LE MALATTIE NEUROLOGICHE AVANZATE e INGUARIBILI:
la perdita progressiva della autosufficenza

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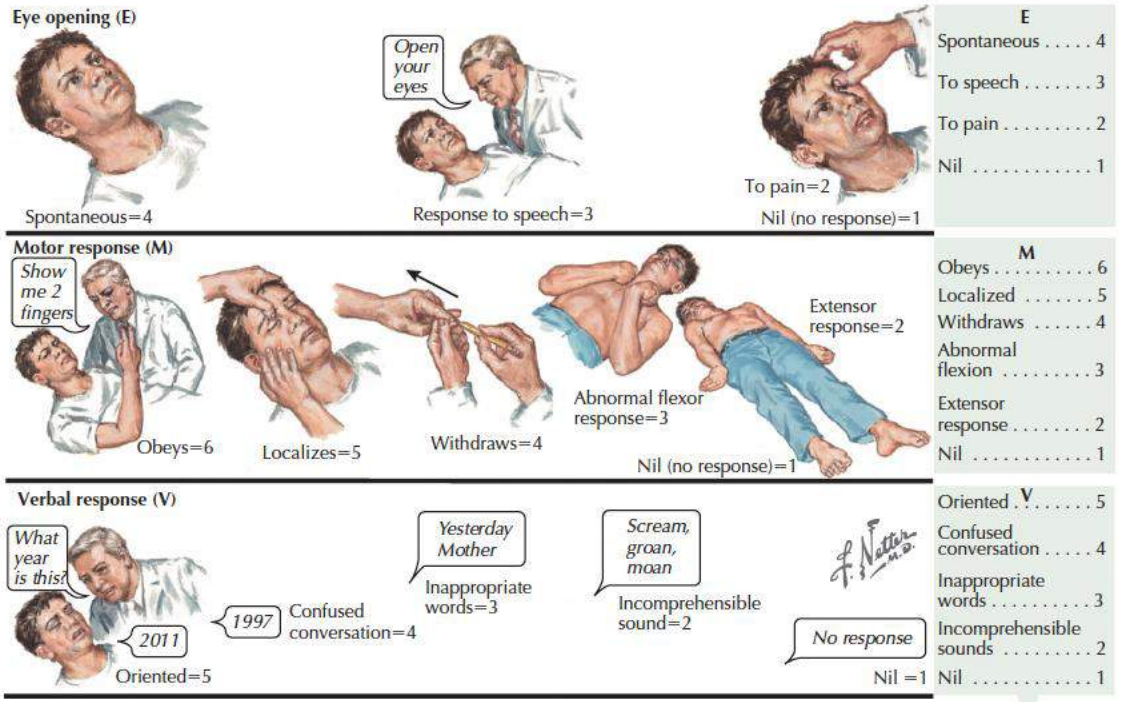
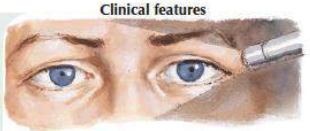
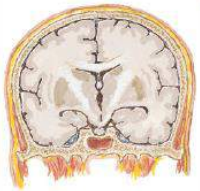
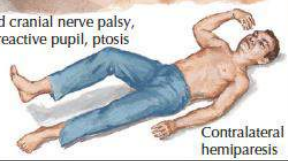
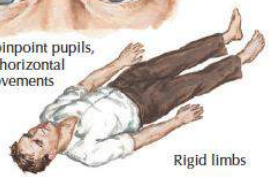
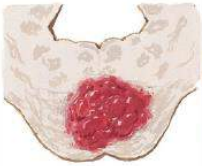
Le basi della valutazione neurologica

- Valutazione clinica con attenta raccolta della storia clinica e familiare
- Accertamenti strumentali più adeguati
- Attento monitoraggio del paziente nella fase diagnostica
- Vantaggio del regime di ricovero (osservazione h 24)

Stato di coscienza

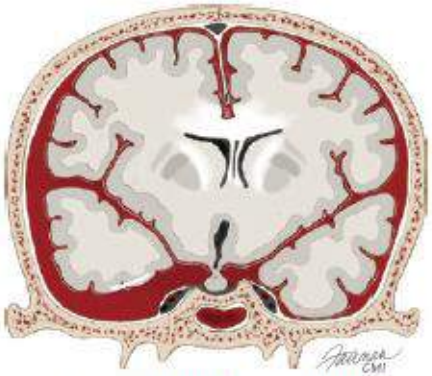


	Clinical features	Pathology (examples)	Etiologies
Bilateral cerebral hemisphere disease	 Normal pupils (equal, reactive) Normal doll's head phenomenon  Normal corneal reflex  Absent or minor focal features (lateral paralysis, sensory or visual loss)	 Bilateral hemispheric swelling (small ventricles, obliterated sulci, rounded edges)	Increased subarachnoid or extracerebral pressure Meningitis Subarachnoid hemorrhage Bilateral subdural hematoma Metabolic encephalopathy Liver coma Kidney coma Carbon dioxide narcosis Hypoxia Hypoglycemia Hypercalcemia Hyponatremia Diabetic acidosis Hyperosmolar coma Toxins or drugs Barbiturates Alcohol Narcotics Other sedative overdose Lead Multifocal cerebral disease Sequential infarctions Multiple abscesses Encephalitis Multiple areas of brain tumor Multiple cerebral contusions
Unilateral cerebral hemisphere lesion with compression of brainstem	 Third cranial nerve palsy, nonreactive pupil, ptosis  Contralateral hemiparesis	 Right temporal hemorrhage from trauma, with swelling of right hemisphere	Cerebral Tumor Hemorrhage Abscess Infarction Contusion Extracerebral Subdural hematoma Epidural hematoma
Primary brainstem lesion	 Small pinpoint pupils, absent horizontal eye movements  Rigid limbs	 Large pontine hemorrhage	Infarction Hemorrhage Servere metabolic disturbance, sedative or phenytoin overdose Severe anoxia
Cerebellar lesion with secondary brainstem compression	 Vomiting Inability to walk or ataxia  Sixth cranial nerve palsy	 Large cerebellar hemorrhage	Infarction Hemorrhage Tumor Abscess Contusion

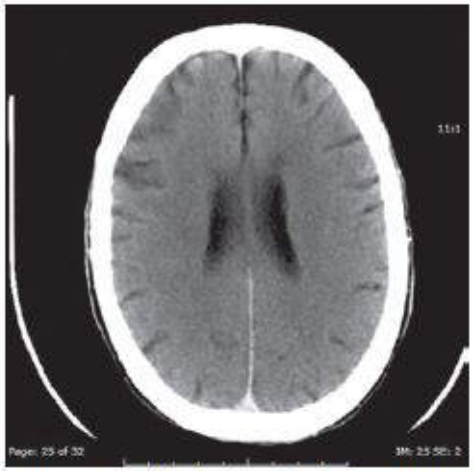
F. Netter M.D.

Condition is called *persistent* when it lasts without change for more than 1 month.

Patients may startle, look about, or yawn, but none of these actions are in conscious response to a specific stimulus.

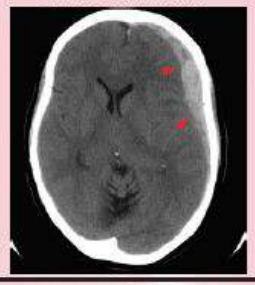
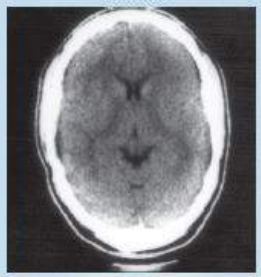
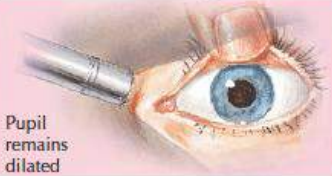
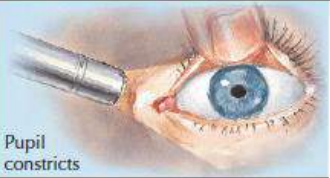
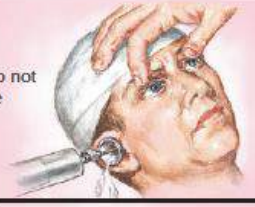
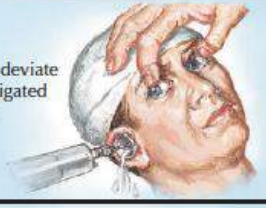


Subarachnoid hemorrhage



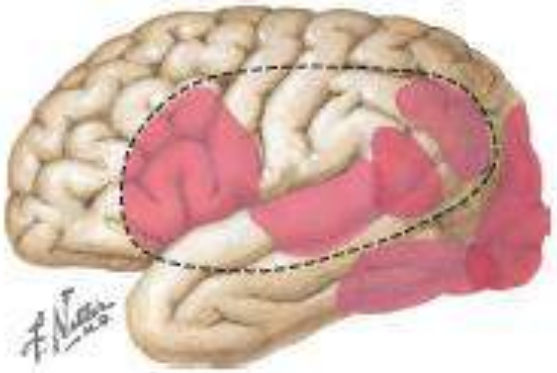
Non-contrast brain CT demonstrating ominous sign of diffuse brain injury and possible prelude to a persistent vegetative state: sulcal effacement (diffuse edema) and subtle disappearance of normal differentiation between gray and white matter.

Persistent Vegetative State.

	Poorer	Better
Glasgow Coma Scale	**3–8**	**9–15**
CT scan Axial noncontrast brain CT: Acute subdural hematoma (arrowheads) with moderate associated mass effect.	Subdural hematoma 	Normal 
Age	Older adult 	Youth 
Pupillary light reflex	Pupil remains dilated 	Pupil constricts 
Caloric testing with ice water	Eyes do not deviate 	Eyes deviate to irrigated side 
Motor response to noxious stimuli	Decerebrate rigidity 	Localizes (defensive gesture) 

Valutazione Paziente Vigile
Linguaggio

Clinical syndromes related to site of region



	Broca aphasia	Wernicke aphasia	Angular gyrus	Global aphasia
Pronunciation, speech rhythm	Dysarthria, stuttering, effortful	Normal, fluent, loquacious	Normal	Very abnormal
Speech content	Missed syllables, agrammatical, telegraphic	Use of wrong or nonexistent words	Often normal	Very abnormal
Repetition of speech	Abnormal but better than spontaneous	Abnormal	Normal	Very abnormal
Comprehension of spoken language	Normal	Very abnormal	Normal	Very abnormal
Comprehension of written language	Not as good as for spoken language	Abnormal but better than for spoken	Very abnormal	Very abnormal
Writing	Clumsy, agrammatical, misspelling	Penmanship OK but misspelling and inaccuracies	Very abnormal, spelling errors	Very abnormal
Naming	Better than spontaneous speech	Wrong names	Often abnormal	Very abnormal
Other	Hemiplegia, apraxia	Sometimes hemianopsia and apraxia	Slight hemiparesis, trouble calculating, finger agnosia, hemianopsia	Hemiplegia

