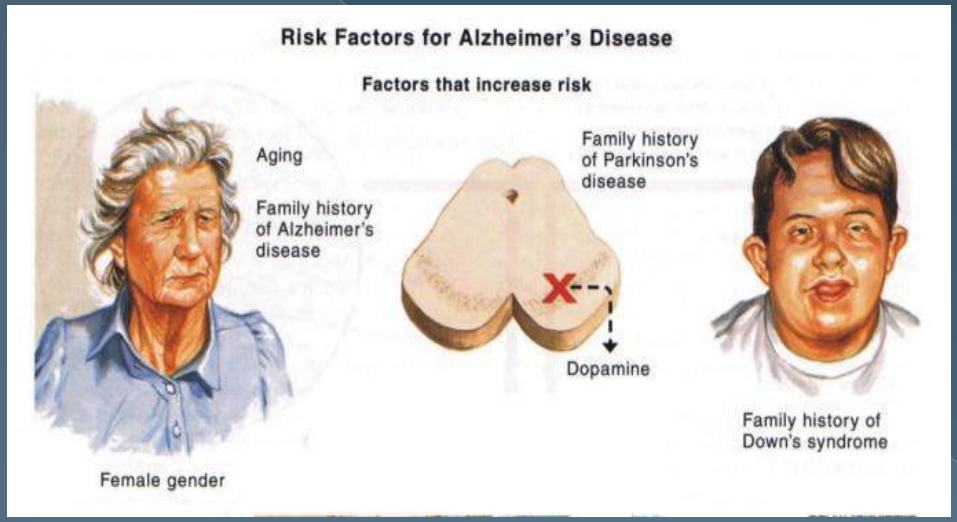
Dementia Alzheimer

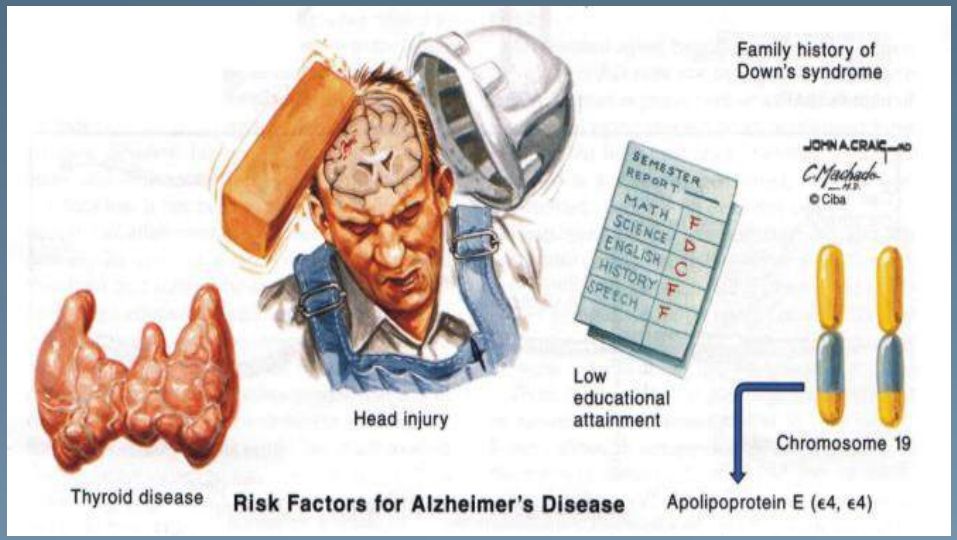
Patologi pd ALZHEIMER

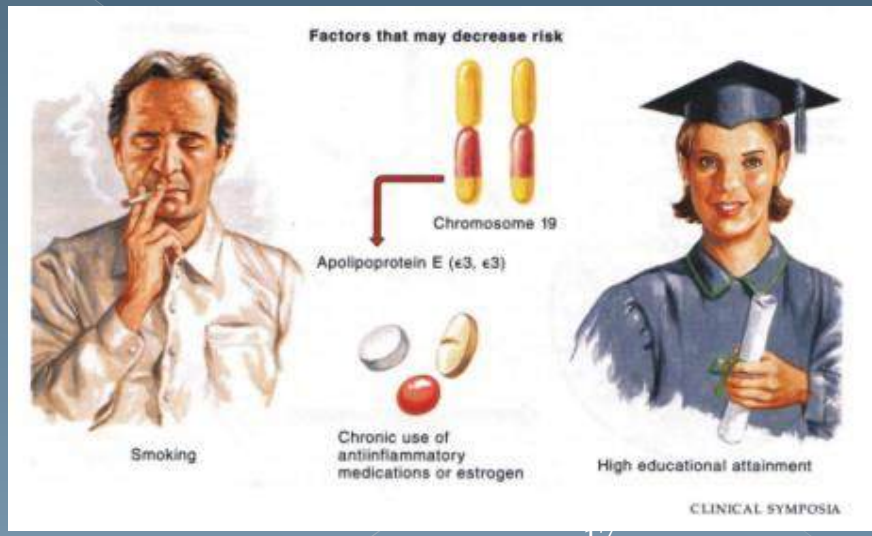


Fx.Resiko AD

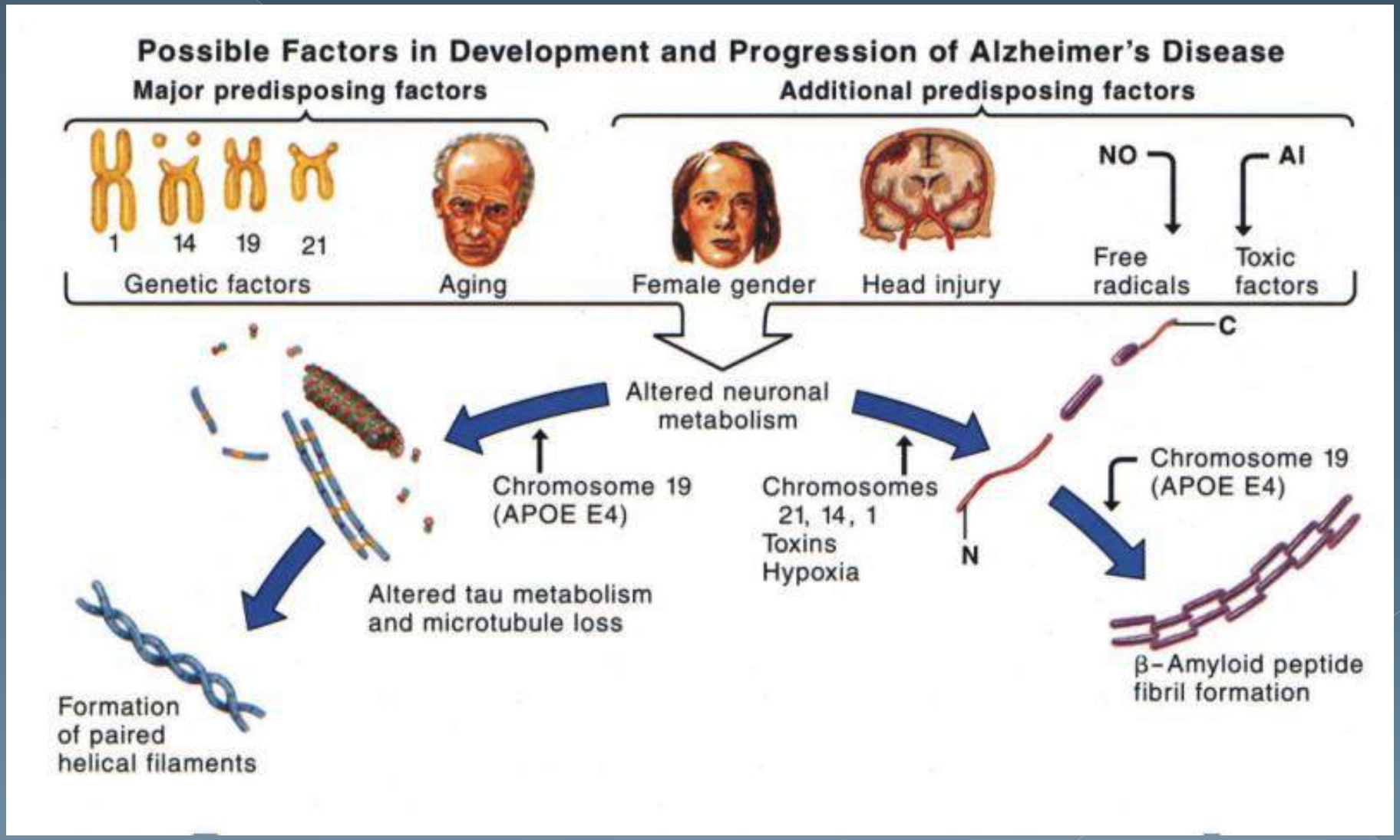
- Umur < 65 **Early**
  > 65 **Late**
- Wanita
- Fam. Parkinson
- Fam. Down S
- Thyroid Disease
- Trauma Kepala
- Chromosom - 1 , 14 , 19