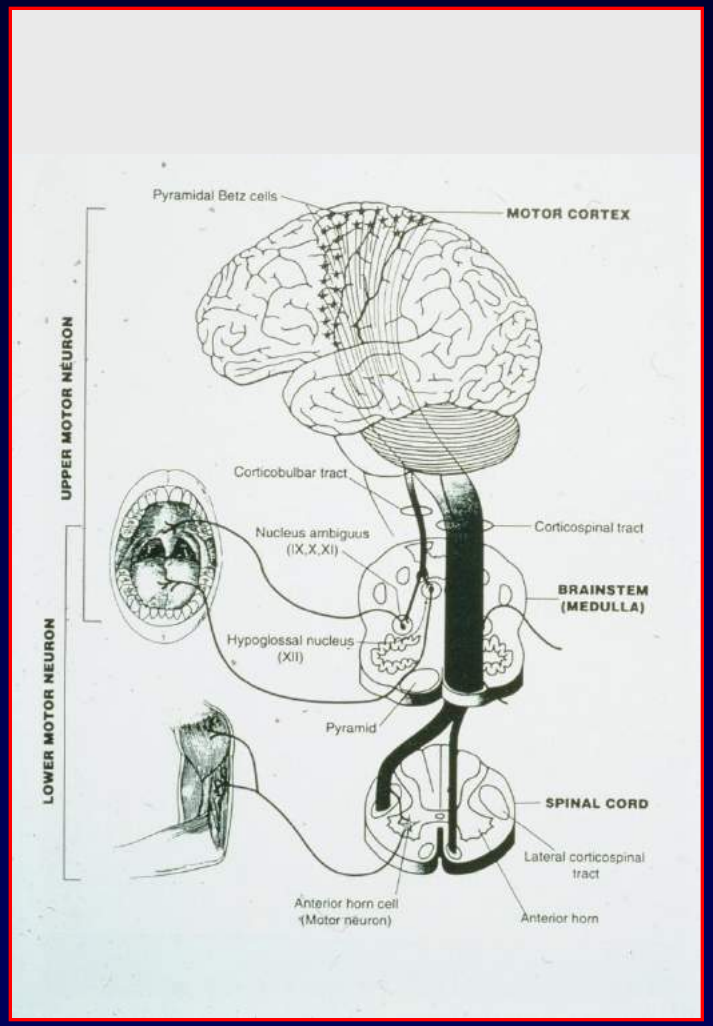
Valutazione Neurologica

Il Sistema Motorio

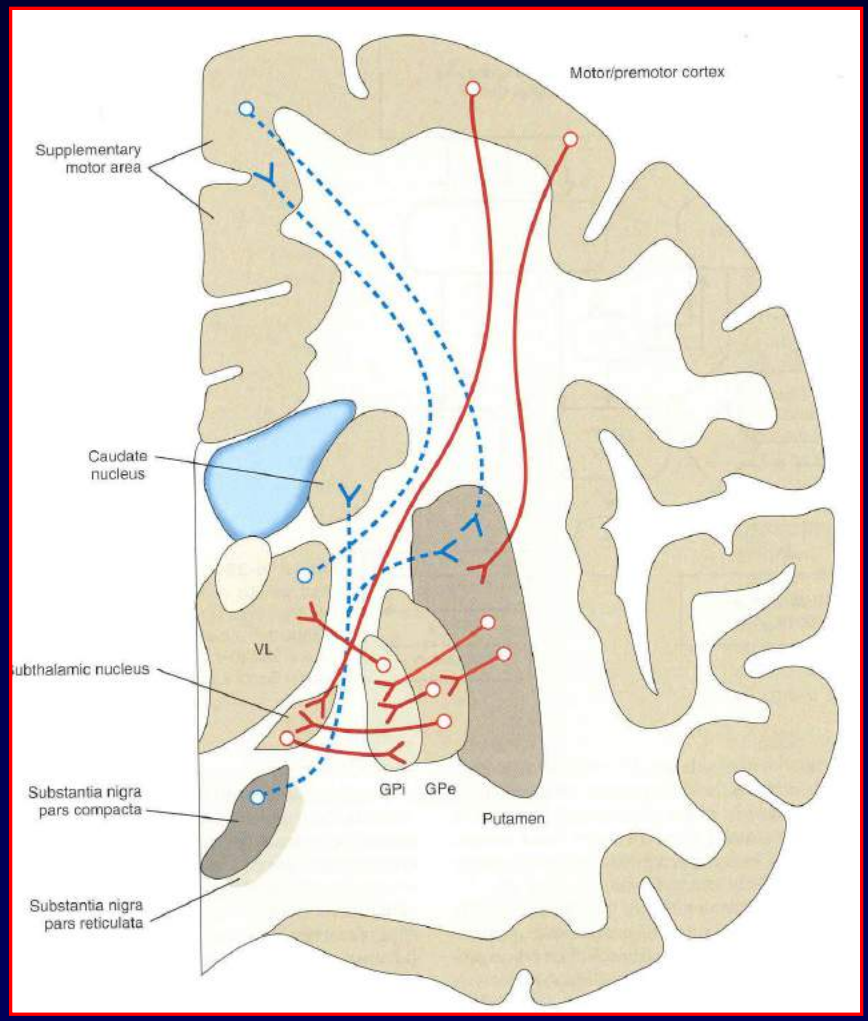
Sistema Piramidale ed Extrapiramidale

I due sistemi

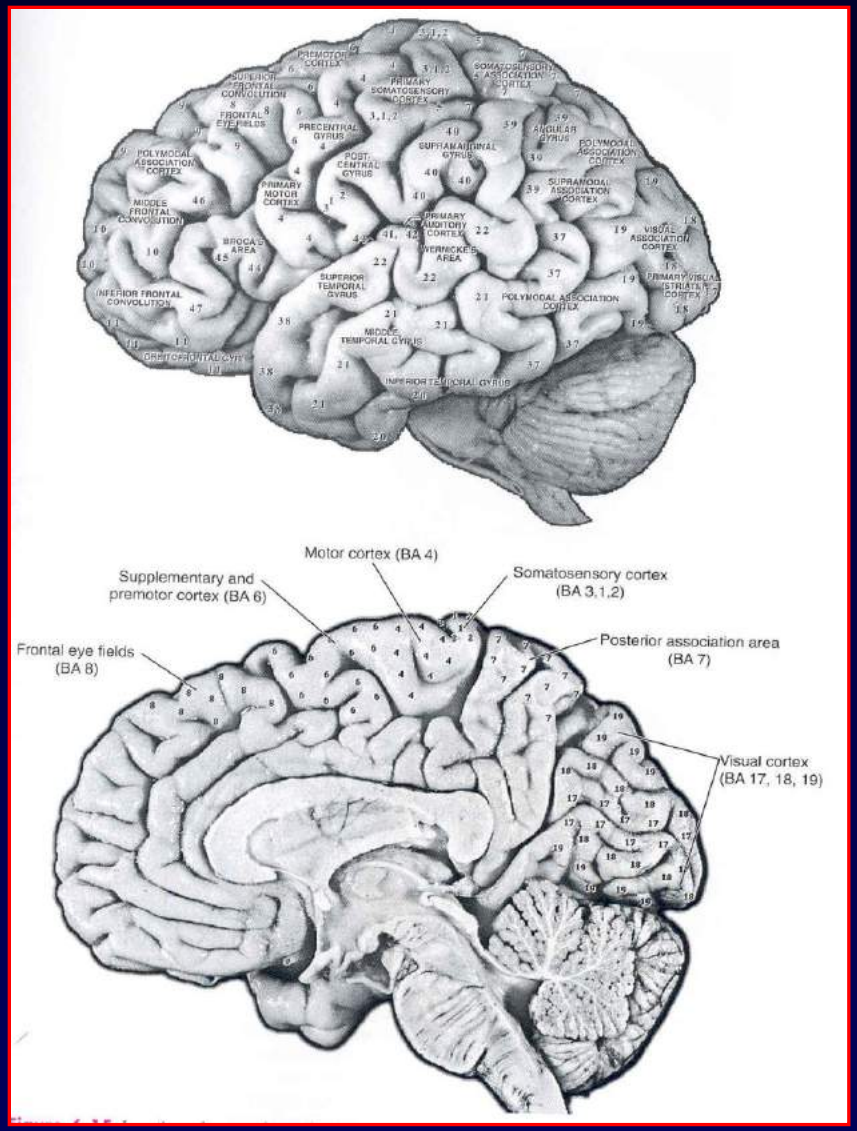
Sistema Piramidale

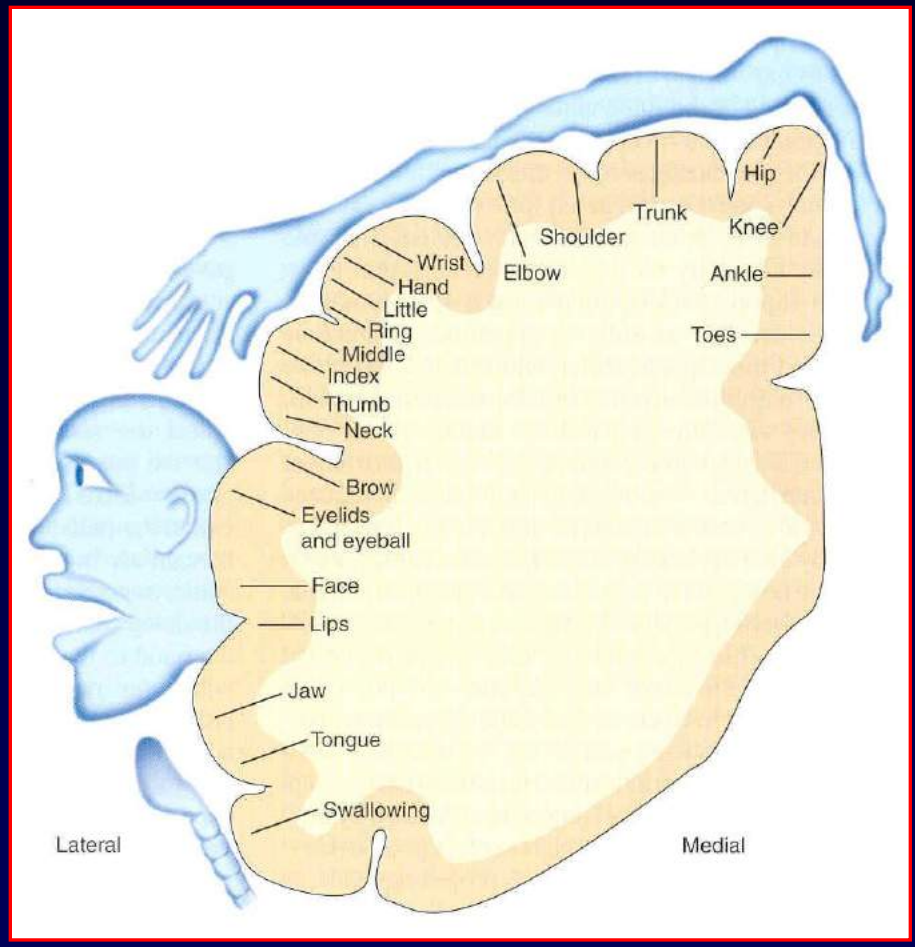


Sistema Extrapiramidale



Sistema Piramidale





A. ANAMNESI DEI DISTURBI MOTORI

❶ Disturbi della marcia e della stazione eretta
❷ Mancanza di forza
❸ Impaccio motorio
❹ Incoordinazione dei movimenti
❺ Sensazione di rigidità
❻ Movimenti involontari

Cosa chiedere al malato: inizio, durata, frequenza, distribuzione, fattori precipitanti (es. lo sforzo) e riducenti (es. riposo) i disturbi.

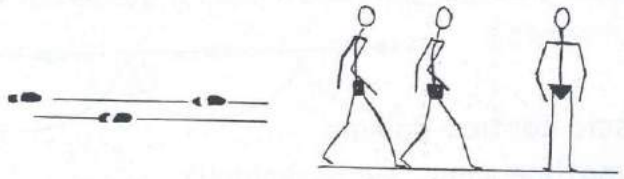
B. ESAME NEUROLOGICO DEL SISTEMA MOTORIO

(come si presenta il malato)

1. Stazione eretta
2. Deambulazione
3. Forza e riflessi osteotendinei arti superiori
4. Forza e riflessi osteotendinei arti inferiori
5. Tono muscolare, clono piede e riflesso plantare
6. Coordinazione

B1. DEAMBULAZIONE (far camminare il paziente per 2-3 m)

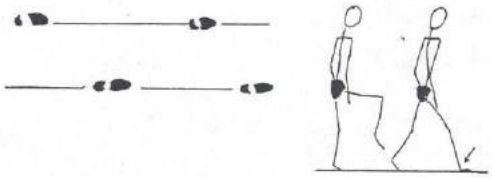
Normale



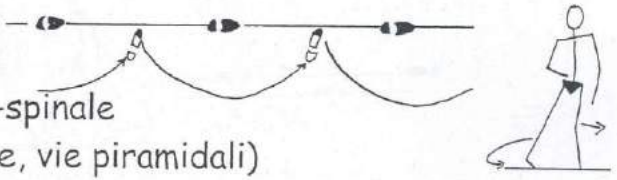
Come interpreti l'esame?

- *Atassica* (base allargata, sollevamento eccessivo dell'arto):

  - cervelletto
  - cordoni posteriori
  - nervi periferici



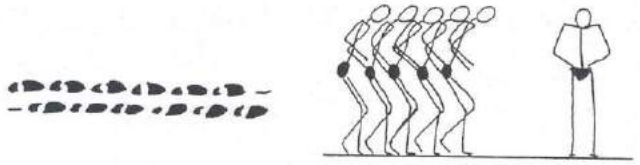
- *Emiplegica* (falciante, striscia il piede sul pavimento):

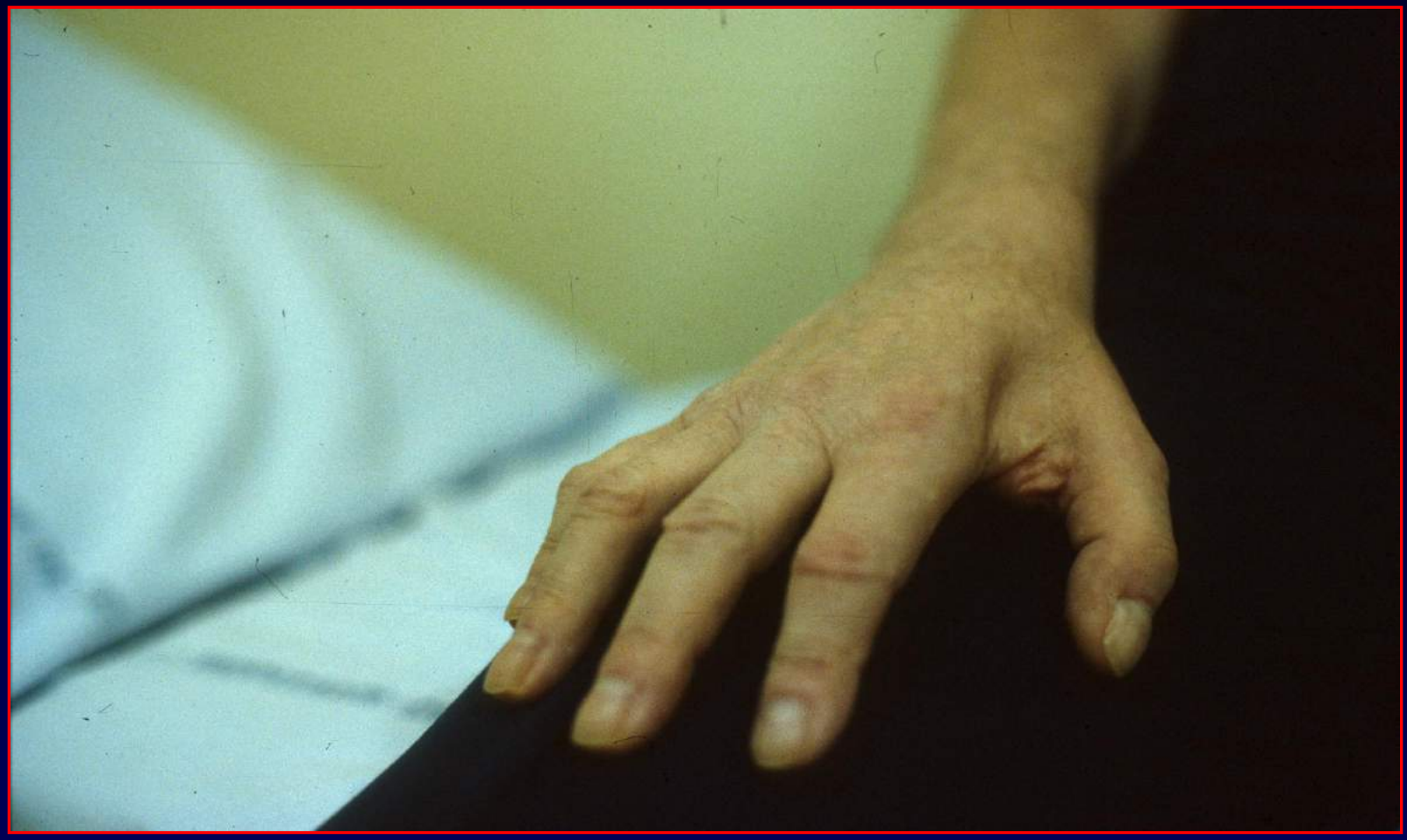


  - fascio cortico-spinale (I motoneurone, vie piramidali)

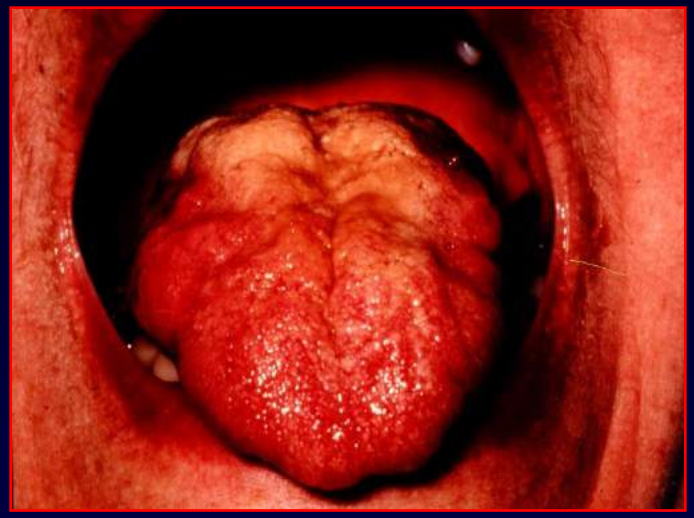
- *Parkinsoniana* (a piccoli passi, tronco flesso in avanti):

  - nuclei della base





Grave atrofia della mano



Grave atrofia lingua
ed arti inferiori

Come interpreti l'esame?

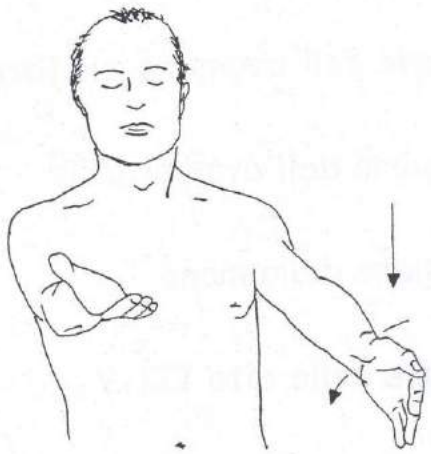
Valuta il grado di resistenza:

Normale: da provare su un compagno

	descrizione	sede di lesione
spastico	Aumenta con la velocità del movimento passivo	I motoneurone vie piramidali
rigido plastico	Non influenzato dalla velocità del movimento passivo	gangli della base
flaccido ipotonico	Ridotto in tutte le posizioni	cervelletto nervi periferici

B3. DISTURBO DI FORZA ARTI SUPERIORI

Prova di forza globale: posizione Mingazzini arti superiori

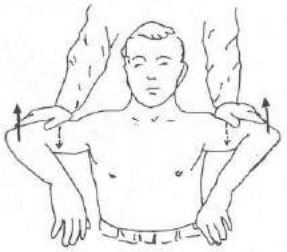


Valuta l'eventuale pronazione e slivellamento

Prove di forza segmentaria arti superiori

1. Abduzione delle spalle
2. Flessione dell'avambraccio (bicipite)
3. Flessione dell' avambraccio (brachioradiale)
4. Estensione dell'avambraccio
5. Estensione della mano
6. Flessione delle dita III-V
7. Opposizione pollice

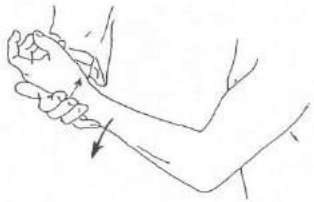
Abduzione delle spalle



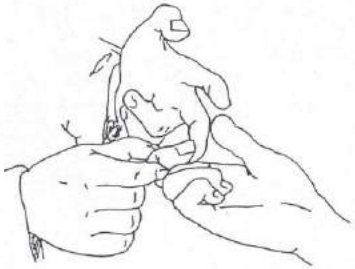
Flessione del gomito (bicipite)

Flessione del gomito (brachioradiale)

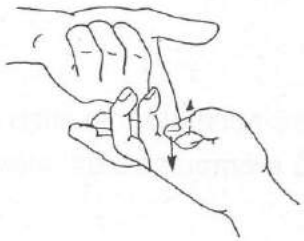
Estensione del gomito



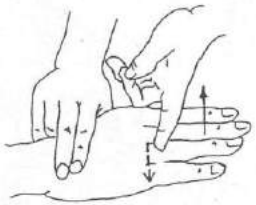
Flessione delle dita



Opposizione del pollice



Estensione delle dita



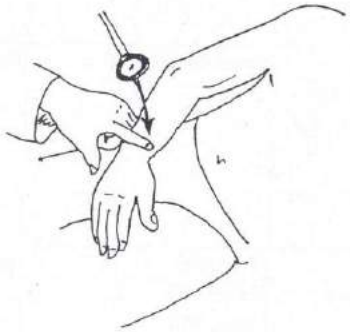
B4. RIFLESSI OSTEOTENDINEI ARTI SUPERIORI

1. Tricipitale
2. Bicipitale
3. Stiloradiale

Valuta se normale, assente o aumentato per rapidità e ampiezza del movimento

Riflesso tricipitale

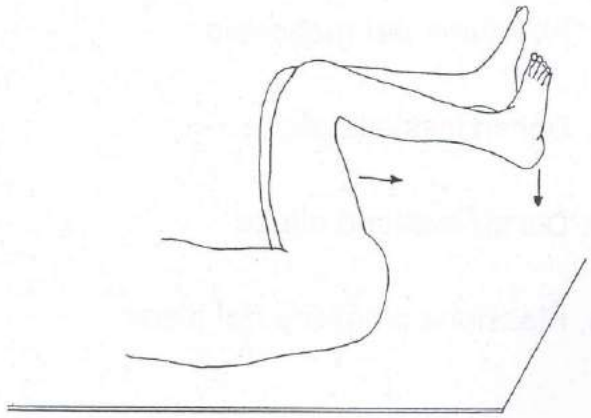
Riflesso stiloradiale



Riflesso bicipitale

B5. DISTURBO DI FORZA ARTI INFERIORI

Prova di forza globale: posizione Mingazzini arti inferiori



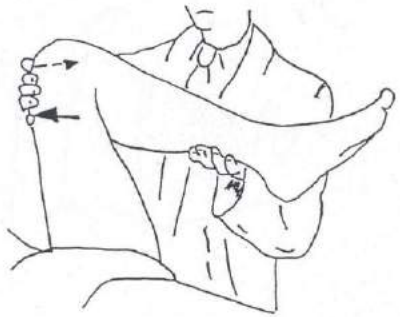
Valuta l' eventuale slivellamento.

Prove di forza segmentaria arti inferiori

1. Flessione della coscia
2. Estensione del ginocchio
3. Flessione del ginocchio
4. Dorsiflessione piede
5. Dorsiflessione alluce
6. Flessione plantare del piede

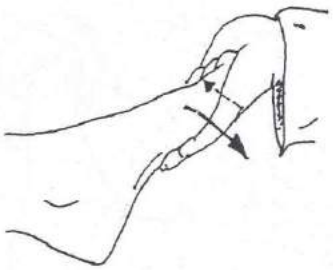
Estensione del ginocchio

Flessione della coscia

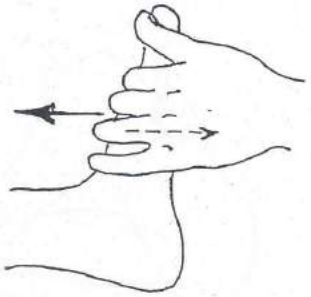


Flessione del ginocchio

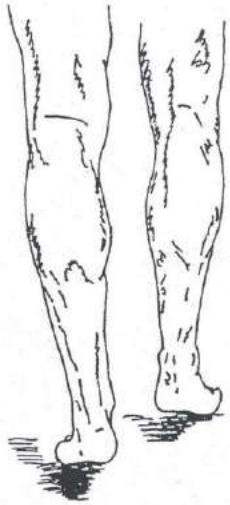
Flessione plantare del piede



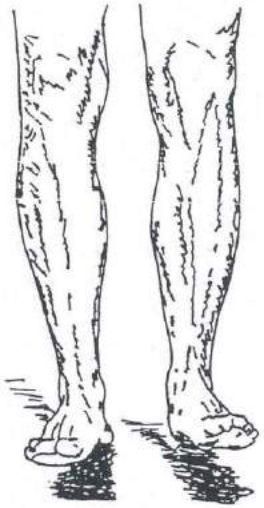
Dorsiflessione del piede



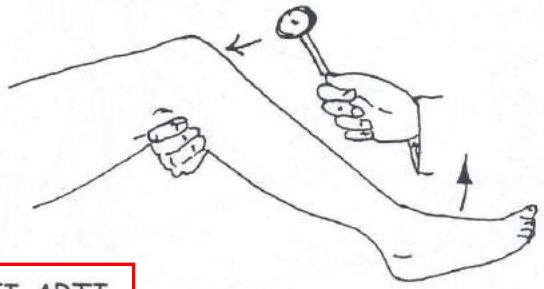
Camminare sulle punte



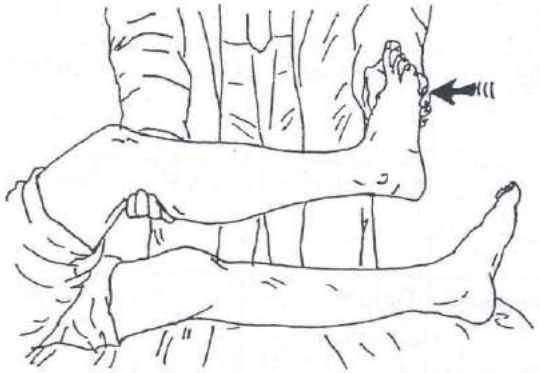
Camminare sui talloni



Riflesso rotuleo



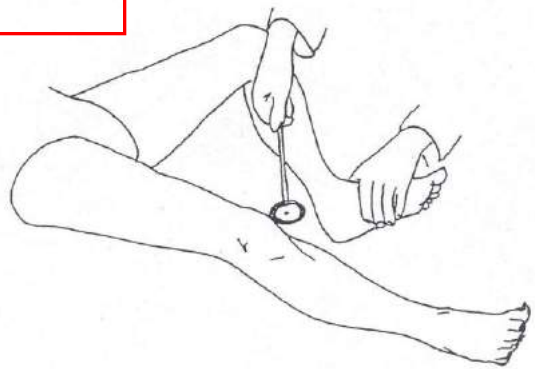
Clono del piede

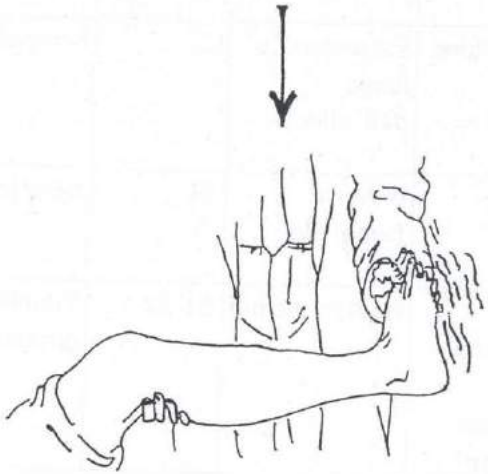


B6. RIFLESSI OSTEOTENDINEI ARTI INFERIORI

1. Rotuleo
2. Achilleo
3. Clono del piede

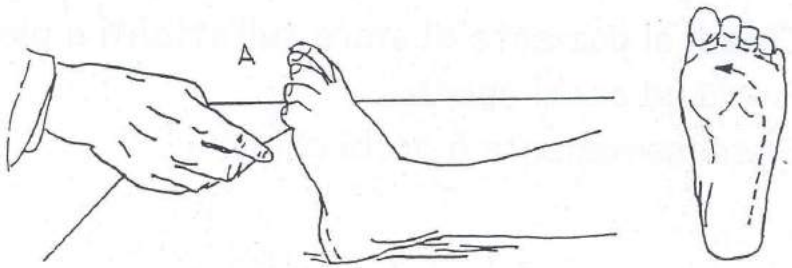
Riflesso achilleo



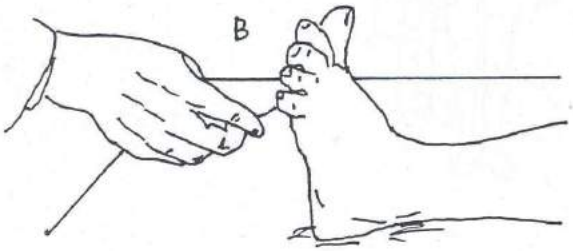


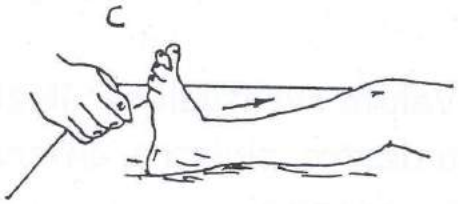
B7. RIFLESSO PLANTARE

Segno di Babinski



Il segno di Babinski negativo (A) = normale
Il segno di Babinski positivo (B-C)= lesione del I motoneurone (vie piramidali)

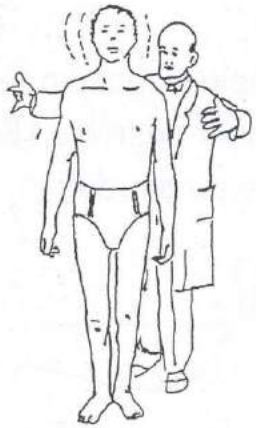




B8. STAZIONE ERETTA

Test di Romberg

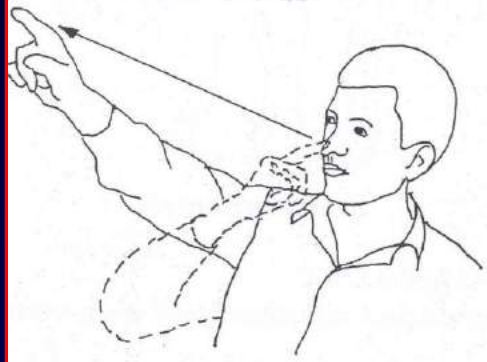
Chiedi al paziente di stare sull'attenti a piedi uniti
Prima ad occhi aperti
Successivamente a occhi chiusi



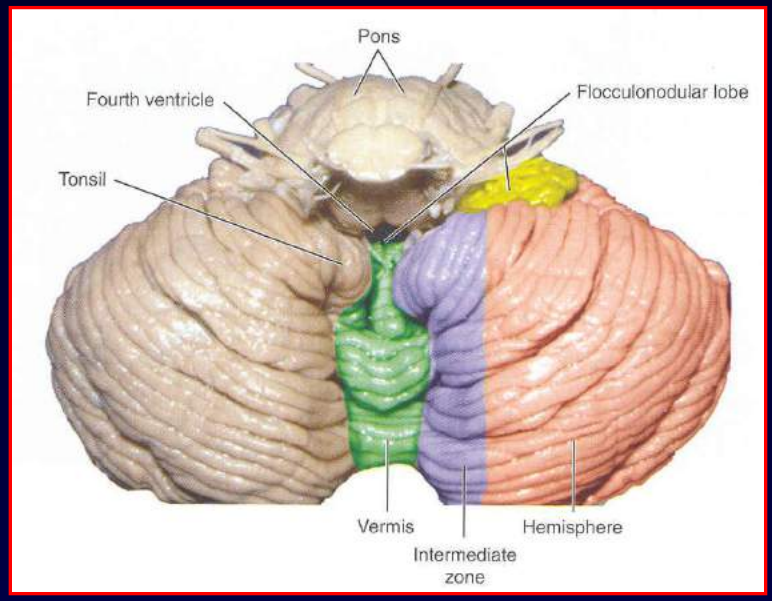
Valuta eventuali oscillazioni e tendenza alla caduta a destra, sinistra, anteriore, posteriore, o in tutte le direzioni

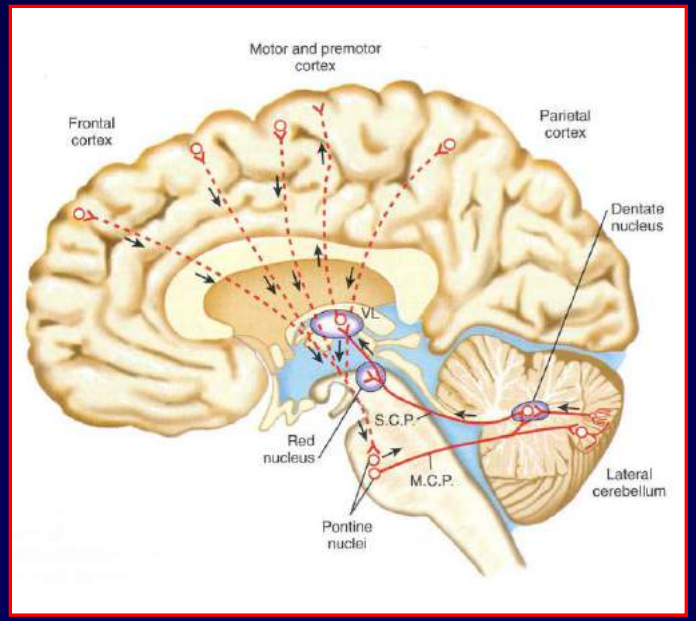
B9. COORDINAZIONE

Chiedi al paziente di toccarsi con il dito la punta del naso (*prova indice-naso*) e con il tallone il ginocchio (*prova tallone-ginocchio*) prima ad occhi aperti, poi ad occhi chiusi