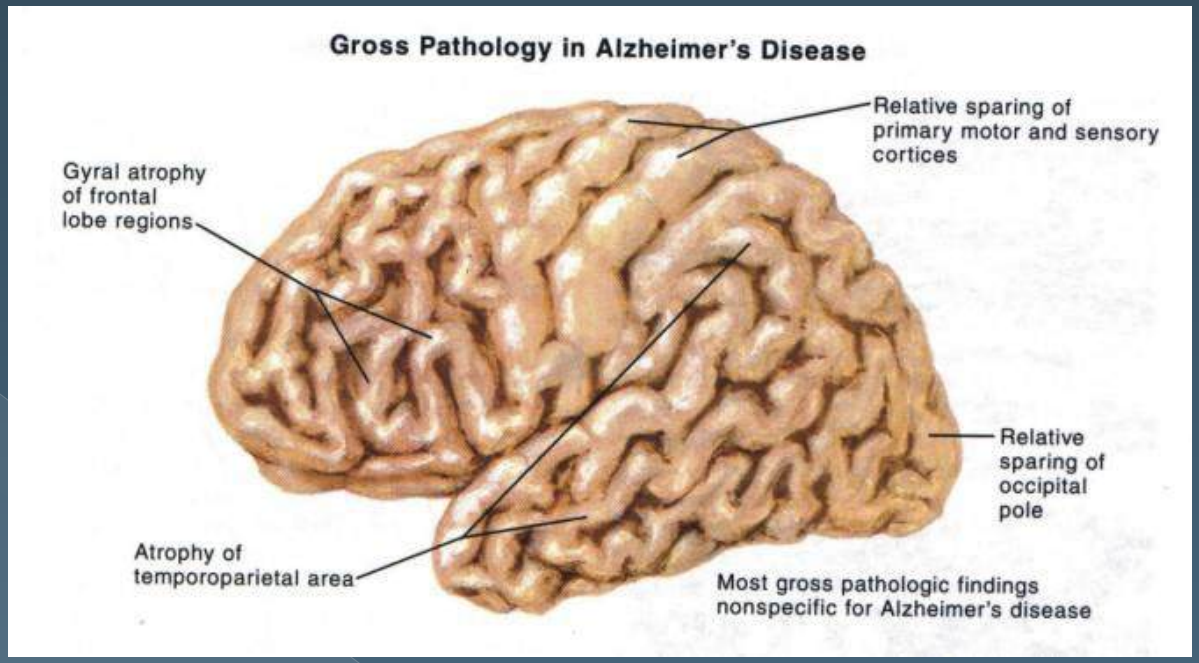


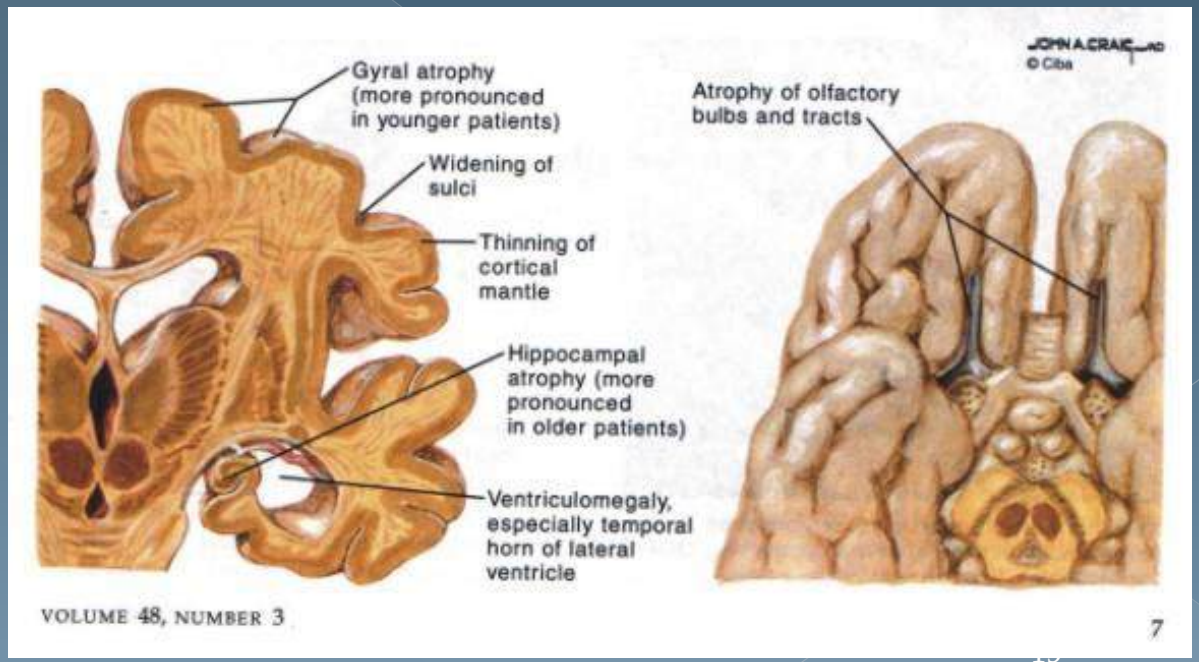
Risk - Patogenesis AD



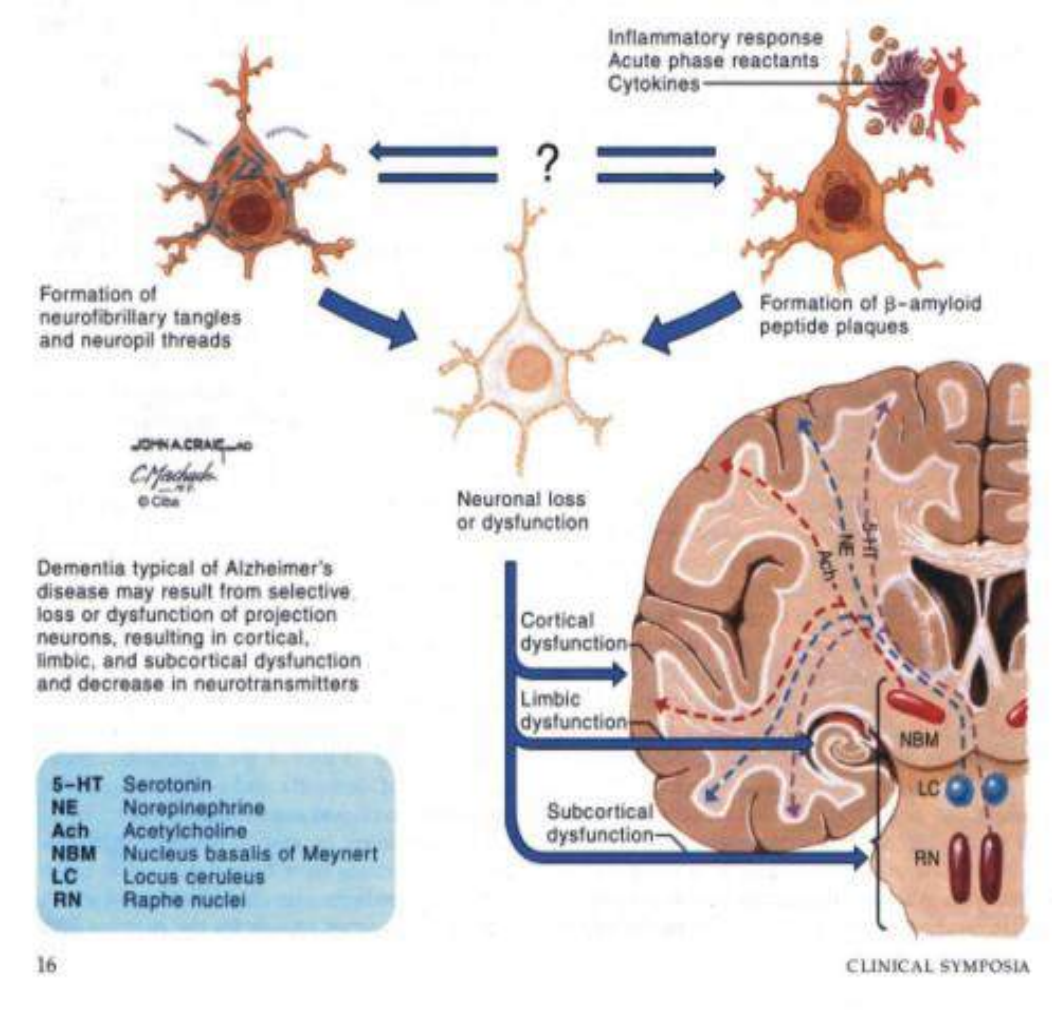
Patologi AD

- SP
- NFT
- N.Loss





Patogenesis AD



Neuron Loss

- Kortek
- Limbik
- Subkortek :

  N.Basal Myenert

  (Acetyl Ch)

  Locus Ceruleus

  (Serotonin)

  Raphe Nucleus

  (Nor Epinefrin)

KLINIS AD

STADIUM AWAL :

1. Gangg. MEMORI :

- Short Memori = ANOMIA = ANOMIC
- Lupa nama benda / istilah
- Lupa Topik bicara , diulang2 , membual
- Lupa Janji , tempat tujuan , letak barang
- Lupa data / daftar belanja
- Long Memori normal

2. GEJALA PSIKIATRIS :

- kurang aktif , tidak cekatan / effisien / lamban , semangat kerja
- kurang tanggap / perhatian / teliti , "egocentris "
- Emosi-affek dangkal, irritabel "tearful "
- Kecemasan , kurang kontrol emosi

STADIUM TENGAH :

- A mnesia
- A fasia
- A gnosia
- A praksia
- A leksia , A grafia

STADIUM LANJUT :

- Amnesia berat: tak kenal diri/keluarga/org
- Afasia berat - Global - mutisme
- Agnosia berat
- Apraxia berat : - tdk dpt makan /minum
  ADL hilang - bedridden
- Paratonic Parkinsonism Chorea
- Inkontinen U/A Epilepsi
- Insomnia Hypersomnia

KRITERIA Dx ALZHEIMER POSSIBLE :

1. Kriteria Demensia positif
2. Variasi onset dan perjalanan
3. Ditemukan penyakit di otak
4. Progresif gejala tidak semua gejala / ada penonjolan salah satu

NINCDS National Institue of Neurologic Communicative Disorders and Stroke

ADRDA Alzheimer's Diseases and Related Disorders Association

KRITERIA Dx ALZHEIMER PROBABLE :

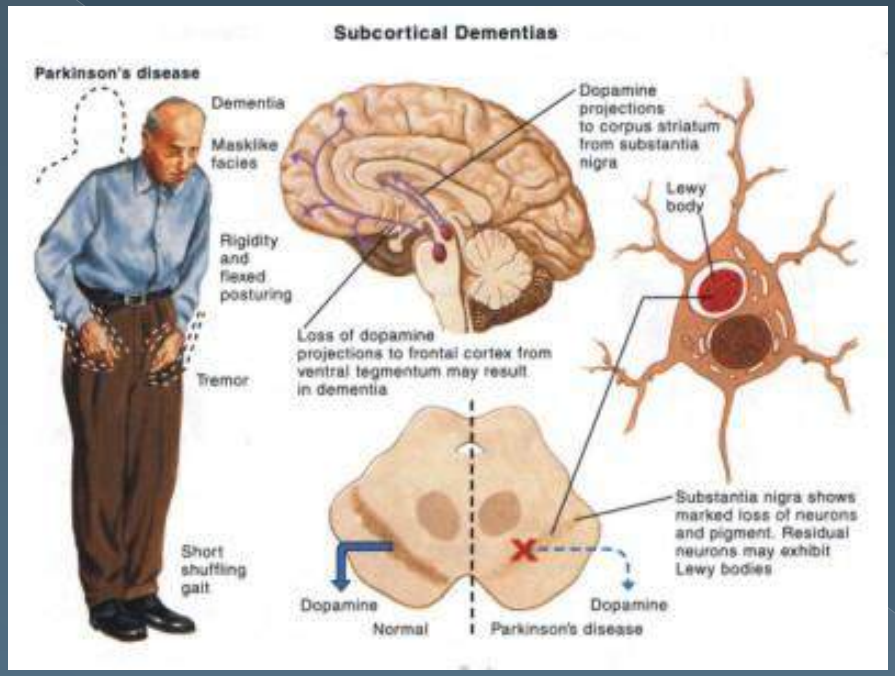
1. Kriteria Demensia positif - Neuropsikologis
2. onset 40 - 90 tahun
3. Defisit memori & kognitif progresif
4. Tidak ada gangguan kesadaran
5. Tidak ada penyakit sistemik / otak

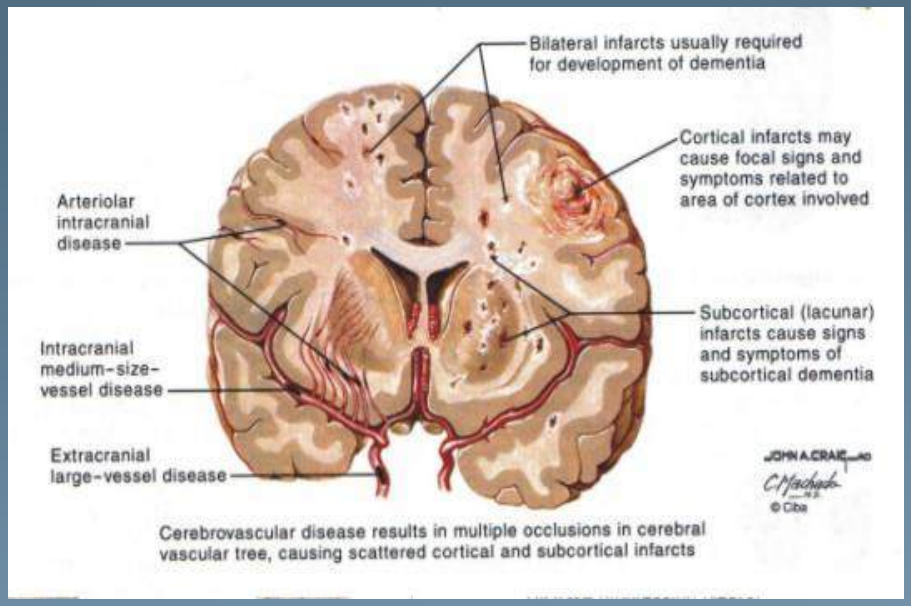
KRITERIA Dx ALZHEIMER PASTI :

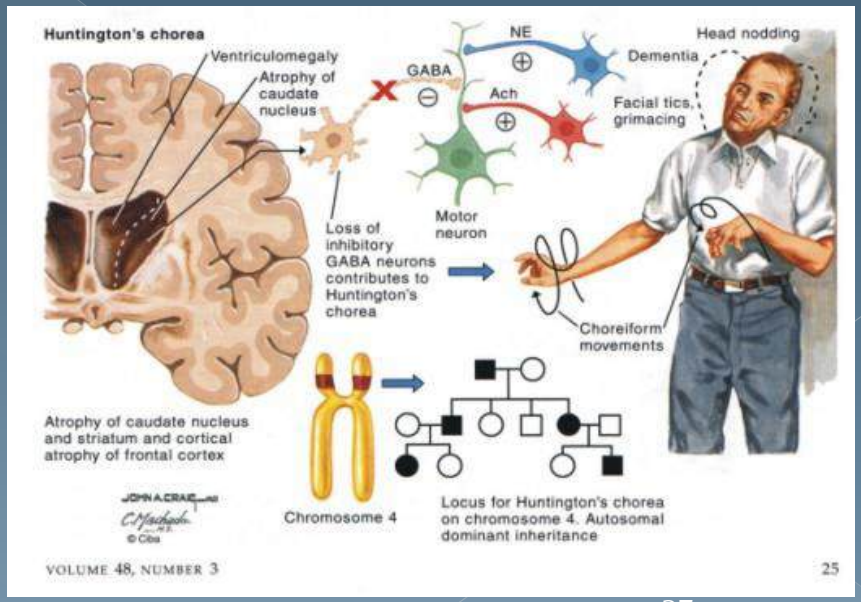
1. Kriteria Demensia Probable +
2. Patologis AD + (biopsi / otopsi)

Dx Diagnosis

1. Pick
2. Creutzfeld Jacob
3. Huntington
4. Parkinson-Demen-Comp.
5. Multi Infark D
6. NP Hidrosefalus







PEMERIKSAAN ALZHEIMER :

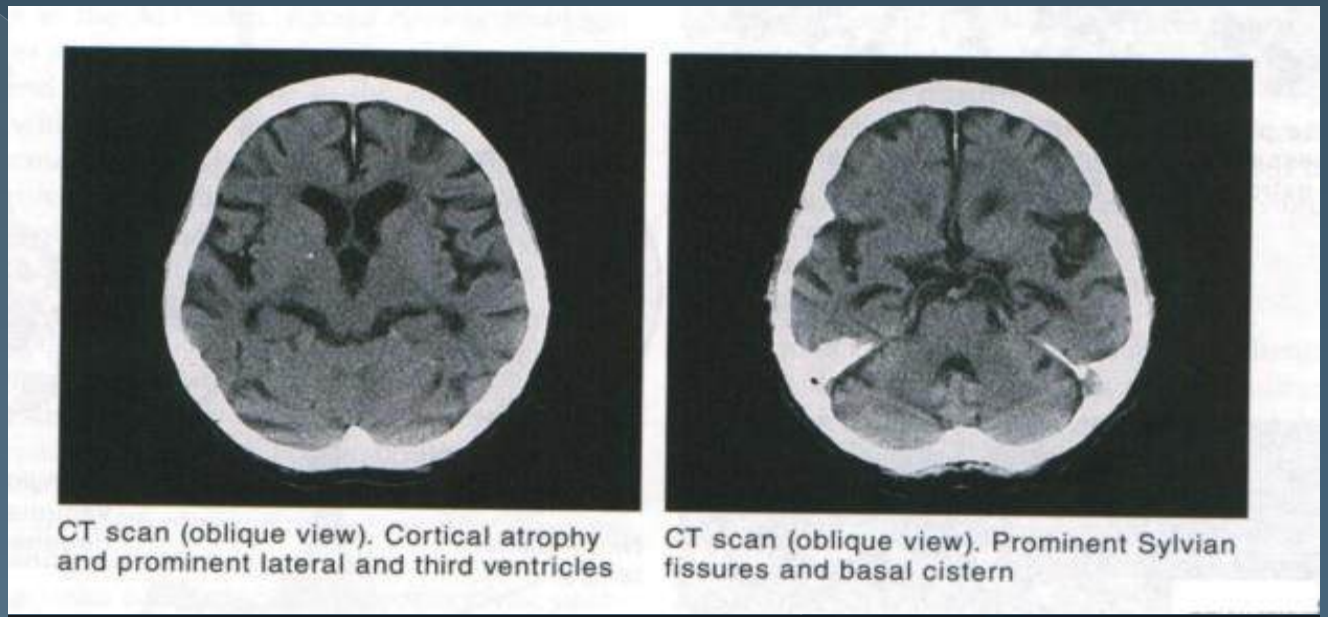
1. Neuropsikologis (MMSE, CDT, dst)
2. Neurologis
3. Laboratorium
4. Neuro - Radiologi
5. Neuro - Fisiologi
6. Neuro - Kimiawi
7. Neuro - Patologi

PEMERIKSAAN ALZHEIMER :

Laboratorium :