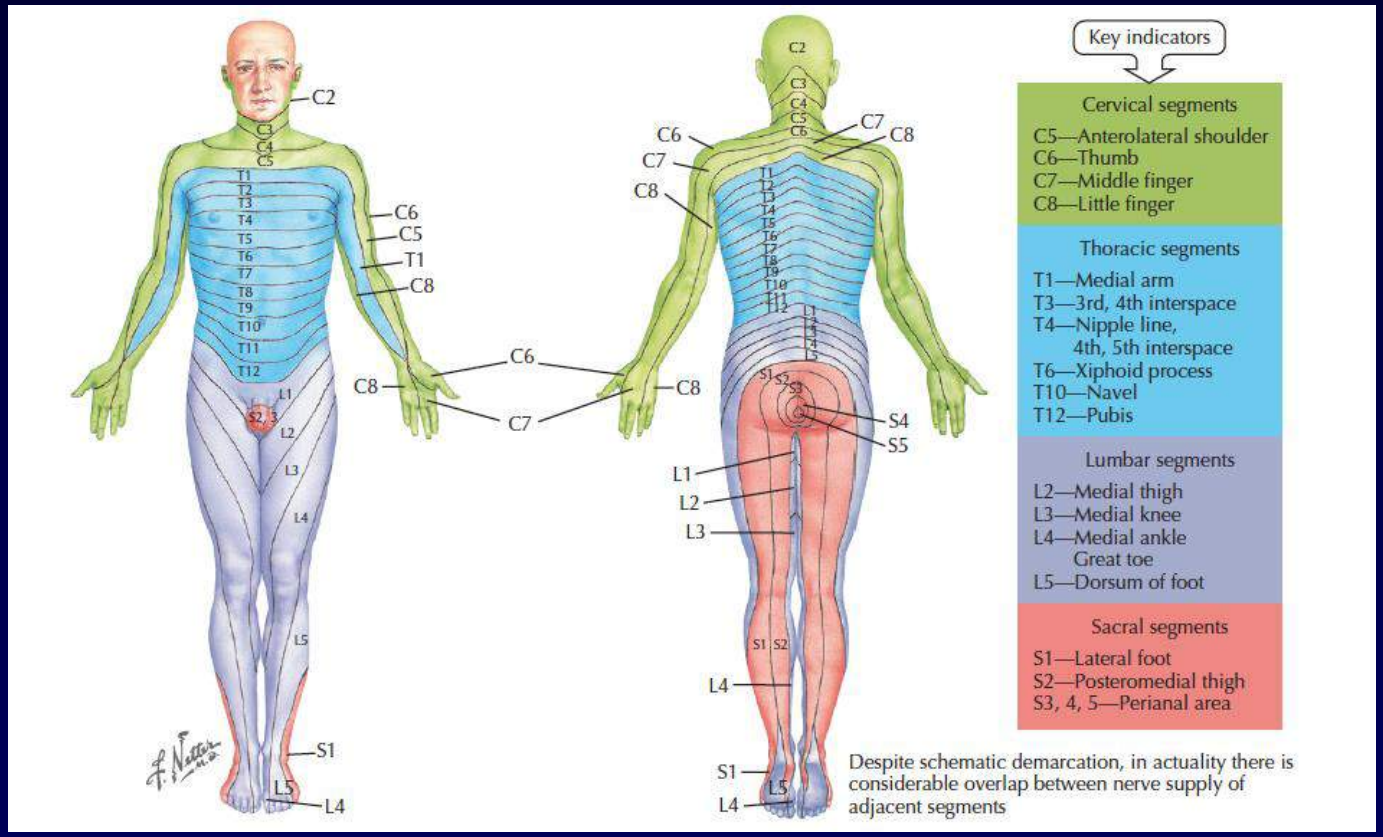


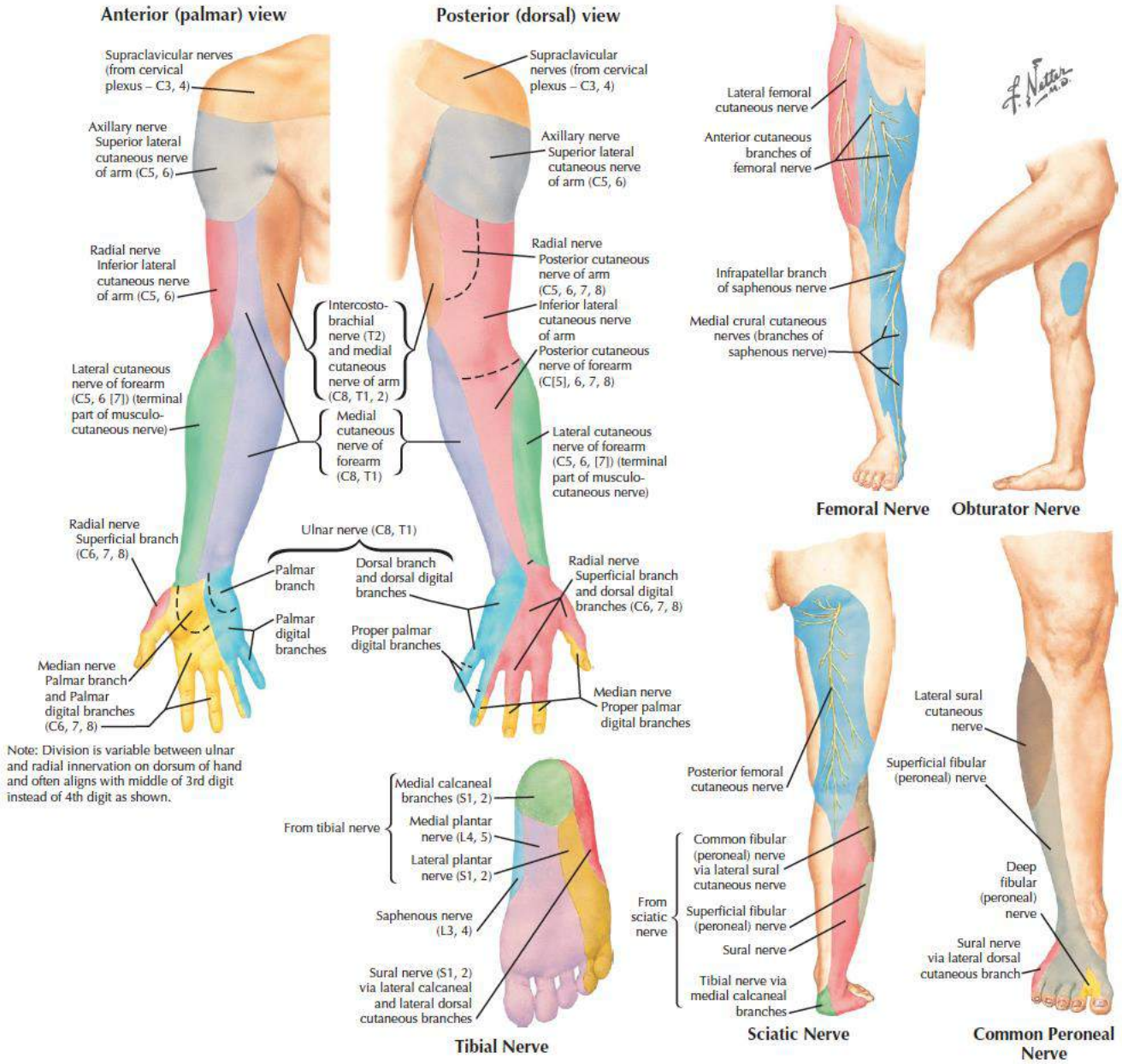
Valuta se è presente atassia, dismetria, tremore





Le sensibilità




Anterior (palmar) view
Supraclavicular nerves (from cervical plexus – C3, 4)
Axillary nerve
Superior lateral cutaneous nerve of arm (C5, 6)
Radial nerve
Inferior lateral cutaneous nerve of arm (C5, 6)
Lateral cutaneous nerve of forearm (C5, 6 [7]) (terminal part of musculo-cutaneous nerve)
Radial nerve
Superficial branch (C6, 7, 8)
Median nerve
Palmar branch and Palmar digital branches (C6, 7, 8)
Note: Division is variable between ulnar and radial innervation on dorsum of hand and often aligns with middle of 3rd digit instead of 4th digit as shown.
Intercosto-brachial nerve (T2) and medial cutaneous nerve of arm (C8, T1, 2)
Medial cutaneous nerve of forearm (C8, T1)
Ulnar nerve (C8, T1)
Palmar branch
Palmar digital branches
Posterior (dorsal) view
Supraclavicular nerves (from cervical plexus – C3, 4)
Axillary nerve
Superior lateral cutaneous nerve of arm (C5, 6)
Radial nerve
Posterior cutaneous nerve of arm (C5, 6, 7, 8)
Inferior lateral cutaneous nerve of arm
Posterior cutaneous nerve of forearm (C[5], 6, 7, 8)
Lateral cutaneous nerve of forearm (C5, 6, [7]) (terminal part of musculo-cutaneous nerve)
Dorsal branch and dorsal digital branches
Proper palmar digital branches
Radial nerve
Superficial branch and dorsal digital branches (C6, 7, 8)
Median nerve
Proper palmar digital branches
From tibial nerve
Medial calcaneal branches (S1, 2)
Medial plantar nerve (L4, 5)
Lateral plantar nerve (S1, 2)
Saphenous nerve (L3, 4)
Sural nerve (S1, 2) via lateral calcaneal and lateral dorsal cutaneous branches
Tibial Nerve
Lateral femoral cutaneous nerve
Anterior cutaneous branches of femoral nerve
Infrapatellar branch of saphenous nerve
Medial crural cutaneous nerves (branches of saphenous nerve)
Femoral Nerve
Obturator Nerve
Posterior femoral cutaneous nerve
From sciatic nerve
Common fibular (peroneal) nerve via lateral sural cutaneous nerve
Superficial fibular (peroneal) nerve
Sural nerve
Tibial nerve via medial calcaneal branches
Sciatic Nerve
Lateral sural cutaneous nerve
Superficial fibular (peroneal) nerve
Deep fibular (peroneal) nerve
Sural nerve via lateral dorsal cutaneous branch
Common Peroneal Nerve

SEDE DELLA LESIONE NEI DISTURBI DI MOTO

Primo motoneurone (sistema piramidale):
Emiparesi, paraparesi ecc.
Ipertonia spastica
Aumento dei riflessi osteotendinei
Babinski alla stimolazione plantare

Secondo motoneurone:
Paresi con distribuzione radicolare o periferica
Atrofia, fascicolazioni
Ipotonia
Riduzione o assenza dei riflessi osteotendinei

Placca neuromuscolare o muscolo:
Disturbo di forza (con esauribilità) a distribuzione non da I o II motoneurone
Riflessi osteotendinei conservati o lievemente diminuiti

SEDE DELLA LESIONE NEI DISTURBI DI MOTO

Unilaterale

Bilaterale

I motoneurone

corticale
capsulare

midollo cervicale

II motoneurone

radice
nervo

polineuropatia

Lesione midollare

Sindromi sensitive dissociate: alterazione di alcune sensibilità e risparmio di altre

Muscolo

Emiparesi

FIG. 23–8. Left hemiparesis of 15 years' duration. The patient circumducts his left leg as he begins walking.

Il cammino !

A Parkinson Disease

1

Stage 1: unilateral involvement; blank facies; affected arm with tremor

2

Stage 2: bilateral involvement with stooped posture; slow, shuffling gait with short steps (petit pas)

3

Stage 3: pronounced gait disturbances, moderate generalized disability; postural instability with tendency to fall

B Spastic Corticospinal

1

Right hemiparesis with flexed right arm secondary to a corticospinal tract lesion

2

Typical spastic gait, circumduction of the leg at the hip and scuffling the toe on affected leg.

C Cerebellar Gait

1

Wide-based gait of midline cerebellar tumor or other lesion

2

Typical wide-based gait of drug intoxication

D Apraxic, Frontal Gait

Apraxic gait of normal-pressure hydrocephalus

E Lumbar Spine Disease

1

Characteristic posture in left-sided lower lumbar disc herniation

2

Patient with lumbar spinal stenosis with forward flexion gait

F Peripheral Neuropathies

1

Patient walks gingerly due to loss of position sense and/or painful dysesthesia

2

Sudden buckling of knee while going down stairs (femoral nerve)

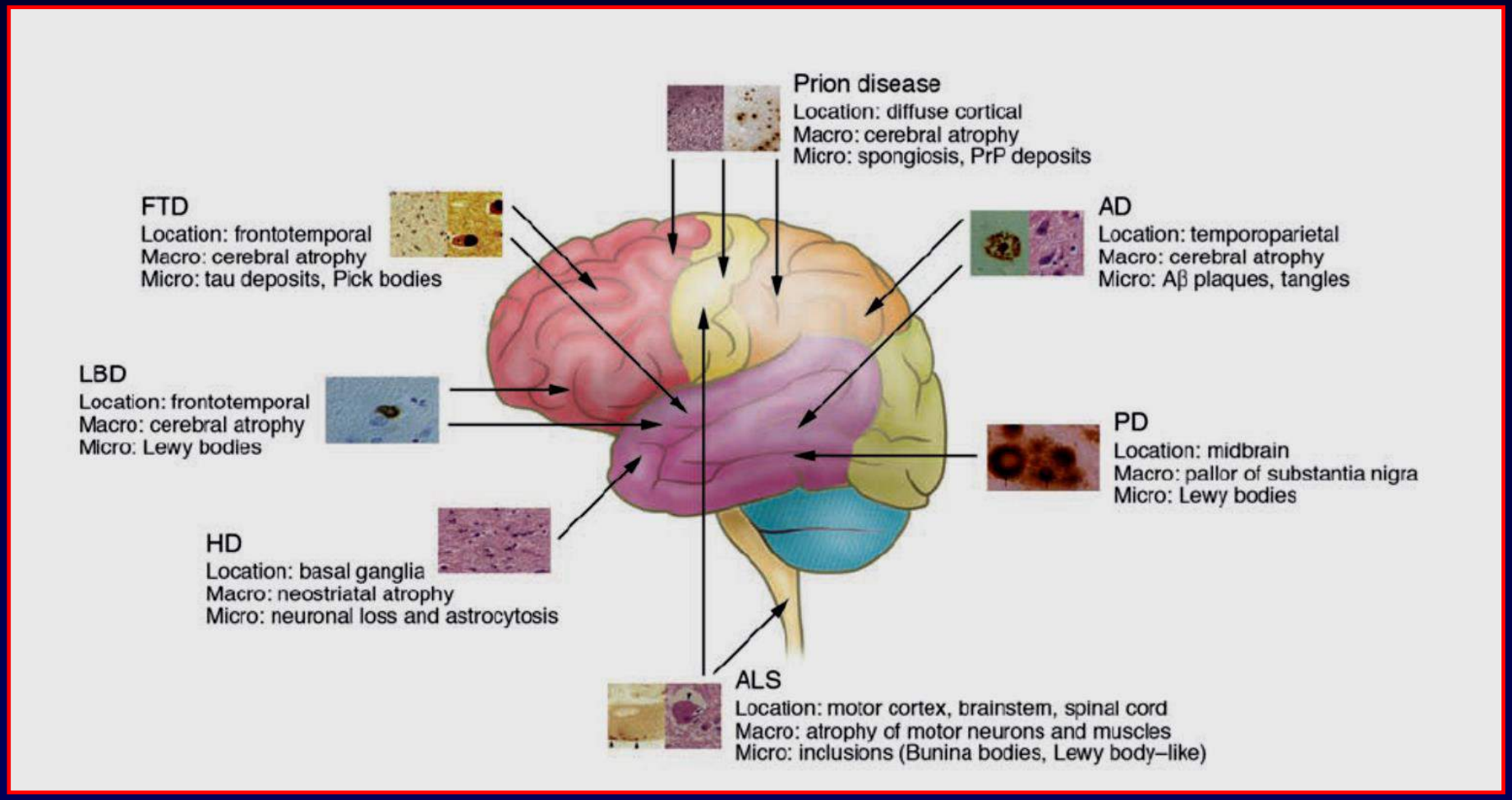
3

Sudden occurrence of foot drop while walking (peroneal nerve)

G Myopathy

Severe myopathy or NMJ lesion with proximal weakness

Quante sono le Malattie Neurodegenerative?



Trattasi delle stesso processo degenerativo
in differenti sistemi neuronali?

Demenze degenerative primarie

- Degenerazioni neuronali senza causa definita.
- La più frequente è la AD, FTD seconde per frequenza (25%), il 15% sono DLB.

Tutte le definizioni di Demenza comprendono tre caratteristiche fondamentali

- compromissione cognitiva acquisita
- deterioramento di domini multipli delle funzioni cognitive
- non compromissione della vigilanza (DD: delirium)

DSM-IV

Criteri di demenza del DSM-IV

Lo sviluppo di deficit cognitivi multipli che comprendono un disturbo di memoria ed almeno uno dei seguenti:
- Afasia
- Aprassia
- Agnosia
- Disturbo delle funzioni esecutive

I deficit cognitivi devono
- Essere sufficientemente severi da causare una compromissione del funzionamento sociale od occupazionale
- Rappresentare un declino rispetto ad un precedente livello di funzionamento

La diagnosi non deve essere formulata se i deficit cognitivi si manifestano esclusivamente durante il corso di un delirium. Comunque, sia la demenza che il delirium possono essere entrambi diagnosticati se la demenza era presente prima che il delirium si sviluppasse

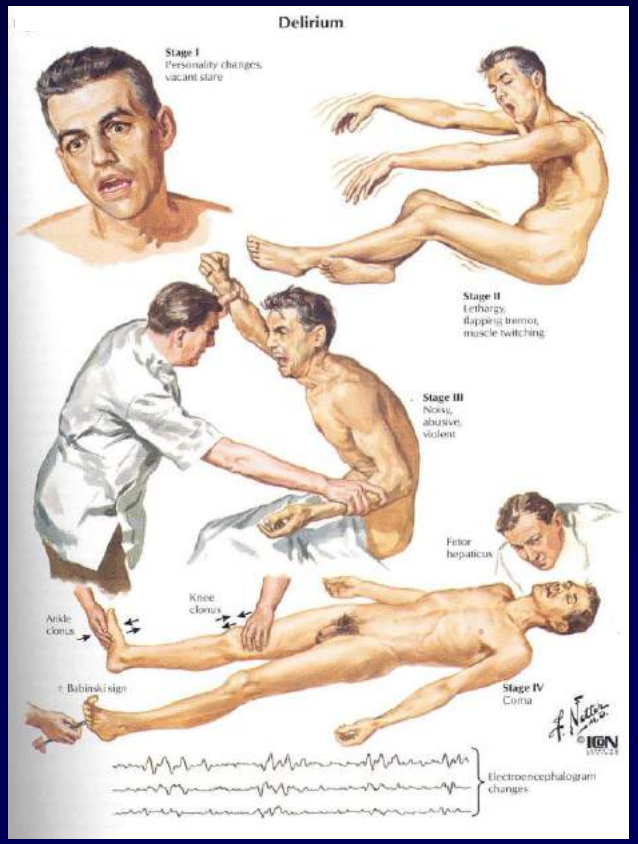
La demenza può essere eziologicamente correlata ad una condizione medica generale, a effetti persistenti di abuso di sostanze (compresa l'esposizione a tossine) od a una combinazione di questi fattori

Fonte: adattato dal *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (IV ed). Washington, DC: American Psychiatric Association, 1994.

Table 3 Clinical features of delirium versus dementia

Feature	Delirium	Dementia
Progression	Fluctuating with lucid intervals, often worse at night	Fairly consistent over the course of a day
Consciousness	Altered	Clear
Attention	Impaired with pronounced distractibility	Relatively normal
Memory	Impaired	Impaired
Thinking	Disorganised, delusional	Paucity of thought
Sleep–wake cycle	Disrupted	Often normal
Perception	Hallucinations and illusions common, often visual	Hallucinations generally absent in early stages

Cooper and Greene, 2005



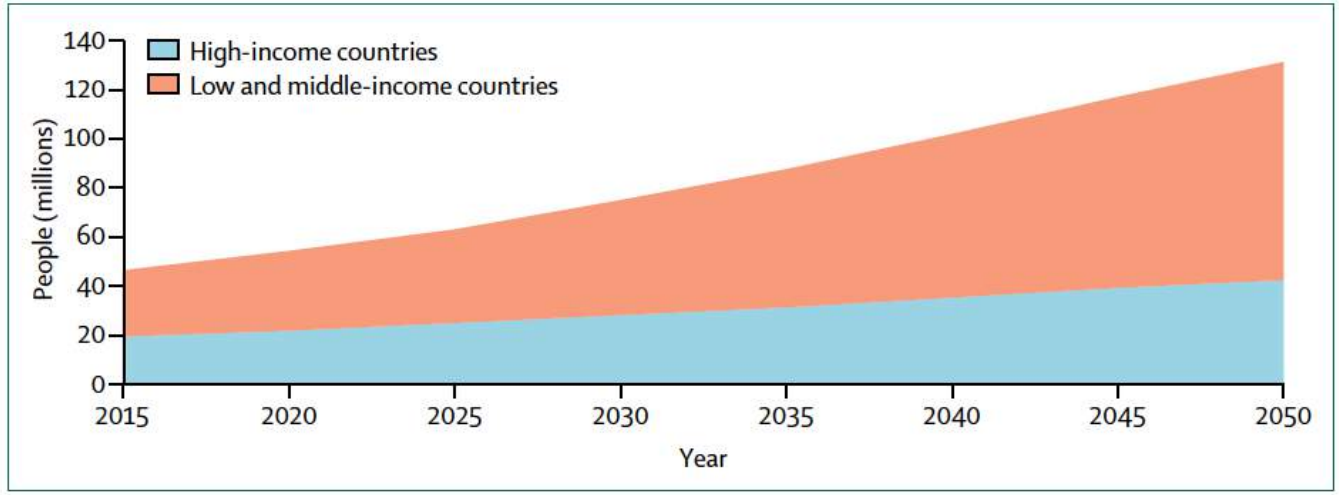
Malattia di Alzheimer

Alois Alzheimer (1863-1915)

Malattia di Alzheimer (AD)

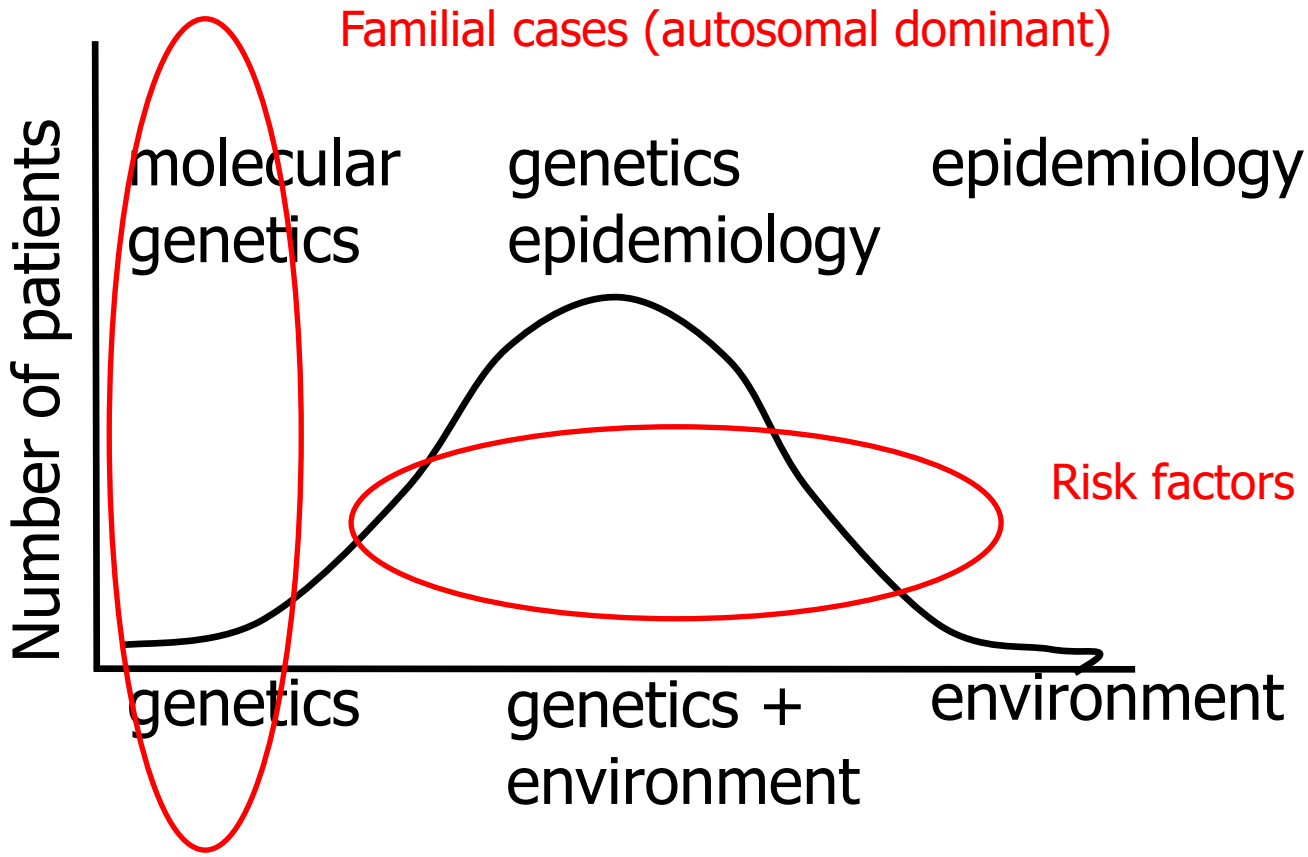
- 1907, Alois Alzheimer descrisse una donna di 51 anni, con delirio paranoide con disturbo mnesico ed afasia.
- Nell' encefalo, accumuno anomalo di materiale usando colorazione argentica con dimostrazione di placche senili organizzate intorno ad un nucleo di amiloide.
- Inoltre, grovigli neurofibrillari citoplasmatici.
- Krepelin introdusse il termine di AD.
- Nel '60, Blessed, Tomlinson, Roth dimostrarono il parallelismo tra no. di placche senili e severità della compromissione cognitiva.
- Prima considerata rara, oggi AD è la quarta causa di morte, una delle più comuni malattie dell' anziano.
- Nel 1932 riportata la prima AD familiare, oggi 10%.

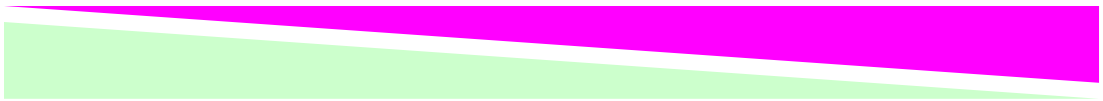
Demenza: l' impatto !