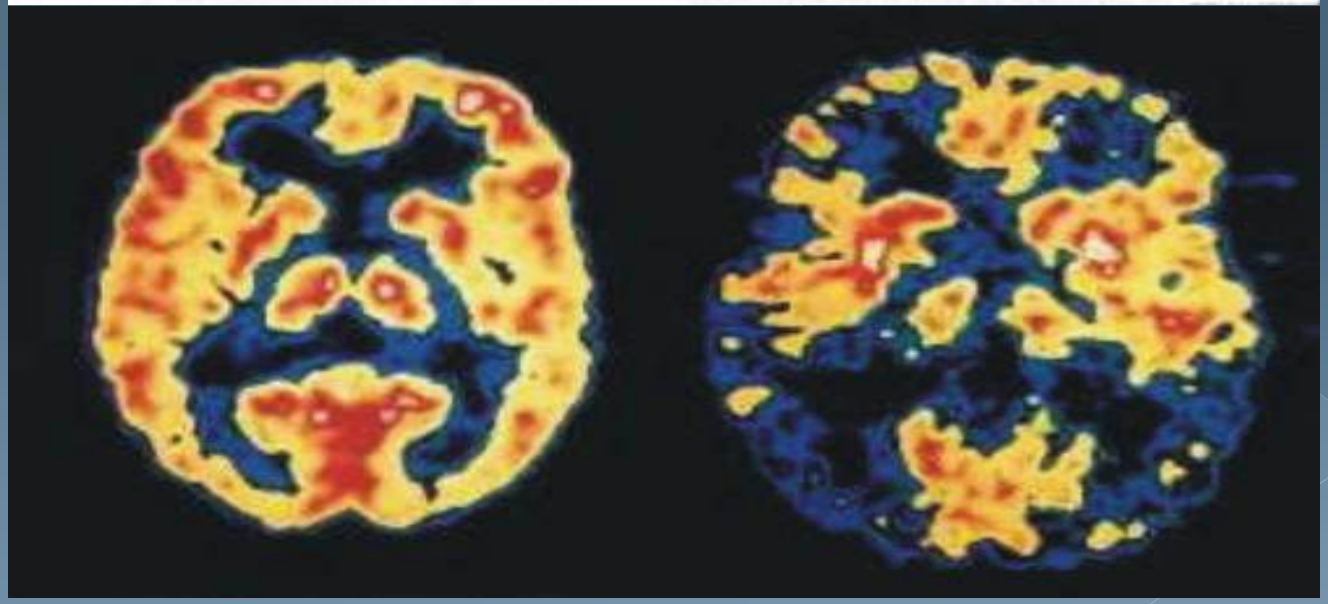
1. Darah : - Hematologi Serologi RFT LFT
   - T3T4TBK - B12 - As Folat - Obat
2. Urine : peny.ginjal , liver , obat
3. LP : Infeksi , SAH , Lues
4. X Foto Thorac : Infeksi Tumor COPD
5. X Foto Skull : SOP TIK ↑ Calcifikasi
6. CT Scan / MRI
7. EEG , Evoked Potential
8. PET , SPECT , Cystenografi

CT Scan & PET



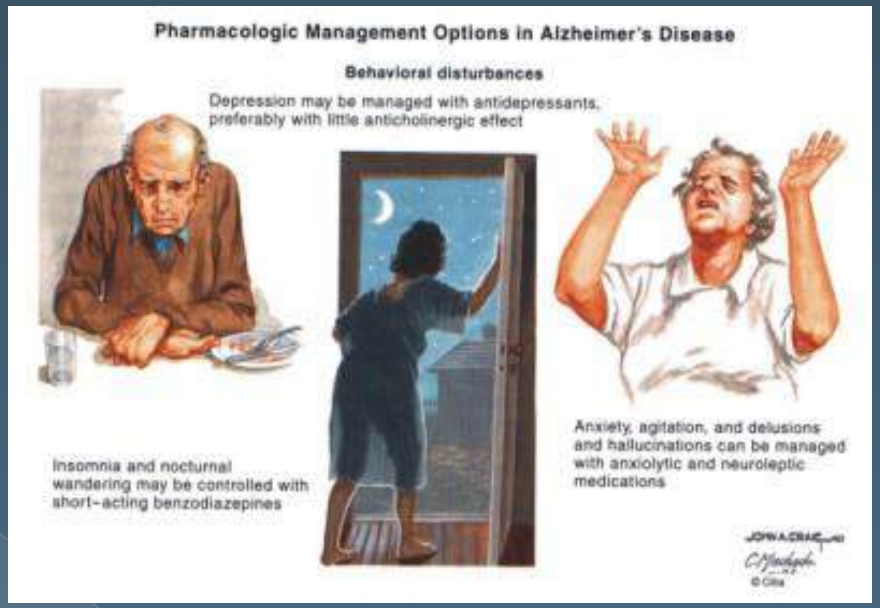
CT scan (oblique view). Cortical atrophy and prominent lateral and third ventricles

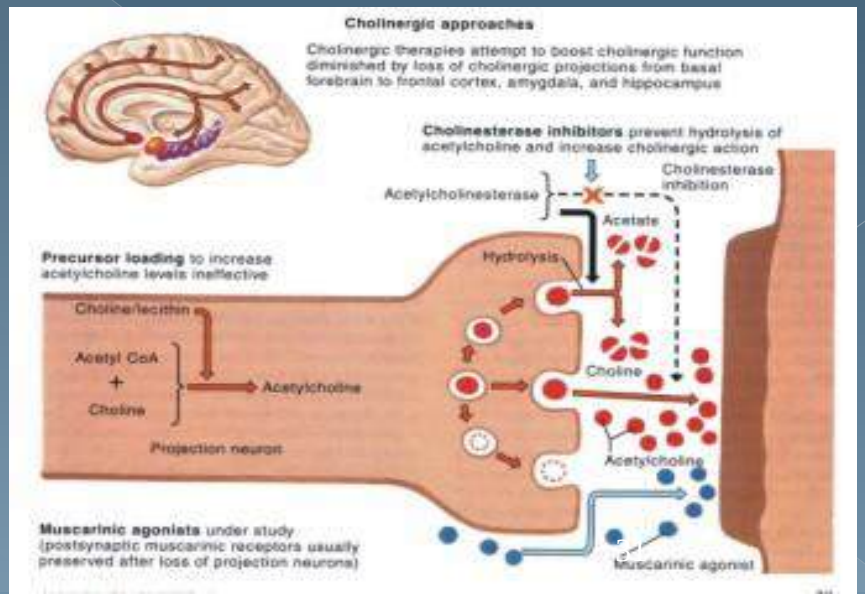
CT scan (oblique view). Prominent Sylvian fissures and basal cistern



Terapi Cholinergic

1. Precursor Cholinergik
2. ↑ Pelepasan Ach
3. Anti Cholinesterase
4. Muscarinic Agonist
5. Nicotinic Agonist





Tx SIMPTOMATIS

TARGET :

A. Mengurangi Kecemasan

B. Menaikan mood

C. Mengurangi Paranoid , Psikosis

D. Kontrol tingkah laku

E. Memperbaiki gaya hidup

Tx LINGKUNGAN

TARGET :

A. Mengganti fungsi yg hilang :

ADL mandi makan minum baju , Hearing aid

B. Aktivitas lingkungan :

Rumah perabot sederhana , sedikit , tdk bahaya

Berkunjung famili / teman / hiburan

C. Mengurangi Cacad

Fisioterapis , Okupational dll RM

Tx LINGKUNGAN

LAMA & HARAPAN HIDUP

@ LAMA : 2 - 16 tahun

@ Rata2 : 5 - 9 tahun

@ Umur : 53 - 91 tahun

Rata2 : 78,4 tahun

Laki : 67,5 tahun

Wanita : 66,8 tahun

SEBAB KEMATIAN

@ Bronchopneumonia : AD 72 % - 40,7 %

@ Peny.Jantung : 31,9 %

Wanita : 82,6 %

Laki : 17,9 %

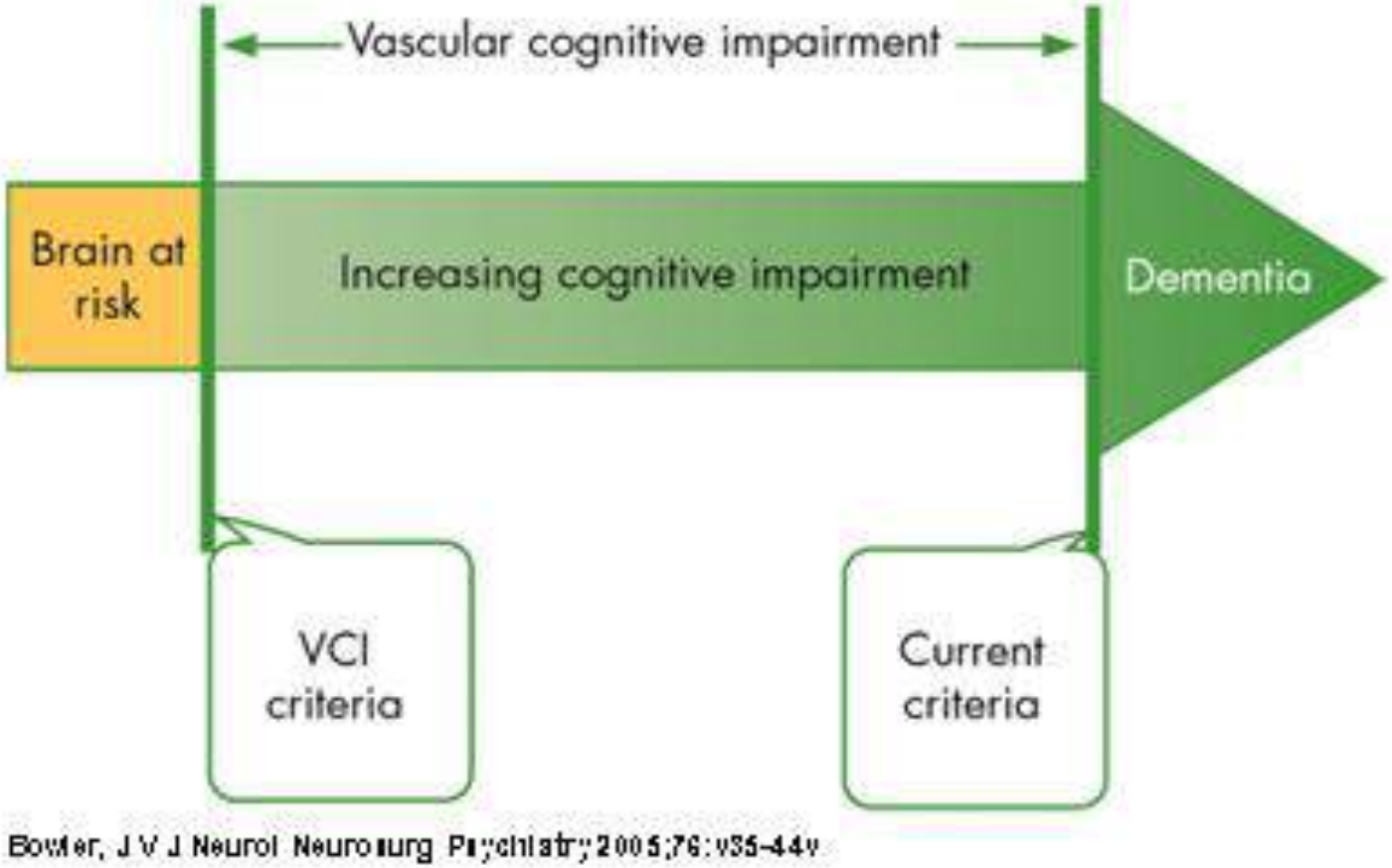
@ CVA : 33 - 73 %

@ Neoplasma : 8,4 %

@ Embolism paru : 5,6 %

Dementia Vaskuler

THE EVALUATION OF VASCULAR COGNITIVE IMPAIRMENT



Bowler, J V J Neurol Neurosurg Psychiatry 2005;76:v35–44v

PREVALENSI & INSIDENSI
(Erkinjuntti 2004)

Prevalensi: 1.2 - 4.2% dalam > 65 tahun

Insidensi VaD per 1000 orang / tahun:

65-69 thn : 0.7%
70-74 thn : 1.2%
75-79 thn : 3.5%
80-84 thn : 5.9%
85-89 thn : 6.1%
> 90 thn : 8.1%

TIPE DEMENTIA (453 px-stroke)

Dementia 26.3% **Types of dementia**	**Patients (%)**
Vascular dementia	57
Alzheimer's disease	39
Other dementias	4

Desmond DW *et al*. Neurology 2000; 54: 1124–31

MODIFIED HACHINSKI ISCHEMIC SCORE (Rosen 1980)

Feature	Score (points)*	
♦ Abrupt onset of symptoms	2	
♦ Stepwise deterioration		1
♦ Fluctuating course		2
♦ Nocturnal confusion		1
♦ Relative preservation of personality	1	
♦ Depression		1
♦ Somatic complaints		1
♦ Emotional lability		1
♦ History or presence of hypertension	1	
♦ History of stroke	2	
♦ Evidence of associated atherosclerosis		1
♦ Focal neurologic symptoms		2
♦ Focal neurologic signs		2

* total score < 4 : primary dementia (Alzheimer's disease)
total score 4-7 : indeterminate (mixed type)
total score > 7 : vascular dementia

Kriteria Demensia Vaskuler (DV)

Gambaran klinik DV :