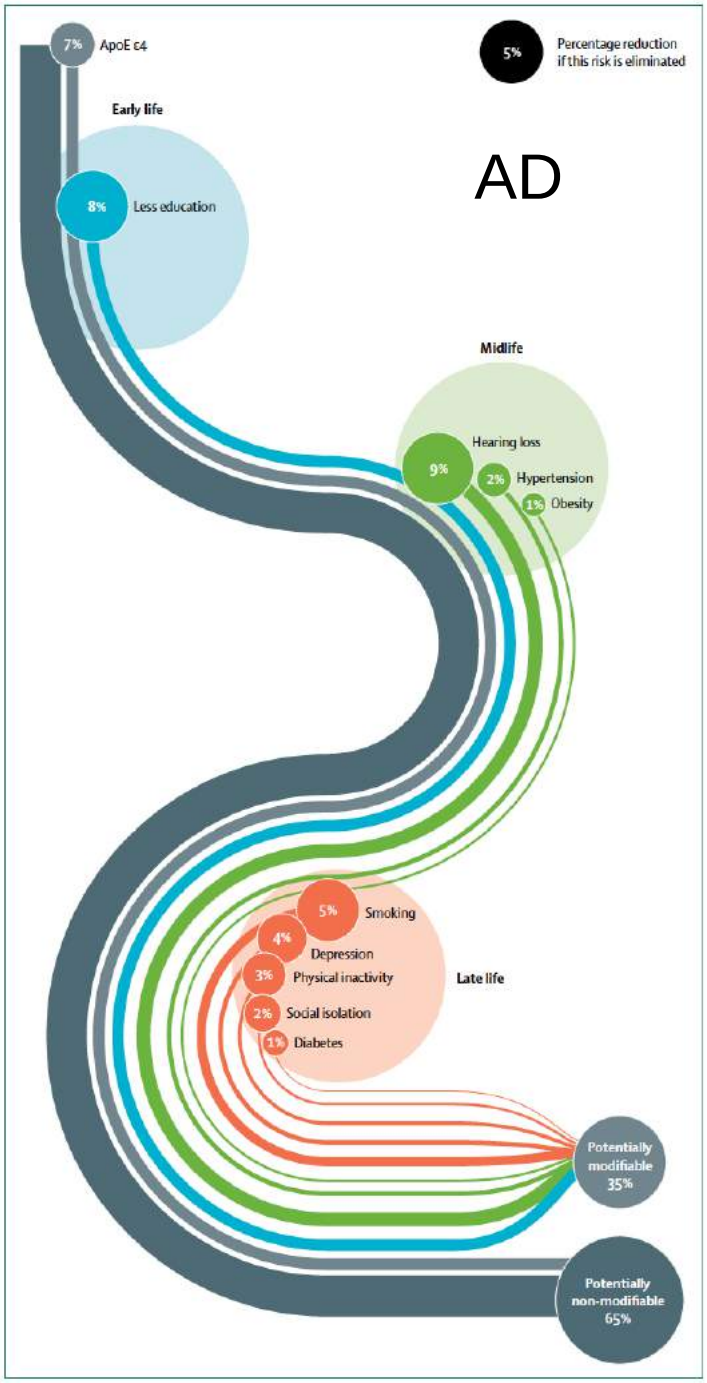


Livingston et al., 2017, The Lancet

AD: multifactorial disease

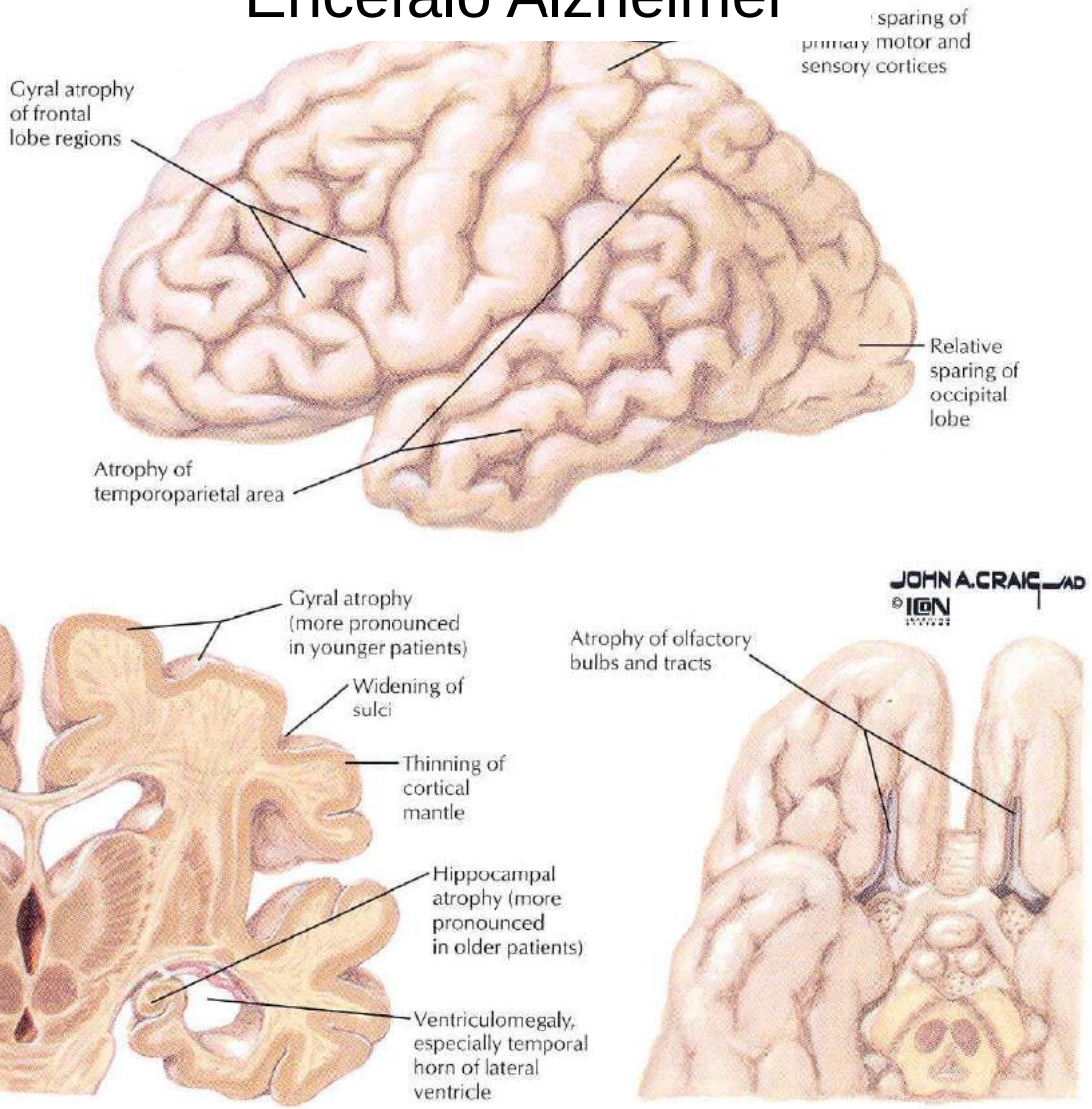


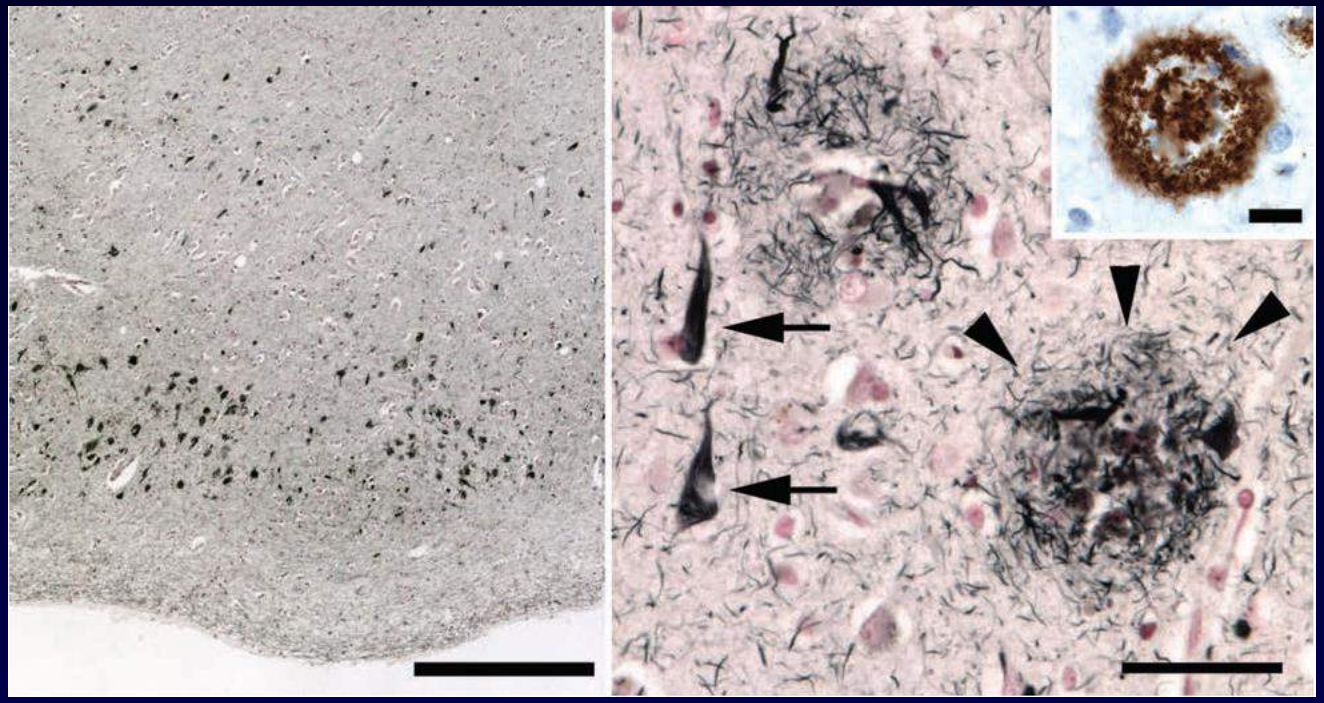


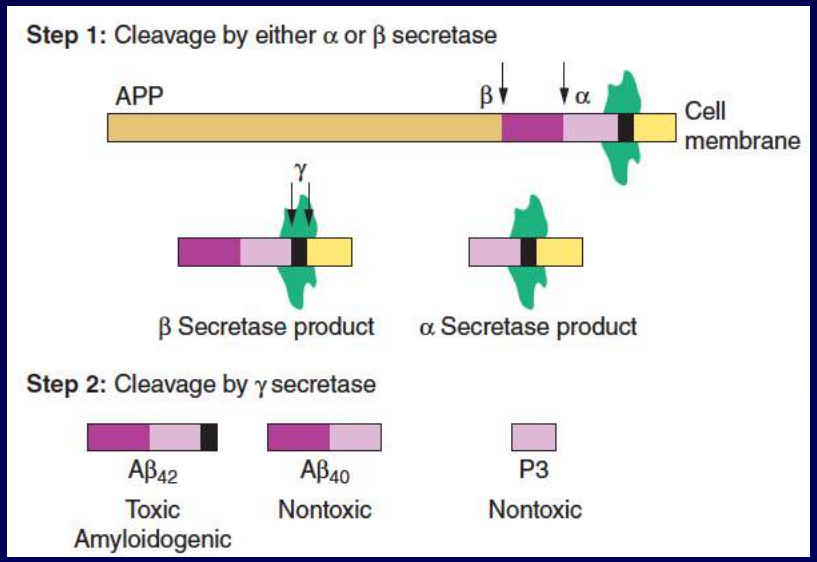


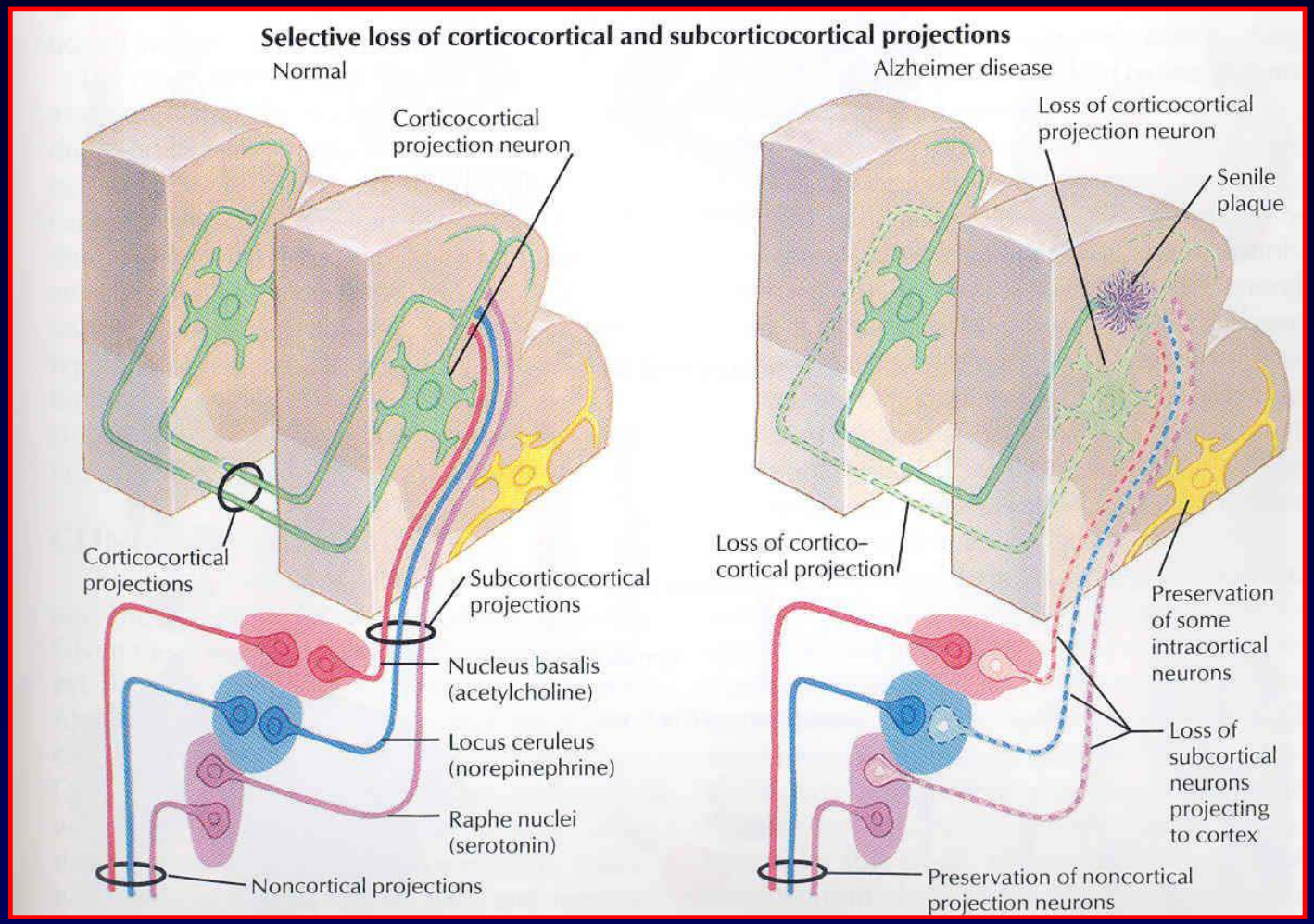
Livingston et al., 2017, The Lancet

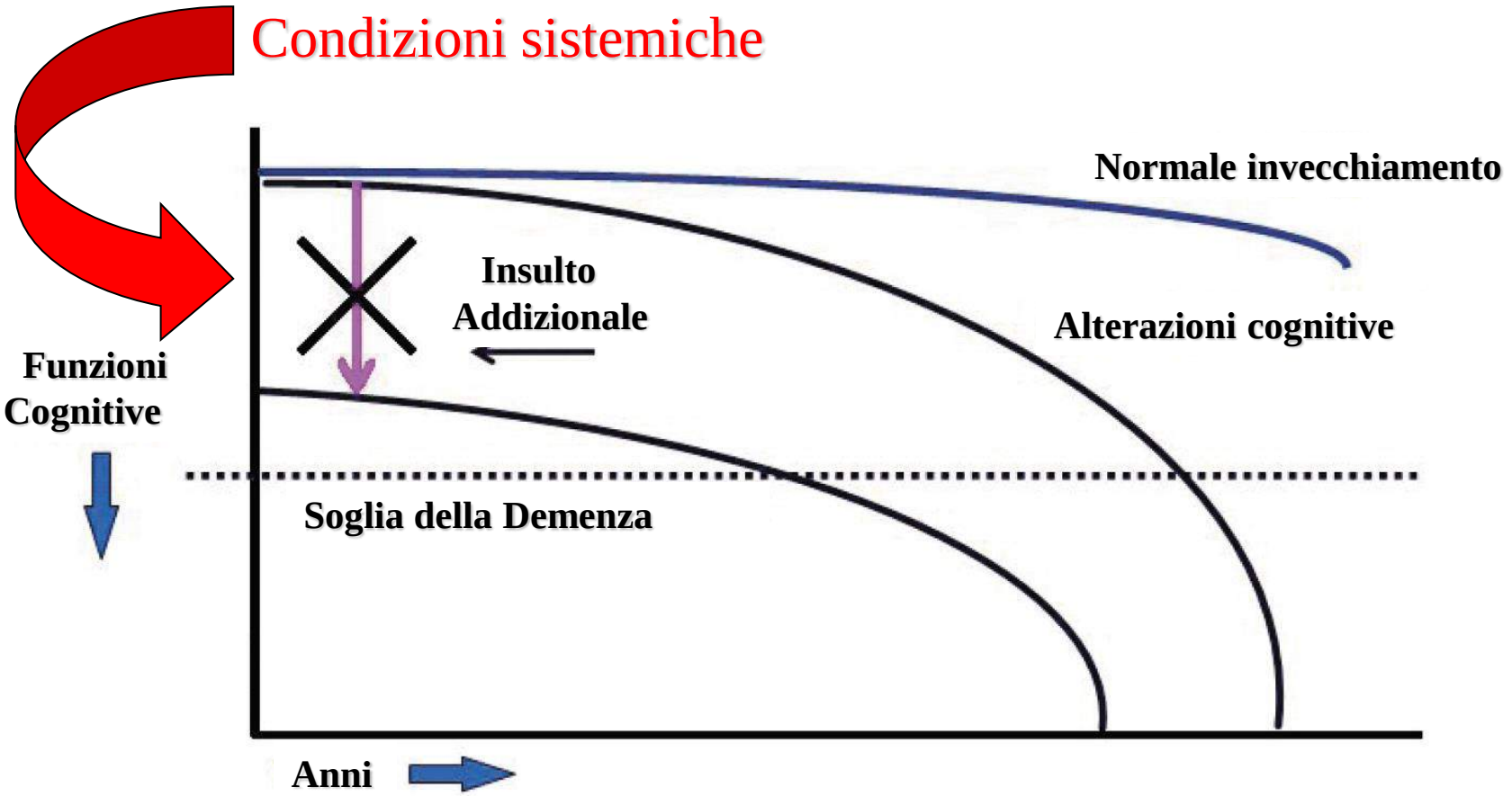
Encefalo Alzheimer






Step 1: Cleavage by either α or β secretase
APP
β
α
Cell membrane
γ
β Secretase product
α Secretase product
Step 2: Cleavage by γ secretase
Aβ42
Toxic
Amyloidogenic
Aβ40
Nontoxic
P3
Nontoxic


Selective loss of corticocortical and subcorticocortical projections
Normal
Corticocortical projection neuron
Corticocortical projections
Subcorticocortical projections
Nucleus basalis (acetylcholine)
Locus ceruleus (norepinephrine)
Raphe nuclei (serotonin)
Noncortical projections
Alzheimer disease
Loss of corticocortical projection neuron
Senile plaque
Loss of cortico–cortical projection
Preservation of some intracortical neurons
Loss of subcortical neurons projecting to cortex
Preservation of noncortical projection neurons



Daffner, 2010

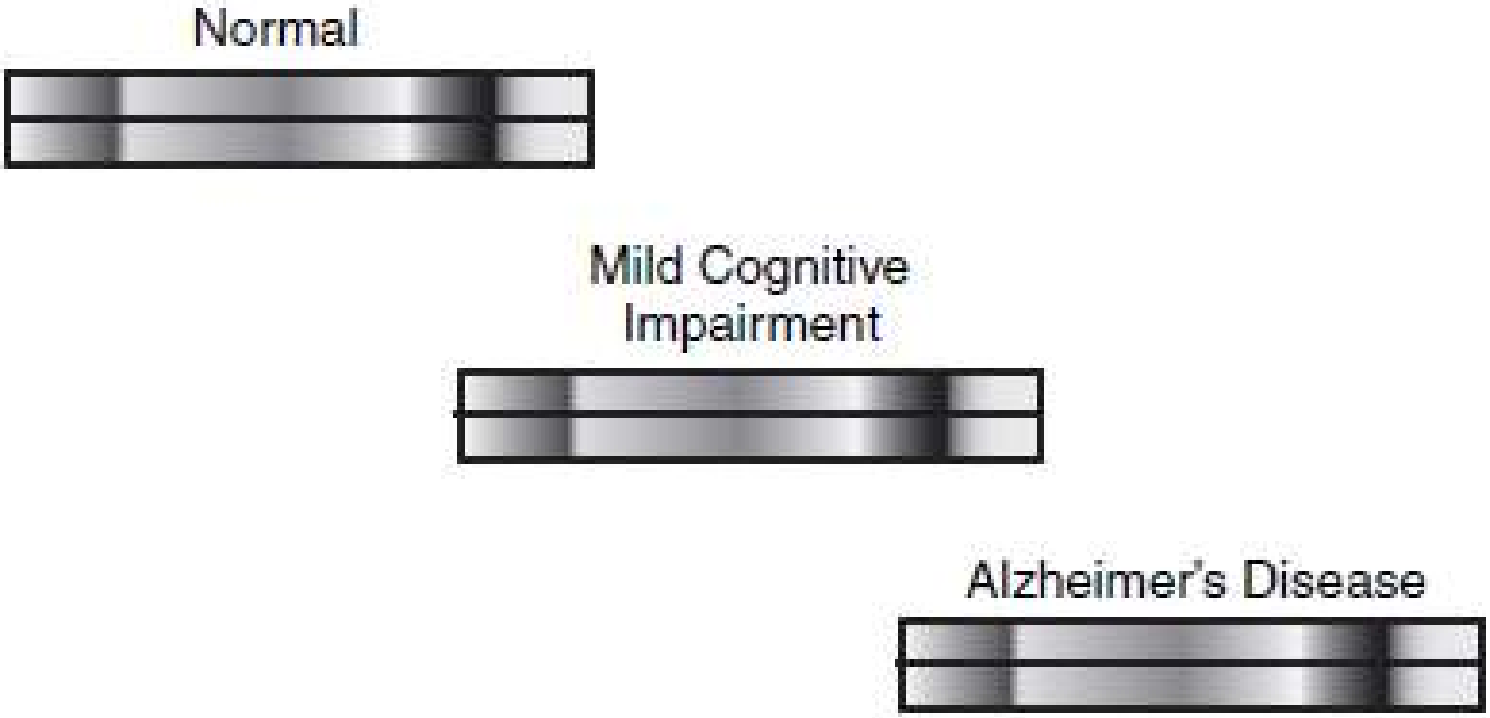
Mild Cognitive Impairment: *An Overview*