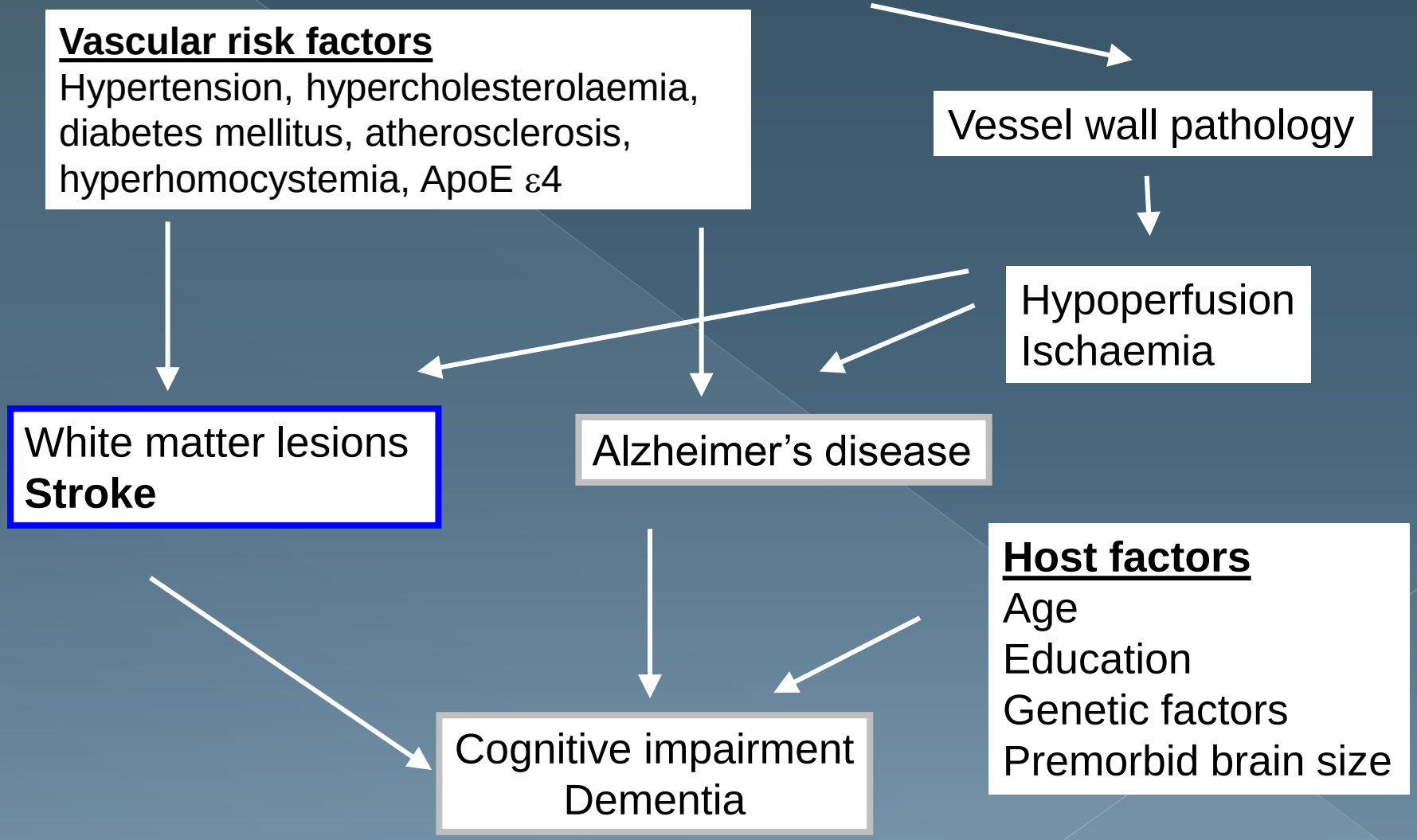
Berdasar skala iskemik (Hachinski et al, 1975)

- **Onset tiba tiba**
- **Didahului riwayat stroke**
- **Perjalanan klinis berlangsung fluktuasi**
- **Gejala fokal neurologi +**
- **Deteriorisasi bertingkat**
- **Kepribadian relatif baik**
- **Depresi**
- **Keluhan somatik**
- **Emosi labil**
- **HT**
- **asosiasi aterosklerosis**

Vascular risk factors

- Hypertension
- Cardiac abnormalities
- Atrial fibrillation
- Myocardal infarction
- Coronary heart disease
- Obesity
- ApoE ε4
- Hypercholesterolaemia
- Diabetes mellitus
- Atherosclerosis
- Smoking
- Advanced age
- Low education

Possible mechanisms



PATHOGENIC MECHANISMS POSSIBLY INVOLVED IN SUBCORTICAL VASCULAR DEMENTIA

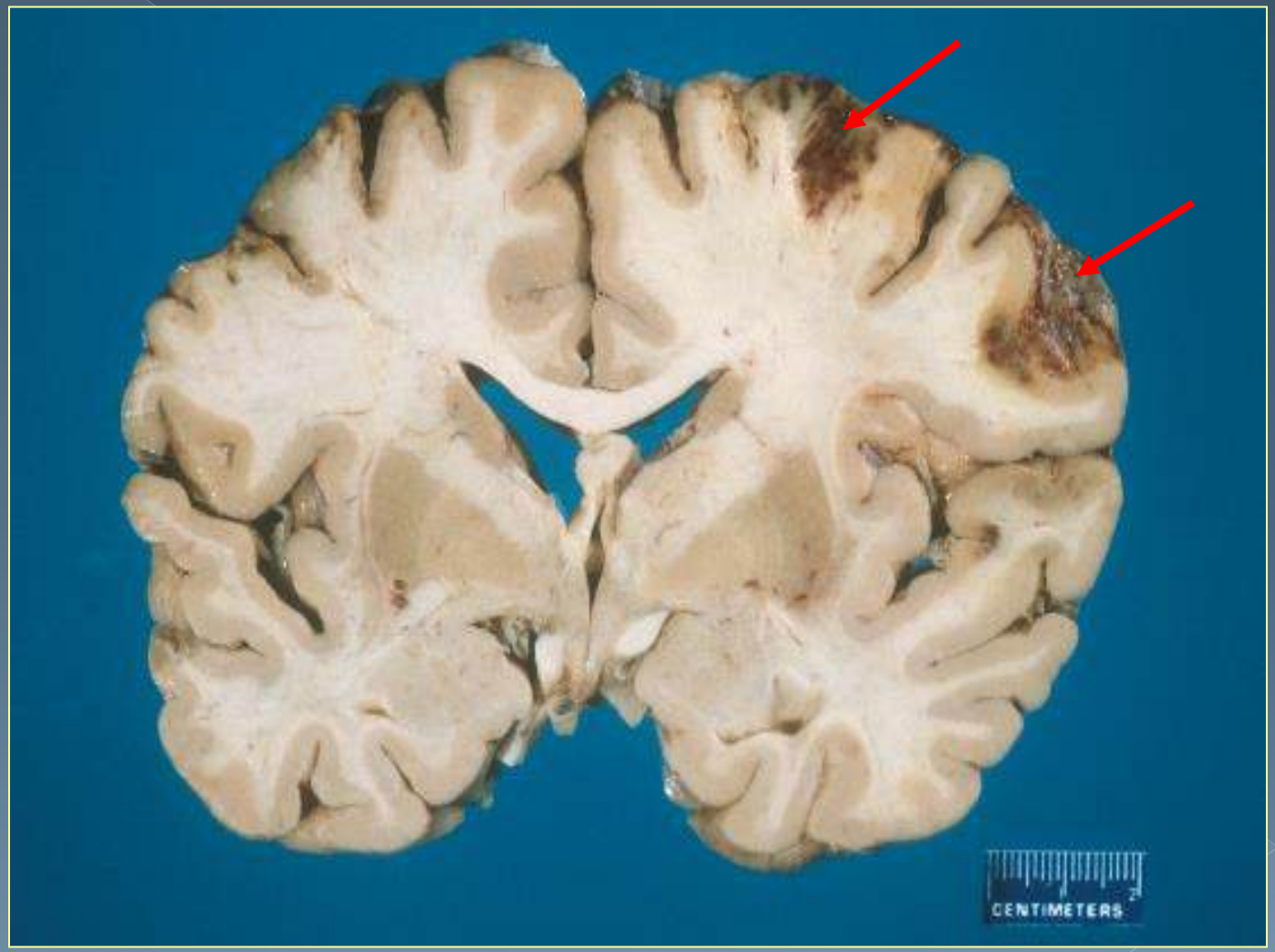
TWO MAJOR FORMS OF CVD

Large-vessel disease → Large cortical and subcortical infarcts

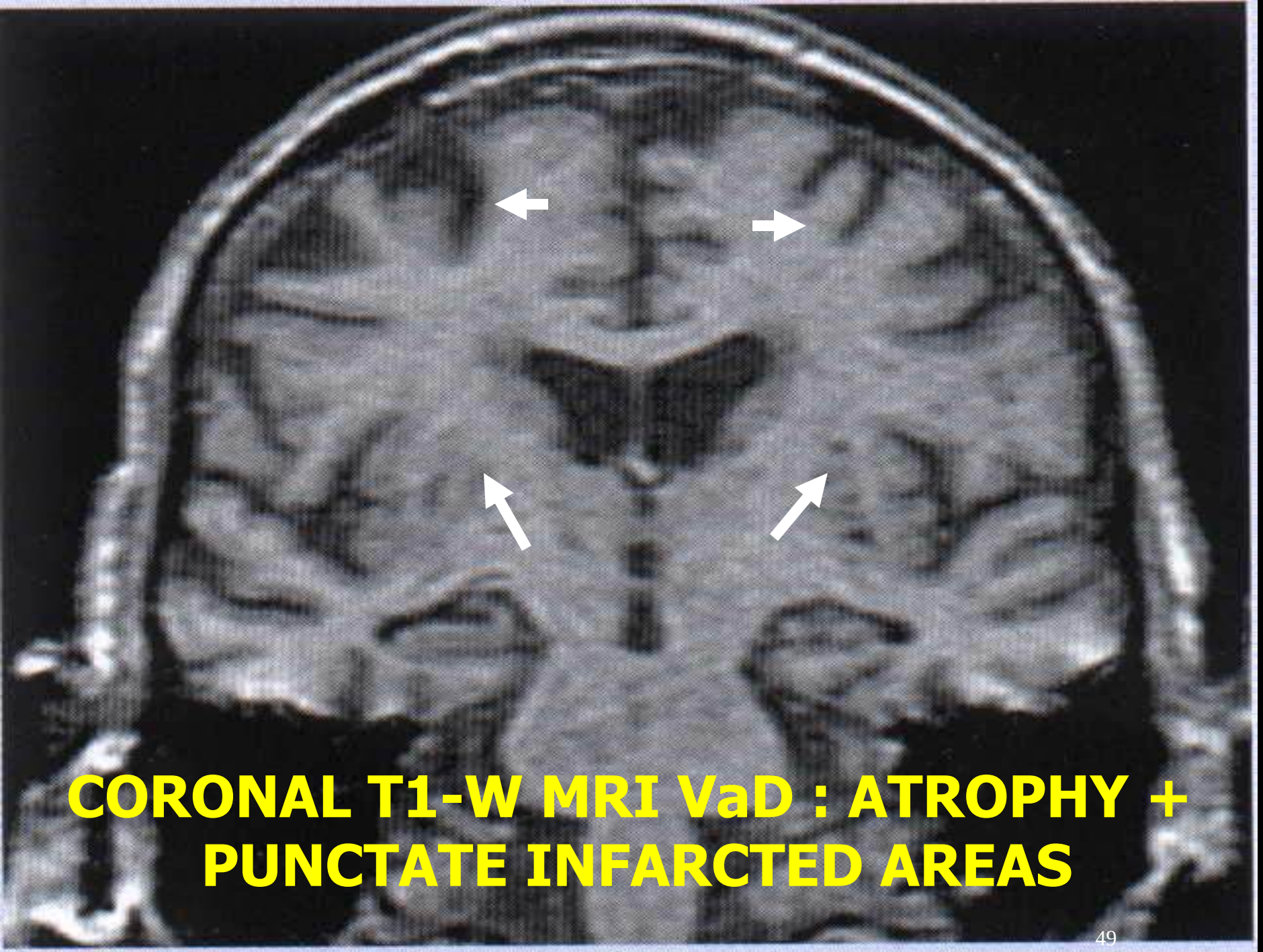
Small-vessel disease → Small subcortical infarcts (lacunes)

Small-vessel disease → Diffuse white matter lesions

Large cortical infarcts



Small infarcts in the basal ganglia



CORONAL T1-W MRI VaD : ATROPHY + PUNCTATE INFARCTED AREAS

PROGNOSIS

Brodaty et al. Arch Neurol 1993 ; 50 : 643

	VaD	AD
FIVE YEAR MORTALITY RATE	63.6%	31.8%
NURSING HOME ADMISSION RATE	31.8%	20.6%

« Justification for treatment »

DRUGS FOR DEMENTIA AND COGNITIVE IMPAIRMENT (Cochrane review 2005)

Drugs	Conclusions	Effect
ASA	No evidence ASA is effective	-
LecithiN	No support for dementia	-
Piracetam	No benefit	-
Propentofylline	Limited evidence of efficacy	-
Selegiline	Disappointing effect	-
Statins	No good evidence of recommendation	-
TENS (head)	No possible benefit	-
Vitamin B12	Insufficient evidence of benefit	-
Vitamin B6	No evidence of benefit	-
Vitamin E	Insufficient evidence of efficacy	-
HRT	Little evidence of effect in postmenoausal women	±
Hydergine	Uncertain efficacy	±
Ginkgo biloba	Inconsistent evident of improvement	±
Nimodipine	Some benefit	+
Nicergoline	Generally consistent results	+
CDP-choline	Some evidence effective in short or medium term	+
Rivastigmine	Beneficial for AD;some evidence of benefit for VaD	+
Galantamine	Beneficial for AD & VaD	+
Donepezil	Beneficial for AD & VaD	+
Memantine	Small beneficial effect	+

PHARMACOLOGIC AGENTS FOR REDUCING SIGNS OF DEMENTIA

Characteristic	Donepezil	Rivagstigmine	Galantamine	Memantine
Time to max. serum concentration (hr)	3-5	0.25-2	0.5-1	3-7
Absorption affected by food	No	Yes	Yes	No
Serum half life (hr)	70-80	2*	5-7	60-80
Protein binding (%)	96	40	0-20	45
Metabolism	CYP2D6, CYP3A4	Non-hepatic	CYP2D6, CYP3A4	Non-hepatic
Dose (initial/max)	5 mg/d-10 mg/d	2 X 1.5 mg-2 X 6 mg	2 X 4 mg-2 X 12 mg	5 mg/d-2 X 10mg
Mode of action	Cholinesterase Inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor+allosteric nAChR modulator	NMDA-receptor antagonist
Side effects:				
Nausea (%)	17	48	37	Hallucination (2)
Vomiting	10	27	21	Confusion (1.3)
Diarrhea	17	19	12	Dizziness (1.7)
				Headache (1.7)
				Tiredness (1.0)

* Rivastigmine is a pseudo-irreversible acetylcholineesterase inhibitor that has an 8-hr half-life for the inhibition of acetylcholineesterase in the brain. (Cummings 2004)

MINI-MENTAL STATE EXAM (MMSE)

(modifikasi FOLSTEIN)