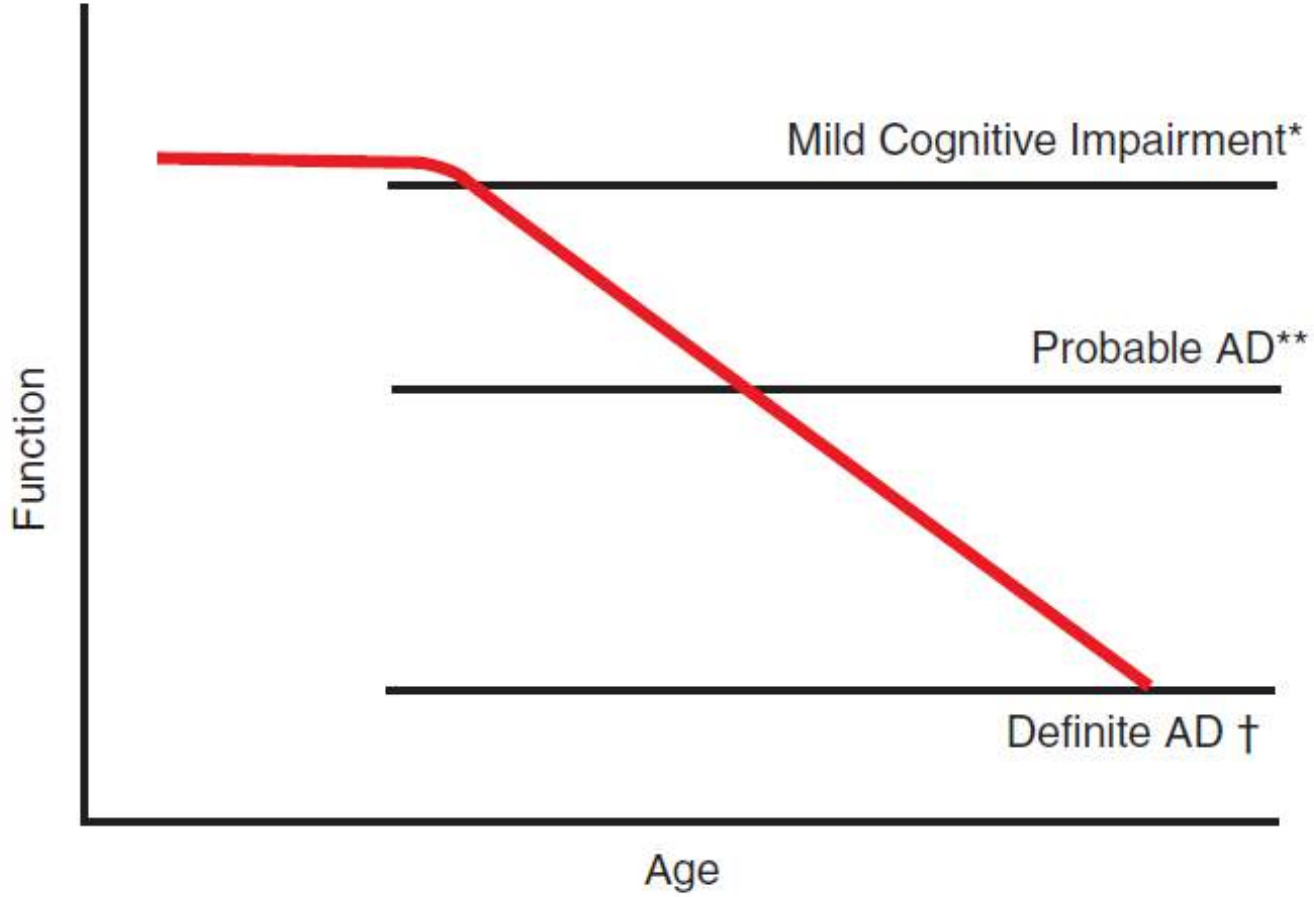
By Ronald C. Petersen, MD, PhD, and Selamawit Negash, PhD

TABLE.
MCI Original Criteria

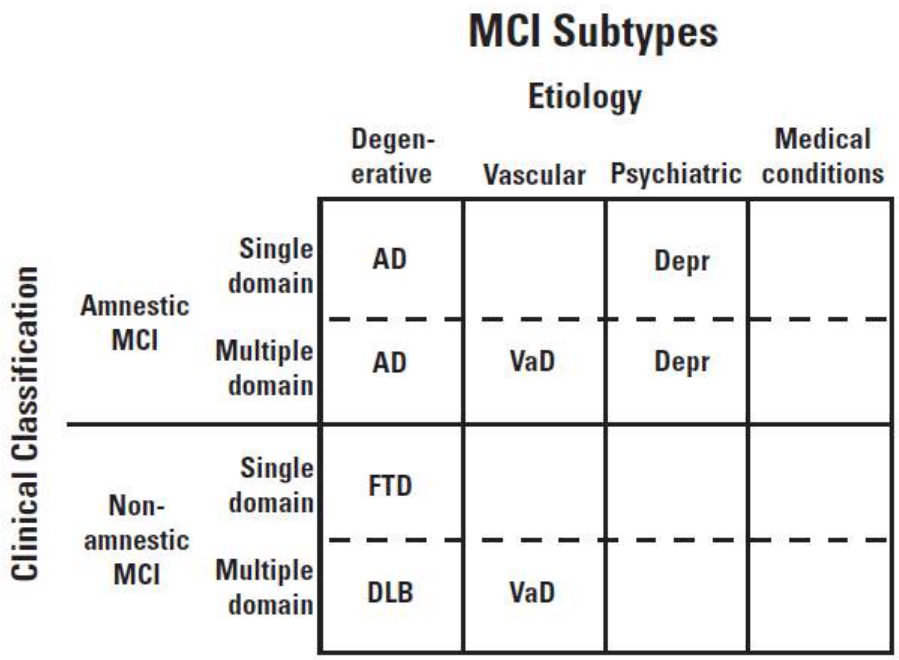
1. Memory complaint, preferably qualified by an informant
2. Memory impairment for age
3. Preserved general cognitive function
4. Intact activities of daily living
5. Not demented

Petersen R, Negash S. *CNS Spectr*. Vol 13, No 1. 2008.


Normal
Mild Cognitive Impairment
Alzheimer's Disease

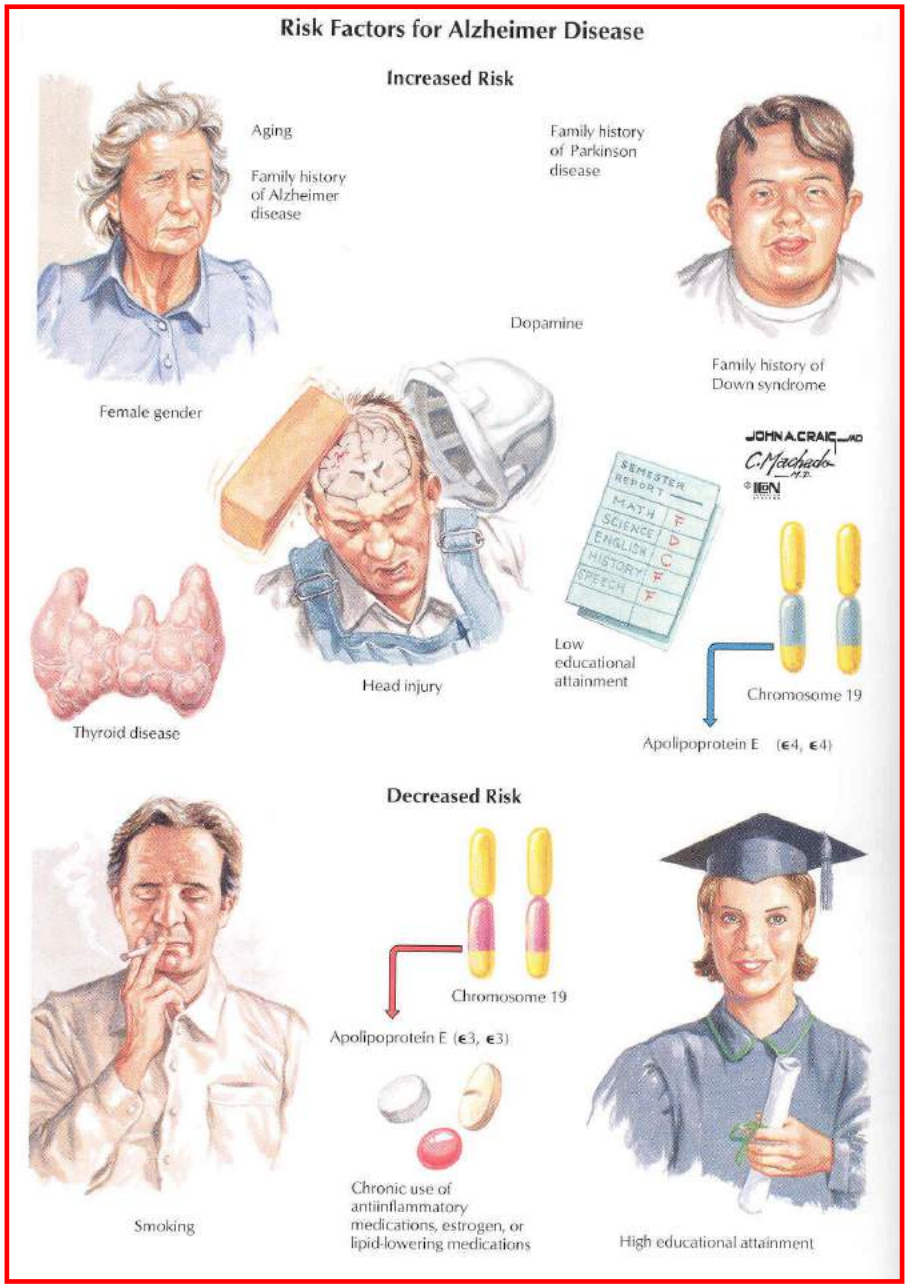

Mild Cognitive Impairment*
Probable AD**
Definite AD †
Function
Age

Predicted outcome of MCI subtypes according to presumed etiology

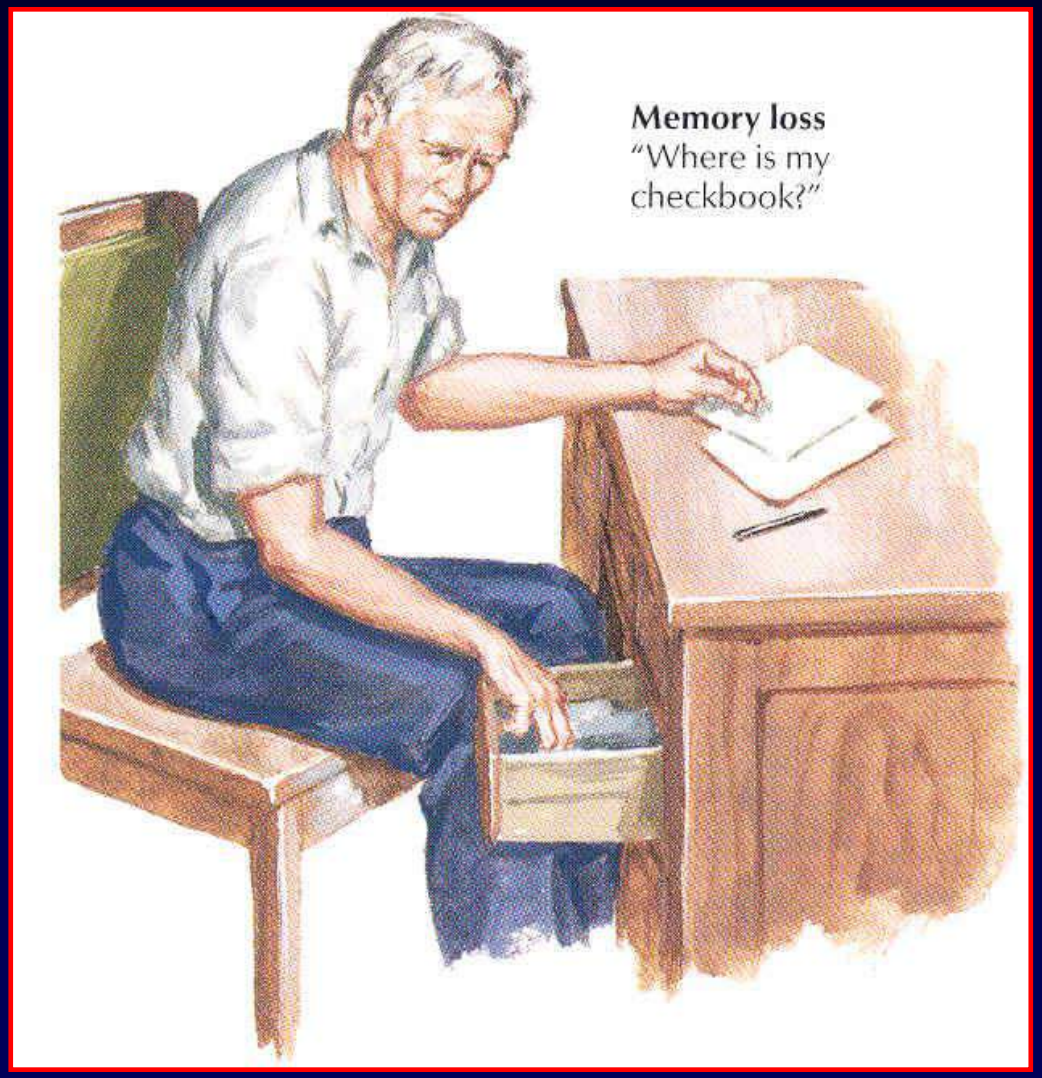


MCI=mild cognitive impairment; AD=Alzheimer's disease; Depr=depression; VaD=vascular dementia; FTD=frontotemporal dementia; DLB=dementia with Lewy bodies.

Petersen R, Negash S. *CNS Spectr.* Vol 13, No 1. 2008.


Risk Factors for Alzheimer Disease
Increased Risk
Aging
Family history of Alzheimer disease
Female gender
Family history of Parkinson disease
Dopamine
Family history of Down syndrome
Head injury
Thyroid disease
SEMESTER REPORT
MATH F
SCIENCE D
ENGLISH C
HISTORY F
SPEECH F
Low educational attainment
JOHN A. CRAIG M.D.
C. Machado M.D.
Chromosome 19
Apolipoprotein E (ε4, ε4)
Decreased Risk
Smoking
Chromosome 19
Apolipoprotein E (ε3, ε3)
Chronic use of antiinflammatory medications, estrogen, or lipid-lowering medications
High educational attainment

I sintomi:



Spatial disorientation
"Could you direct me to my office? I have the address written down here somewhere, but I can't seem to find it."

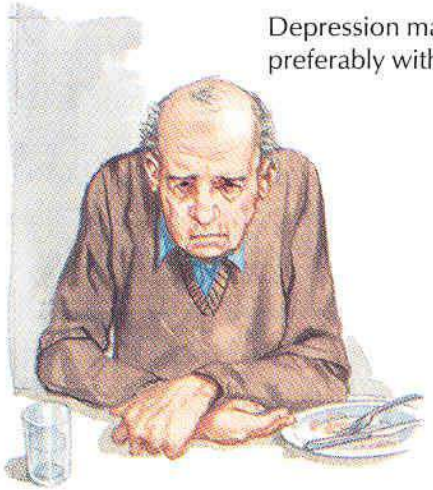
Circumlocution
Asks husband, "John dear, please call that woman who fixes my hair."

More advanced phase
Sloppy dressed, slow, apathetic, confused, disoriented, stooped posture

Pharmacologic Management Options in Alzheimer Disease

Behavioral disturbances

Depression may be managed with antidepressants, preferably with little anticholinergic effect.

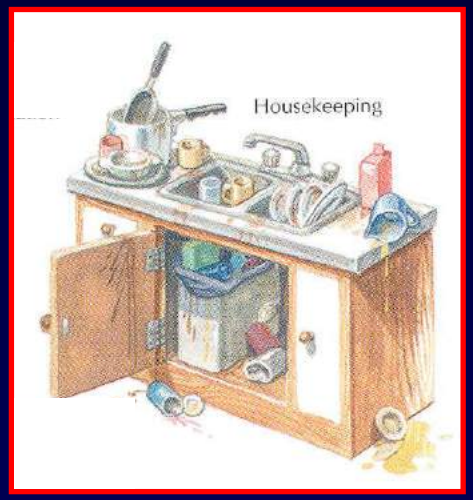


Insomnia and nocturnal wandering may be controlled with short-acting benzodiazepines.

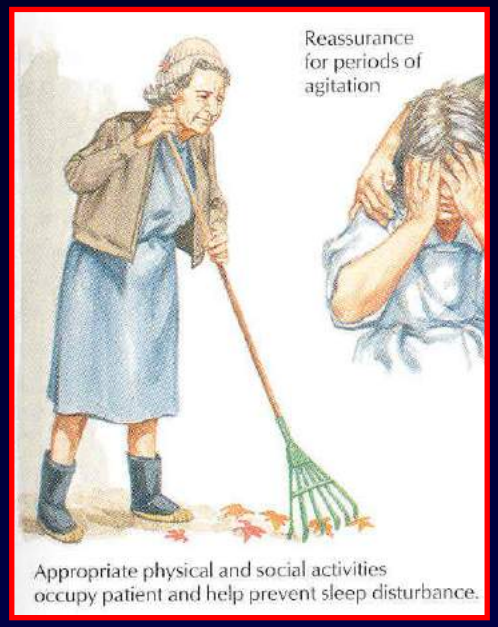
Anxiety, agitation, and delusions and hallucinations can be managed with anxiolytic and neuroleptic medications.