Nama Pasien:……(Lk / Pr) Umur:……Pendidikan……Pekerjaan:……

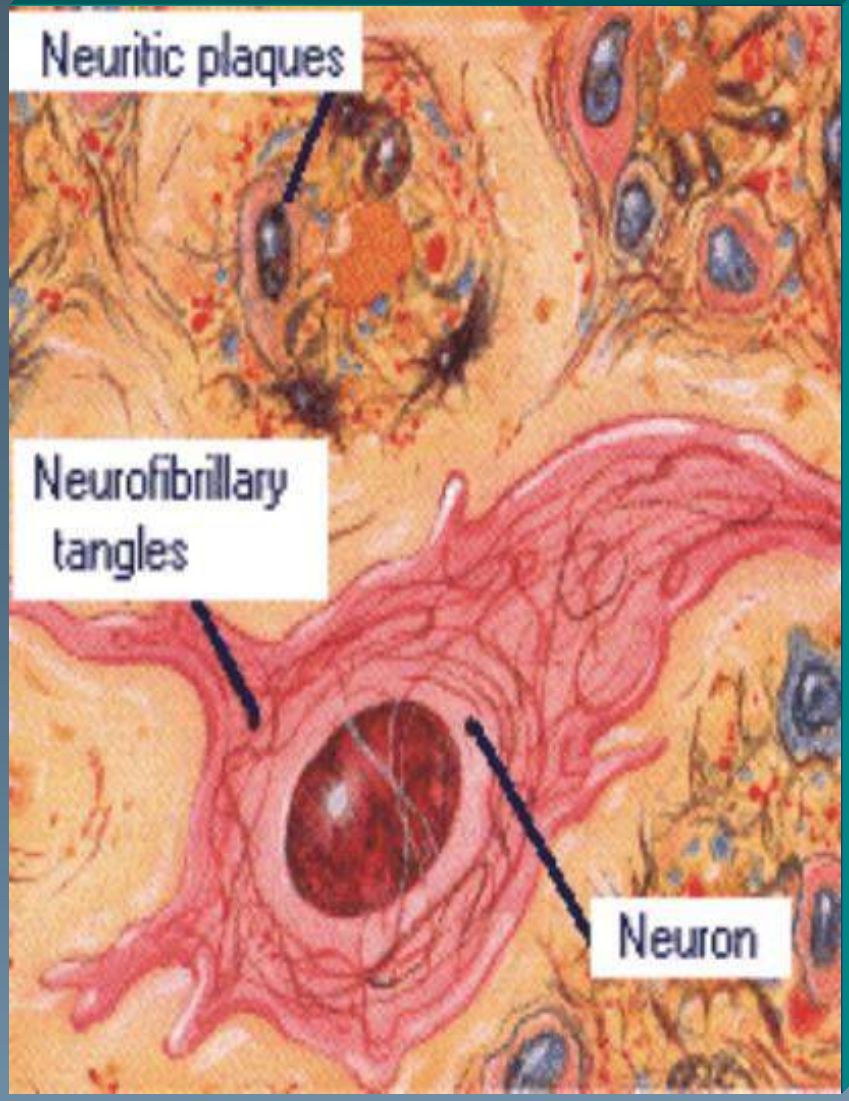
Riwayat Penyakit: Stroke( ) DM( ) Hipertensi( ) Peny.Jantung( ) Peny. Lain……

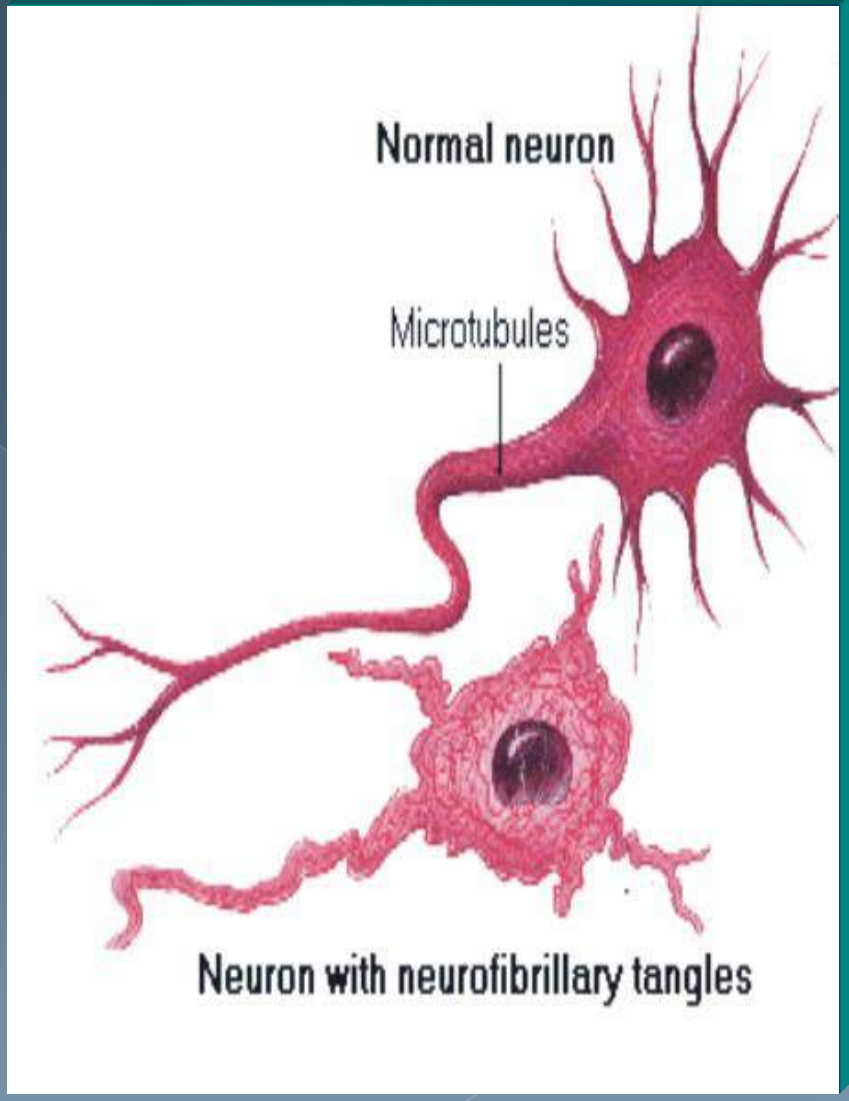
Pemeriksa:…… Tgl ……

Item	Tes	Nilai maks.	Nilai
	ORIENTASI		
1	Sekarang (tahun), (musim), (bulan), (tanggal), hari apa?	5	…
2	Kita berada dimana? (negara), (propinsi), (kota), (rumah sakit), (lantai/kamar)	5	…
	REGISTRASI		
3	Sebutkan 3 buah nama benda (**jeruk, uang, mawar**), tiap benda 1 detik, pasien disuruh mengulangi ketiga nama benda tadi. Nilai 1 untuk tiap nama benda yang benar. Ulangi sampai pasien dapat menyebutkan dengan benar dan catat jumlah pengulangan	3	…
	ATENSI DAN KALKULASI		
4	Kurangi 100 dengan 7. Nilai 1 untuk tiap jawaban yang benar. Hentikan setelah 5 jawaban. Atau disuruh mengeja terbalik kata " WAHYU" (nilai diberi pada huruf yang benar sebelum kesalahan; misalnya uyahw=2 nilai)	5	…
	MENGINGAT KEMBALI (***RECALL***)		
5	Pasien disuruh menyebut kembali 3 nama benda di atas	3	…
	BAHASA		
6	Pasien diminta menyebutkan nama benda yang ditunjukkan (pensil, arloji)	2	…
7	Pasien diminta mengulang rangkaian kata :" **tanpa kalau dan atau tetapi** "	1	…
8	Pasien diminta melakukan perintah: " Ambil kertas ini dengan tangan kanan, lipatlah menjadi dua dan letakkan di lantai".	3	…
9	Pasien diminta membaca dan melakukan perintah "Angkatlah tangan kiri anda"	1	…
10	Pasien diminta menulis sebuah kalimat (spontan)	1	…
11	Pasien diminta meniru gambar di bawah ini 	1	…
	Skor Total	30	…

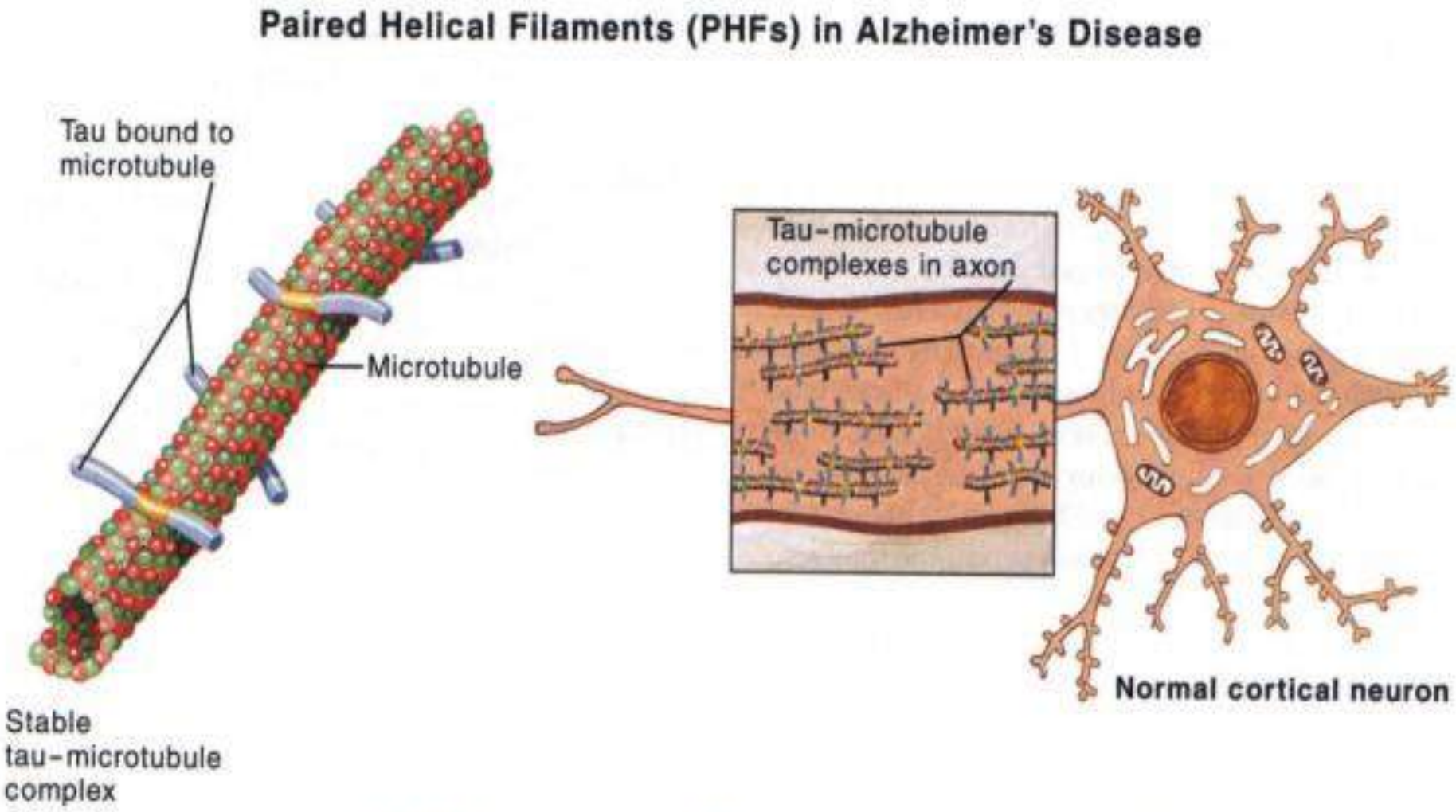
Terima Kasih

Patologi SP & NFT

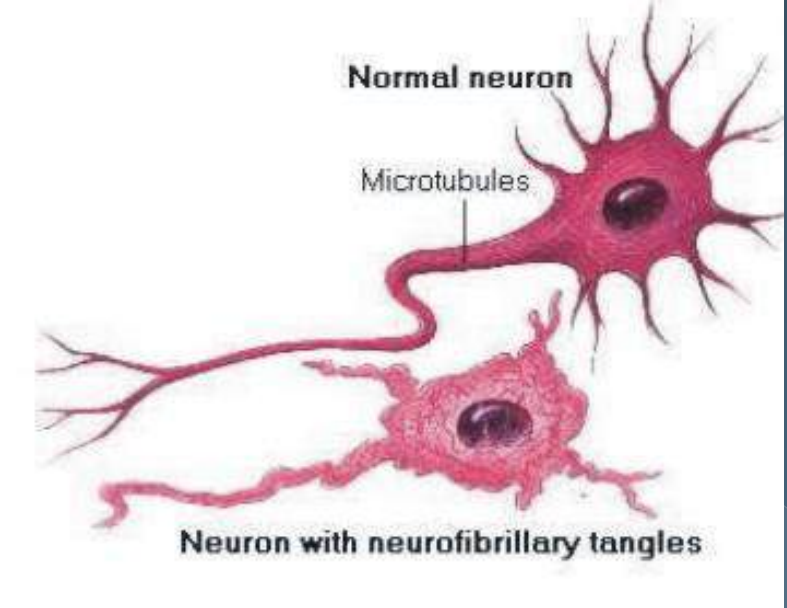


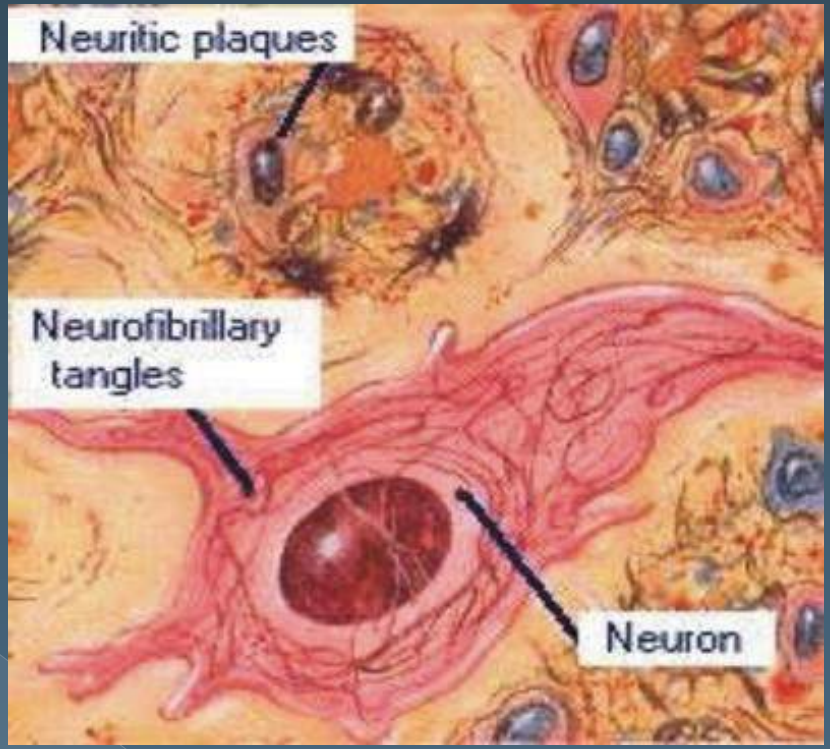


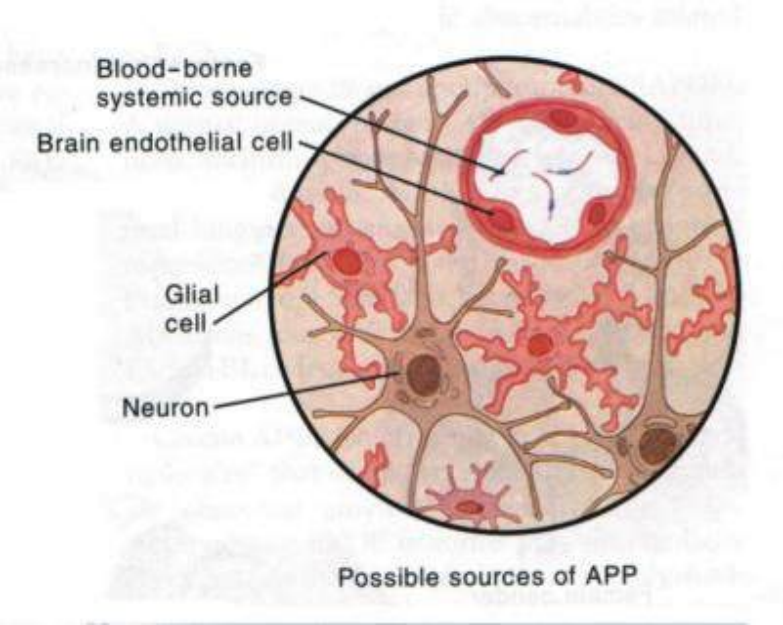
Neuroskeleton

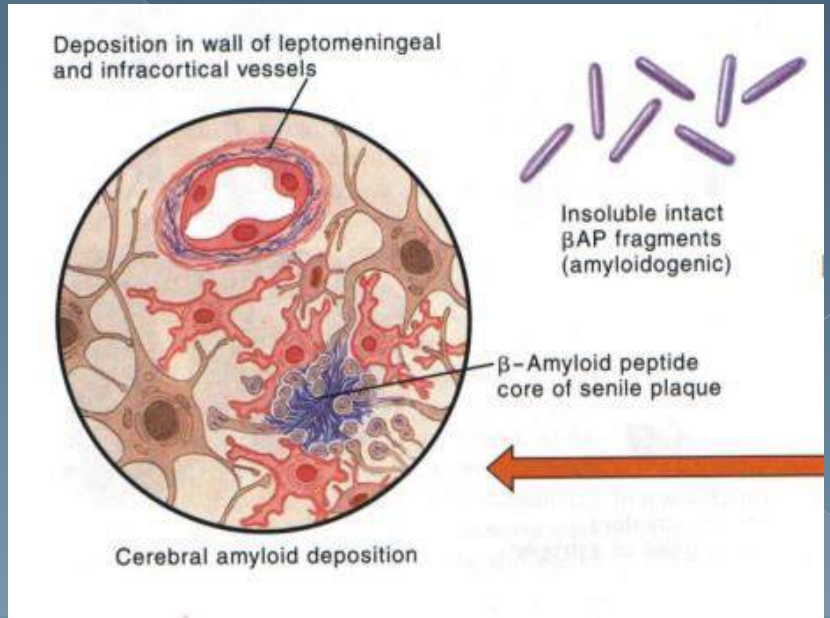


NFT & SP

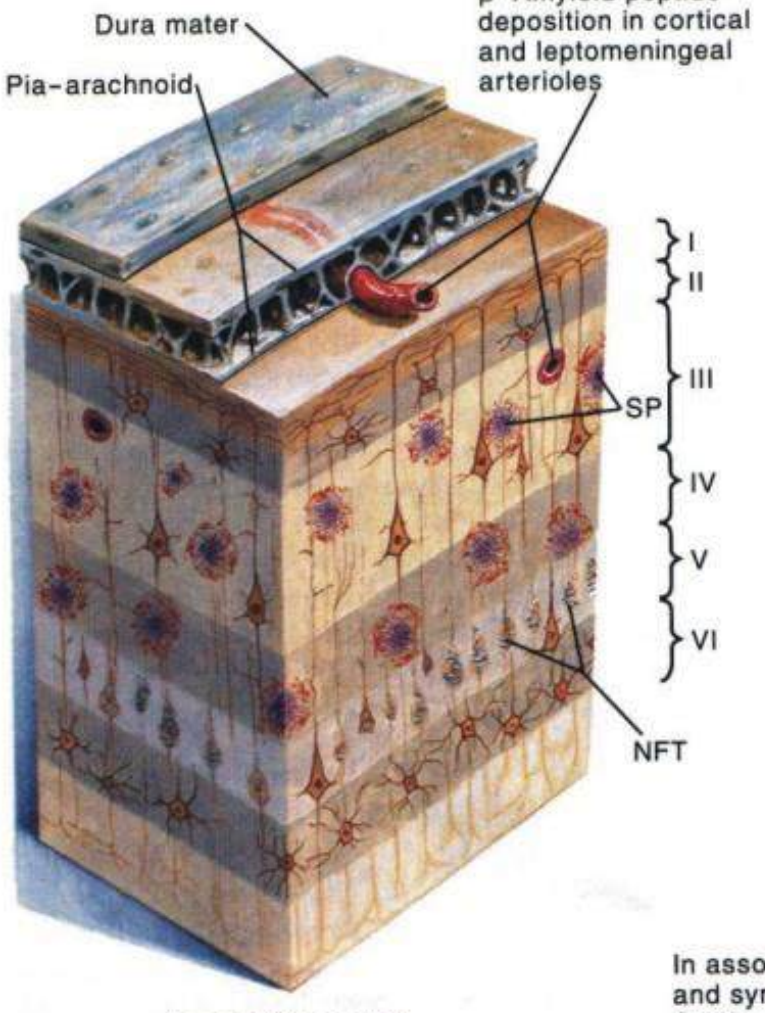

Normal neuron
Microtubules
Neuron with neurofibrillary tangles


Neuritic plaques
Neurofibrillary tangles
Neuron

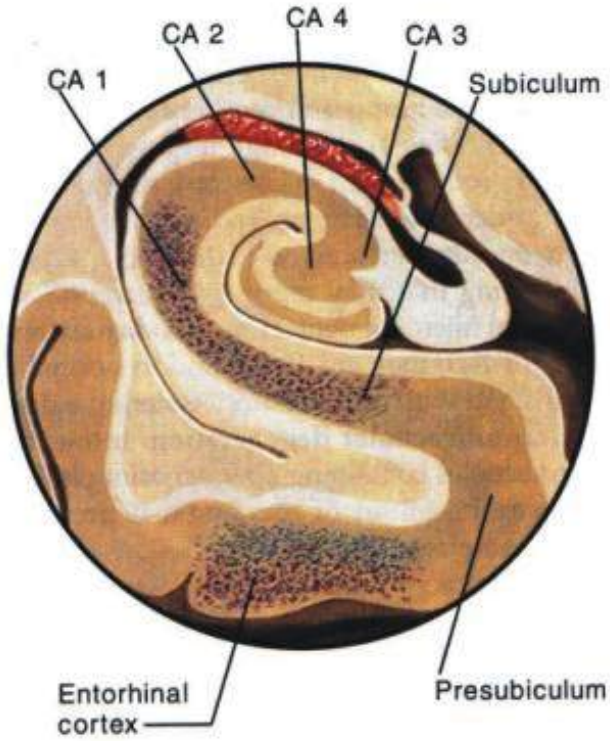

Blood-borne systemic source
Brain endothelial cell
Glial cell
Neuron
Possible sources of APP


Deposition in wall of leptomeningeal and infracortical vessels
Insoluble intact βAP fragments (amyloidogenic)
β-Amyloid peptide core of senile plaque
Cerebral amyloid deposition

Distribusi NFT - βAP



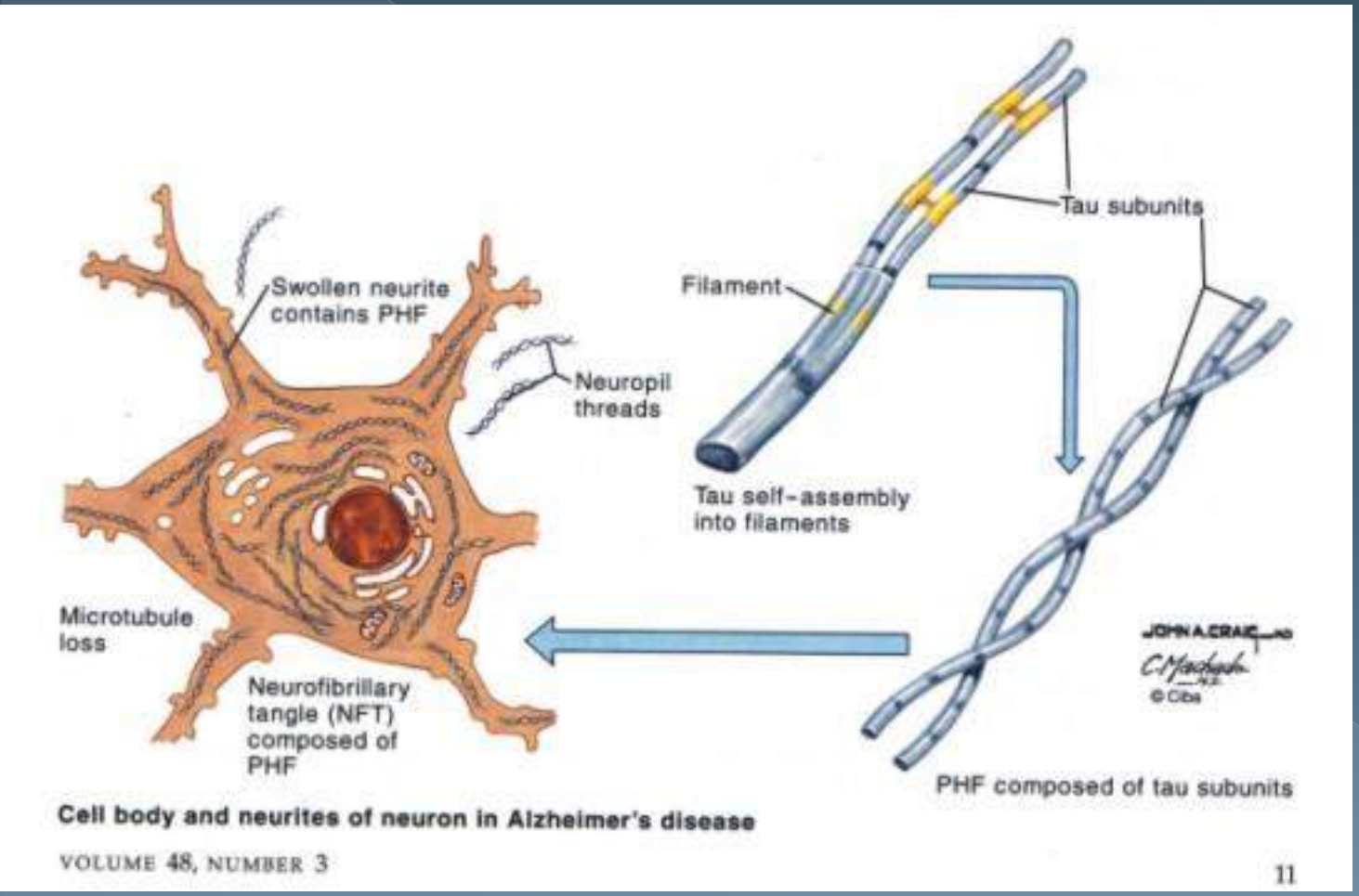
Association cortex



In hippocampus, neurofibrillary tangles, neuronal loss, and senile plaques primarily located in layer CA 1, subiculum, and entorhinal cortex

In association cortex, neurofibrillary tangles (NFTs) and synaptic and neuronal loss predominate in layer V. Senile plaques (SPs) occur in more superficial layers

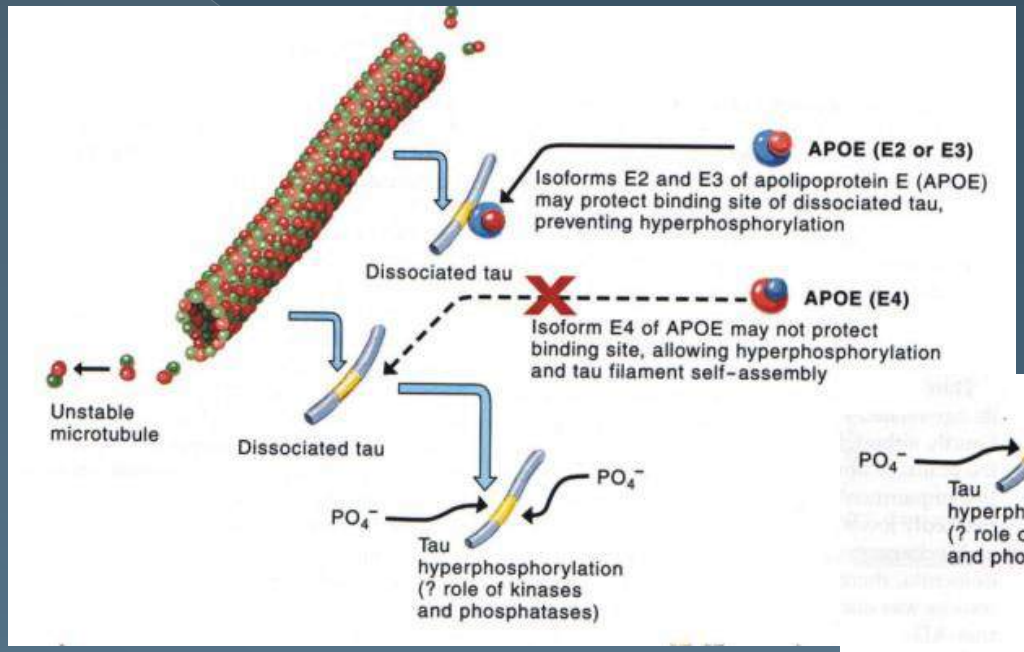
Neuro Fibrilary Tangle NFT - PHF



Cell body and neurites of neuron in Alzheimer's disease

Pair Helical Filament tersusun dari Protein " Tau "

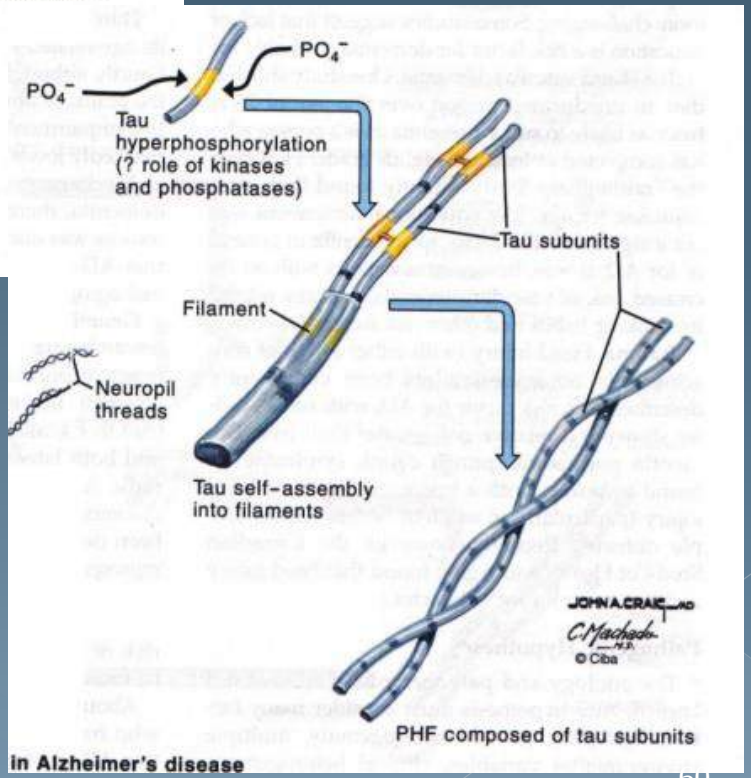
Protein “ Tau “ - APO E4 & PHF



APO E2 & E3 Normal

Chromosom 19

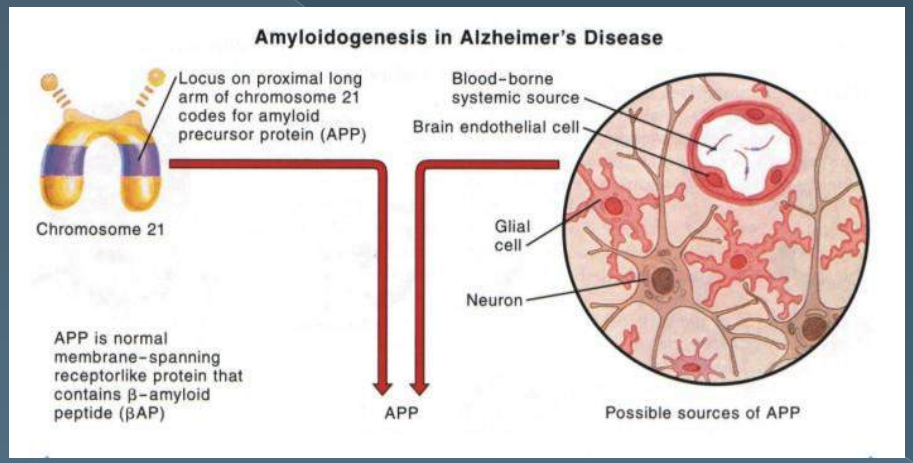
APO E4 Abnormal



Protein “ Tau “

Hiperfosforilisasi

APP - β AP -

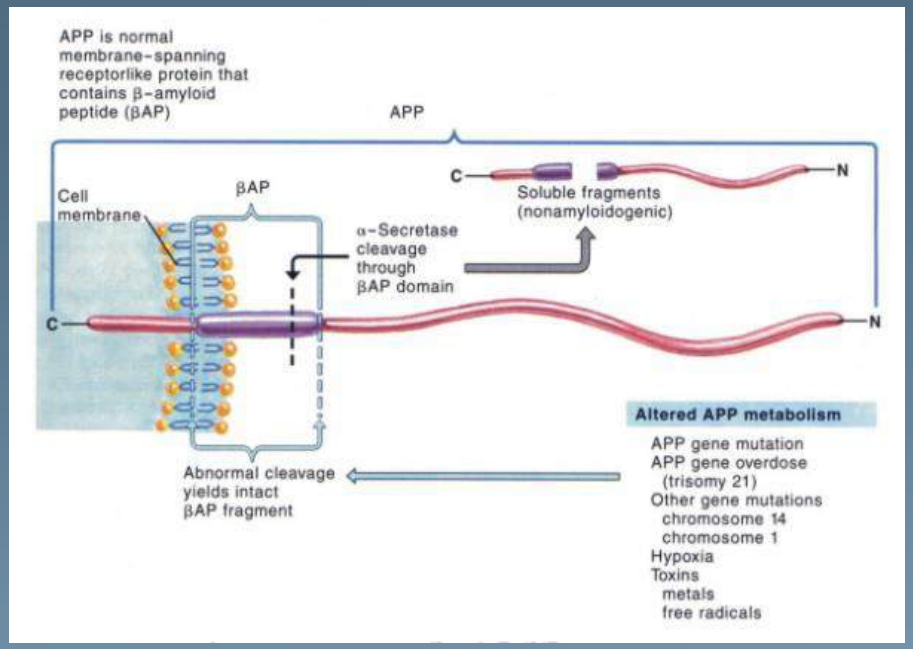


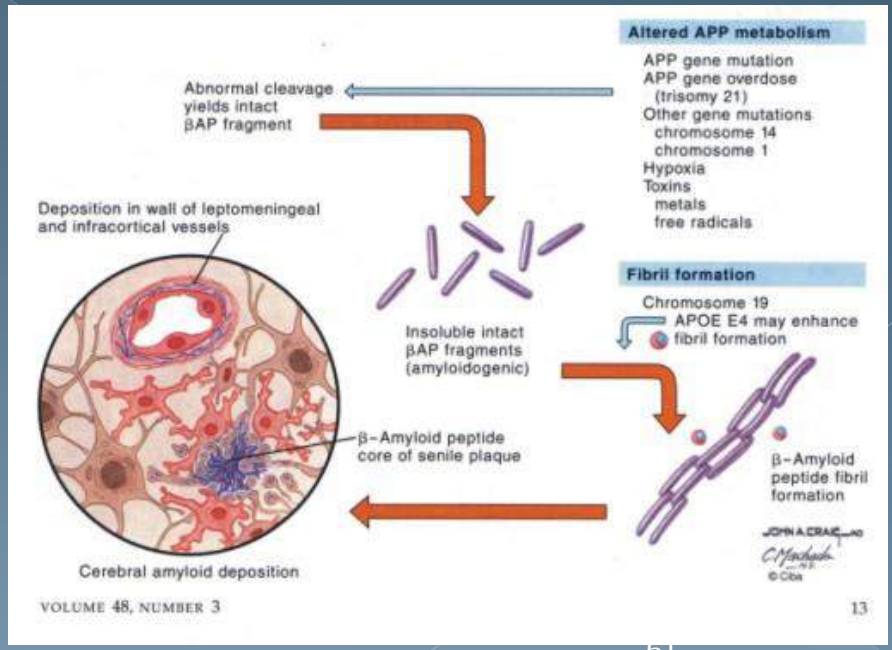
Chromosom 21

?A myloid

P recursor

P rotein





B1. GEJALA MEMORI :

- Gangg. Short Memori lebih berat
- Gangg. " LONG TERM MEMORI "
- ANOMIA = ANOMIK AFASIA
- Gangg. Retention , Recall :

  Lupa data kecil / daftar / topik
- AKALKULIA / DYSKALKULIA
-  " SENILE AMNESTIC STATE "

B2. AFASIA / DYSFASIA :

- Anomia Anomik Afasia 100 %
- Palilalia , Echolalia 100 %
- Parafasia Semantik : arti kata 83 %
- Parafasia Phonemik : ucapan salah
- Alexia / Dyslexia : 77 %
- Apraksia , Agrafia 61,5 %
- Dialoqlalia / Psuedo-dialoq
- Logoclonia : putus2 , loncat ok lupa kata

B3. AGNOSIA :

- Visual Agnosia / Visuo-Spatial
- Color Agnosia
- SEMANTIK Agnosia : Guna barang
- Autopagnosia / Finger Agnosia
- PROSOPAGNOSIA : " MIRROR SIGN "
- " WANDERING "
- Auditiv-Agnosia

B4. APRAKSIA :

- Contruksional Apraxia : salah letak
- Ideasional Apraxia : Kegunaan ?
  Berbahaya : keliru pasang alat listrik
  Kompor gas
- Dressing Apraxia
- Echopraxia

B5. PSIKIATRI :

- Tidak tenang / gelisah / Agitasi
- Emosi labil : - Explosive Crying / tertawa
- Pseudo afektiv Hyperpathia
- Euphoria , Logorrhea , Confabulasi
- Abulia , Depresif
- Curiga Cemburu Permusuhan
- Paranoia , Paranoid
- Sulit rencana /bedakan /keputusan

B6. TINGKAH LAKU :

- ADL menurun : mandi rambut pakaian
- Salah pakai alat makan / minum
  Akhir harus disuap , gizi menurun
- Sikap fleksi gen., Marche apetit pas
- Paratonic Rigid, Inkontinen U/A
- Parkinsonism 45% , Chorea 27%
- Epilepsi 75% Grand 44%, Abscen 64%
- Insomnia / Hypersomnia / Bulimia

Terapi Cholinergic

1. Precursor Cholinergik : Cholin Lecithin Carnitin
2. ↑ Pelepasan Ach :

   Linopiridin Bespiridin 4-Aminopiridin
3. Anti Cholinesterase
   - Physostgmin - Scopolamin
   - **TACRINE :** 1996 FDA 40 - 80 mg/hr , SE >>
   - **DONEPEZIL HCl :** 1996 FDA 1x 5 -10 mg
4. Muscarinic Agonist : Bethanicol . Arecoline
5. Nicotinic Agonist : Nicotine α Bungorotoxin

Terapi Neurotransmitter lain

1. Besipiridin HP 749 : Multi modal
2. D-Cyclosterin : ↑ Glutamat
3. Glycin Agonist : NMDA
4. Milacemide : Pro-Drug Glycine
5. Tyrosine : Precursor Dopamine
6. Trypthopan : Precursor Serotonine
7. Bromocryptin
8. Ldopa
9. Naloxone
10. Naltexan

NOOTROPHIC :

Dihydro Ergotoxine Piracetam Pyritinol

ENDOCRINE :

ACTH TRH Vasopressin

MAO Inhibit Estrogen

ANTI OKSIDAN :

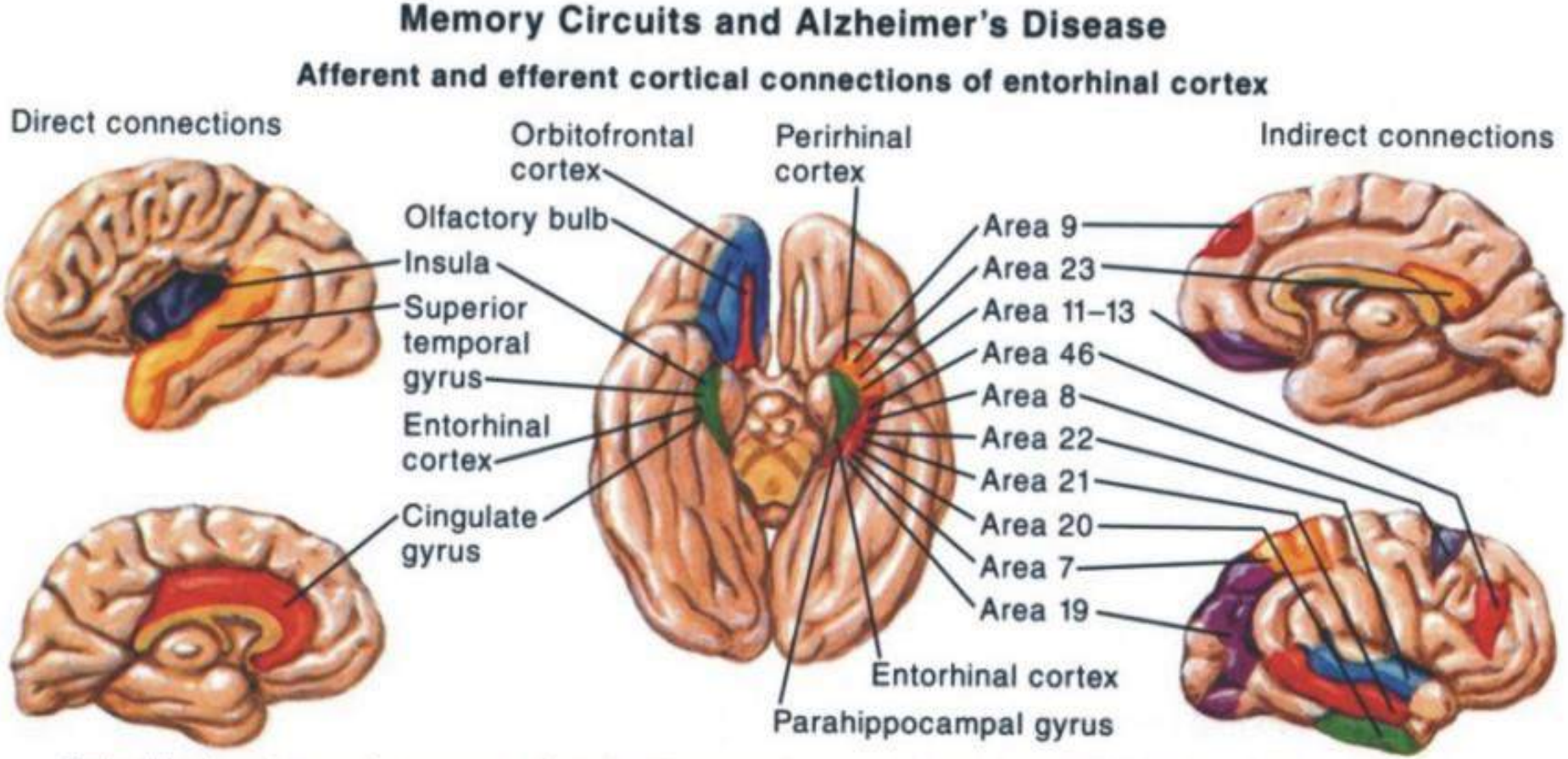
Vitamine E

Selegiline

Penyebab Demensia

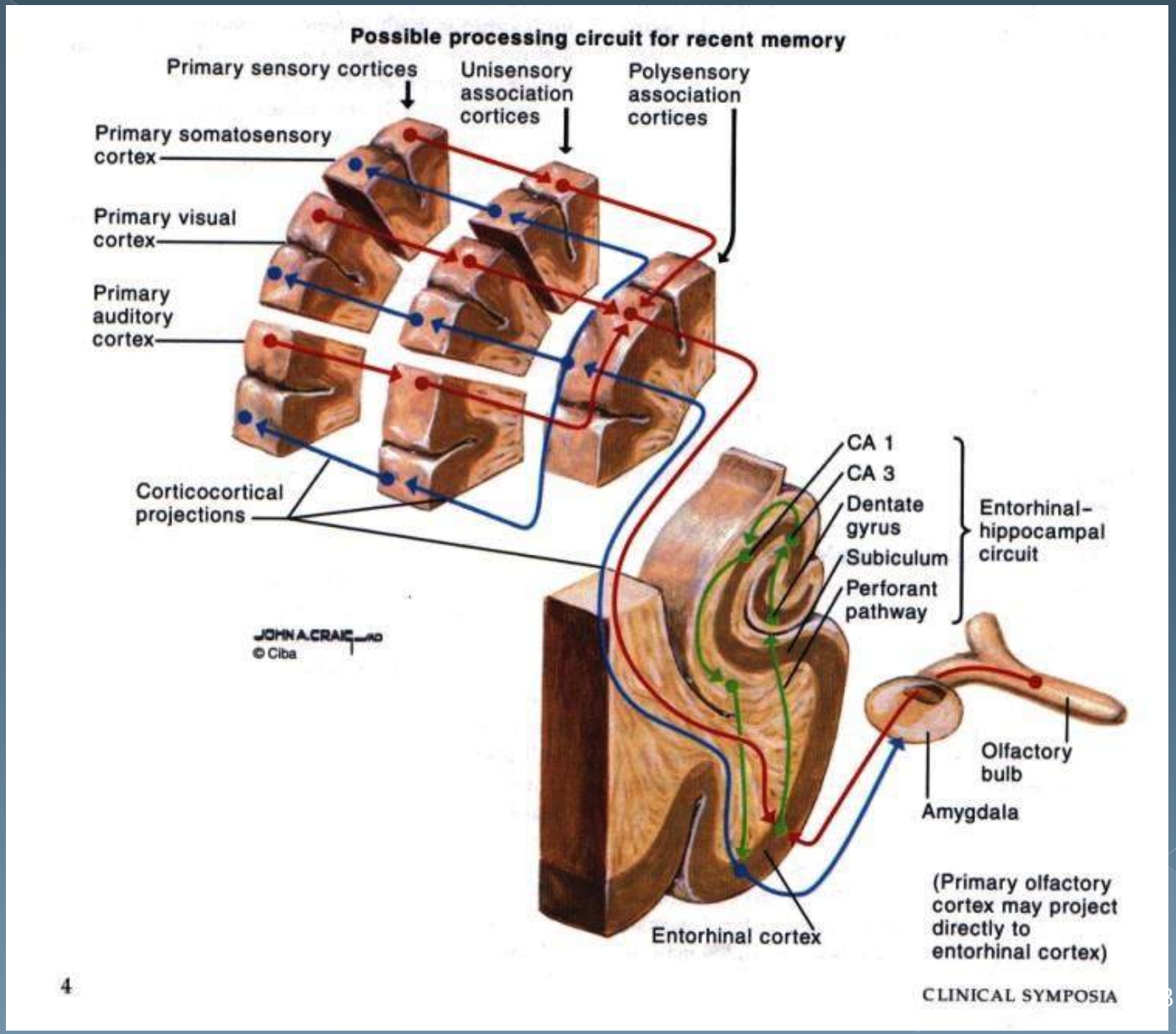
• Alzheimer Disease	50 - 60%
• Vascular Demensia	10 - 30 %
• Depressi	5 - 15 %
• Alkoholik	1 - 10 %
• Metabolik	1 - 10 %
• Intoksikasi	1 - 10 %
• Hidrosefalus	1 - 5 %
• Anoksia Otak	1 - 2 %
• Infeksi SSP	1 - 2 %
• Tumor Otak	1 - 2 %
• Hematom Subdural	1 - 2 %
• Lain2	10 - 20 %

Kortek & Memori

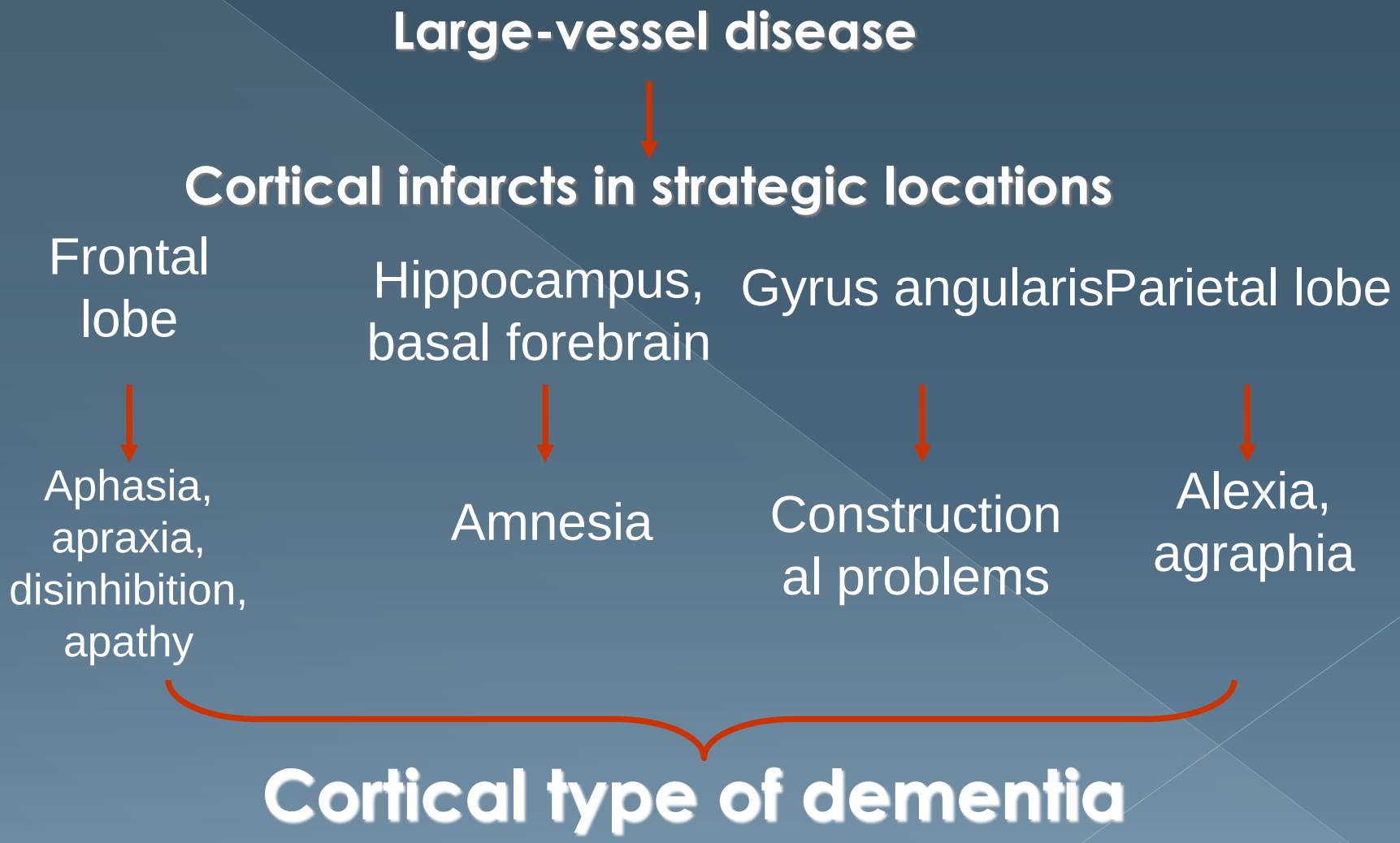


Entorhinal cortex major source of projections to hippocampus (major processing center for recent memory). Polysensory association cortices project directly to entorhinal cortex or indirectly via perirhinal cortex or parahippocampal gyrus. Association cortices receive reciprocal projections from entorhinal cortex

Memori Proses



ACCUMULATION OF FOCAL CORTICAL SYMPTOMS



DISRUPTION OF SUBCORTICO-CORTICAL CIRCUITS

Small-vessel disease

↓

Subcortical infarcts in strategic locations
Thalamus, caudate, pallidum, internal capsule, talamocortical projection

↓

Disruption of specific fronto-subcortical circuits or non-specific thalamo-cortical projections

↓

Executive dysfunction | Apathy | Attentional deficit | Personality change

Subcortical type of dementia

NON-SPECIFIC DISCONNECTION OF CORTEX

Small-vessel disease

↓

Diffuse white matter lesions

↓

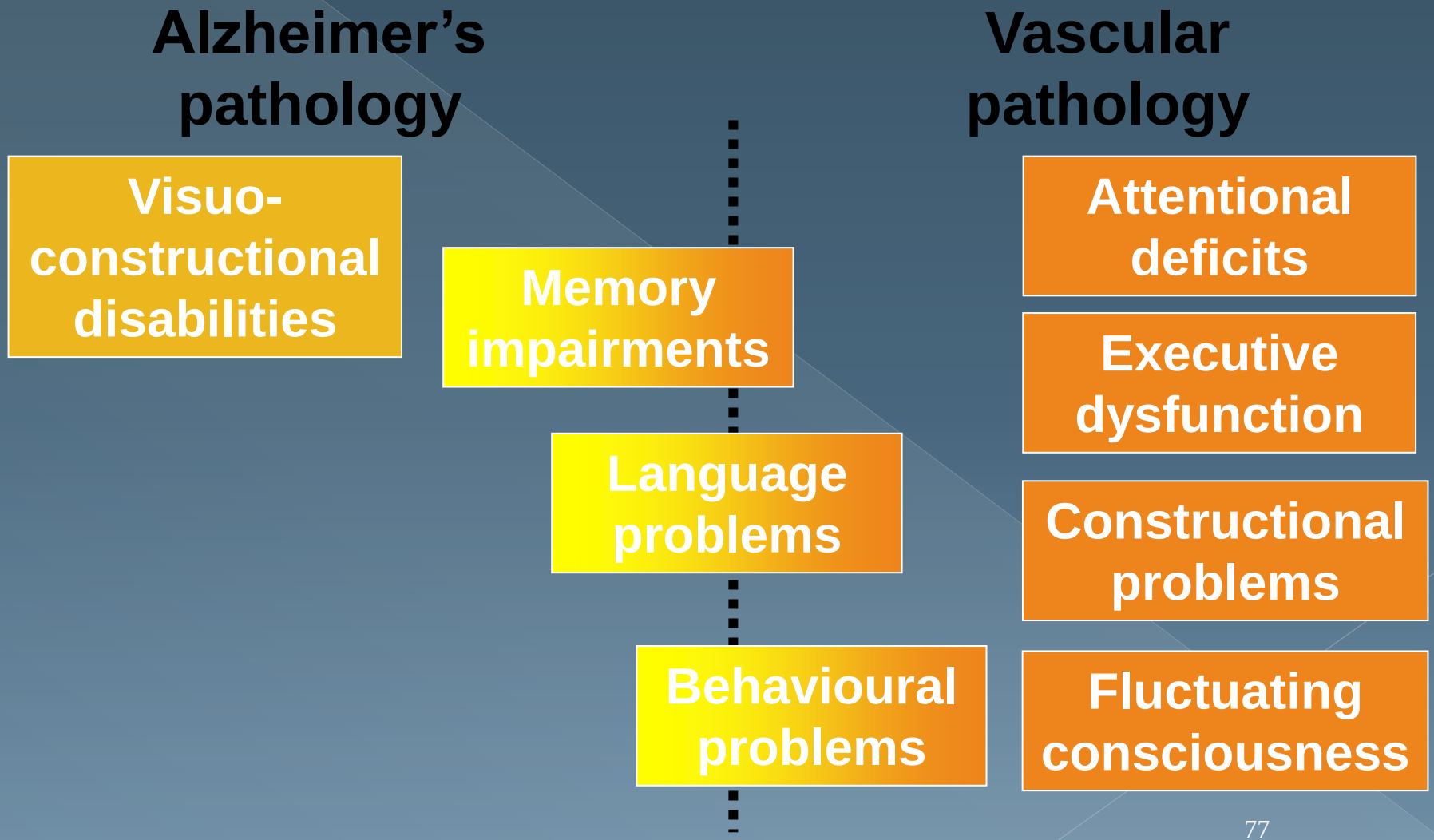
Disruption of cortico-cortical pathways

↓

Frontal, temporal and parietal cortical deficits

Mixed cortical / subcortical type of dementia

CLINICALLY-RELEVANT SYMPTOMS OF DEMENTIA



Related Research and Community Services

1. **Nursyamsu, S.H**, Sarah Y, Laili, N, Mawaddatu, S. 2023. Penyuluhan Deteksi Dini Demensia di Lingkungan Pabrik
2. **Rahayu. 2022.** The Differences Between the Effect of Oral and Intraperitoneal Induction of Aluminum Chloride (AlCl3) on the Memory Function of White Rats (Rattus norvegicus strain wistar) Menopause Model