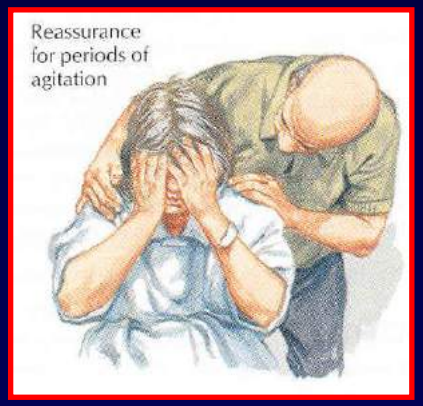
Daily Living Assessment and Nonpharmacologic Management

Caregiver assessment

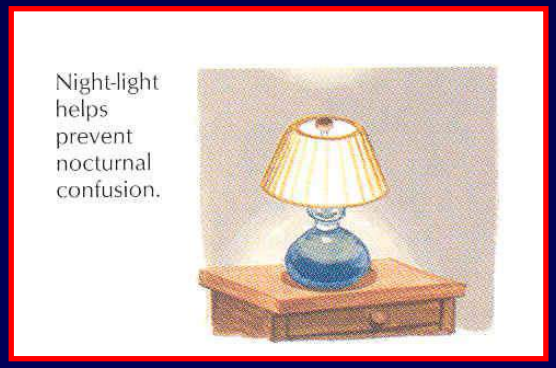


Opzioni:

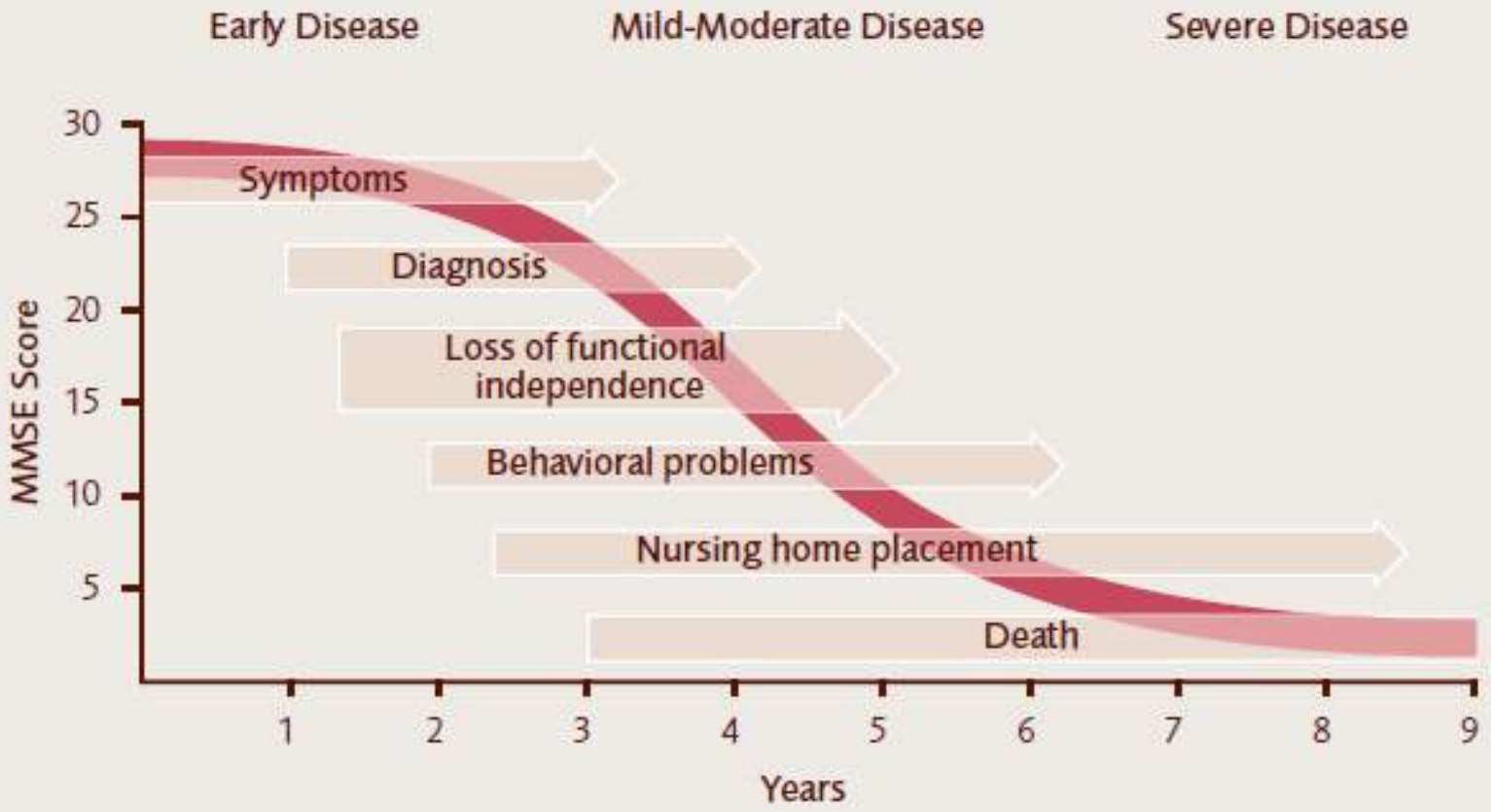

Reassurance for periods of agitation
Appropriate physical and social activities occupy patient and help prevent sleep disturbance.

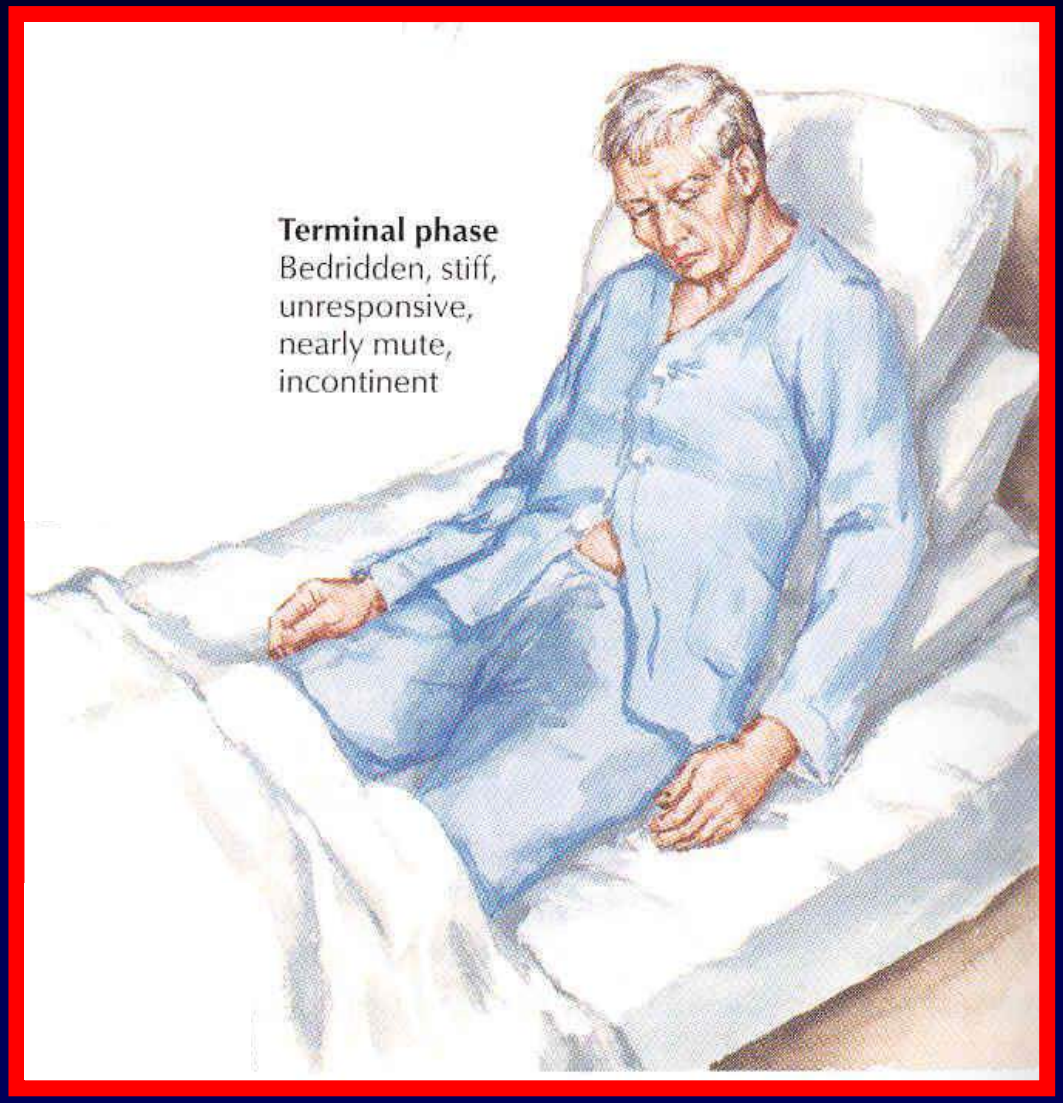

Reassurance for periods of agitation


Identification bracelet for wandering patients
JANE DOE
102 ELM COURT
327-0000
Motion detectors warn of wandering.


Night-light helps prevent nocturnal confusion.

Storia naturale della AD



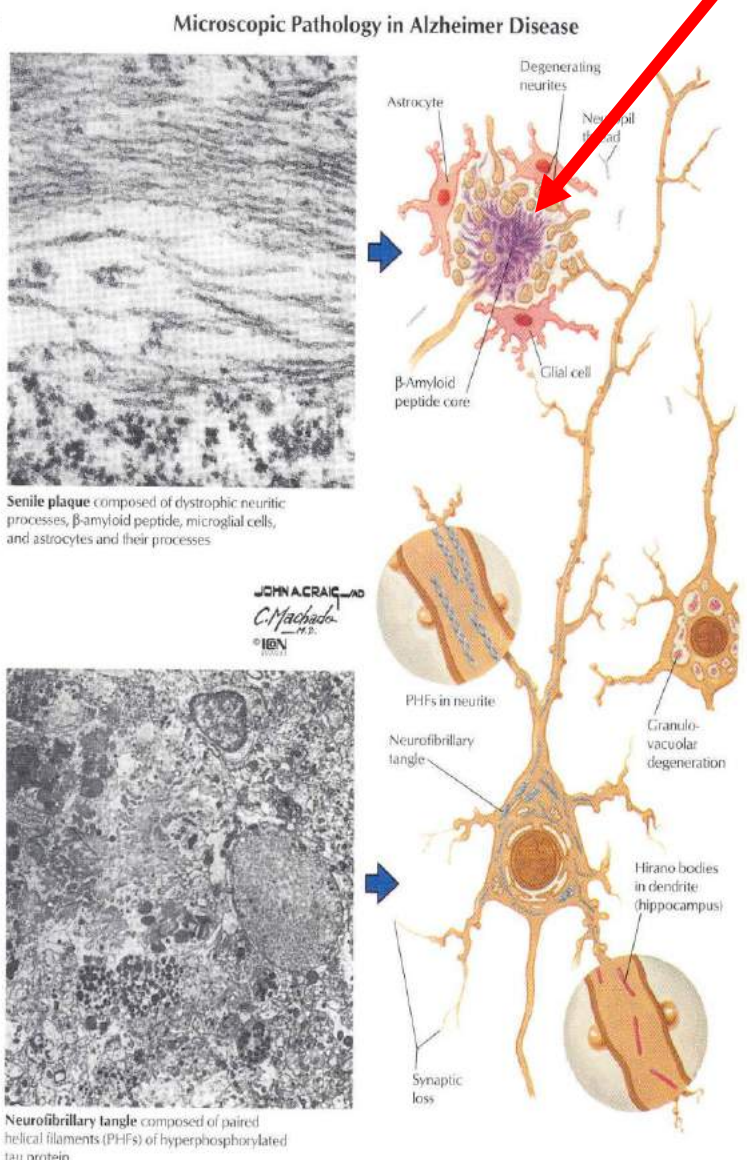

Terminal phase
Bedridden, stiff,
unresponsive,
nearly mute,
incontinent

Encefalo

PiB >

LCR

Plasma



Ab42 <

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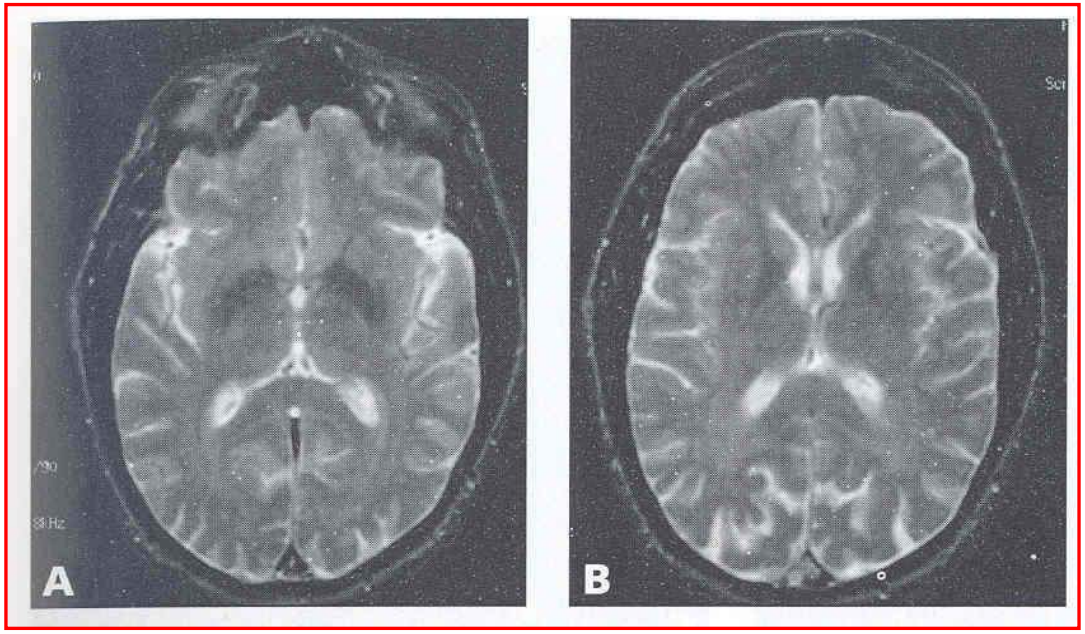
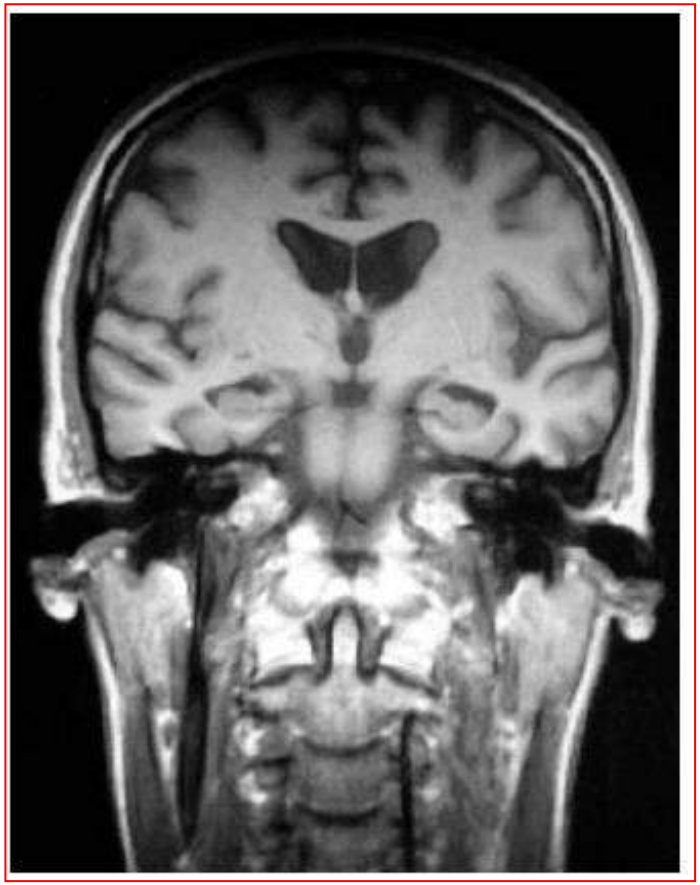
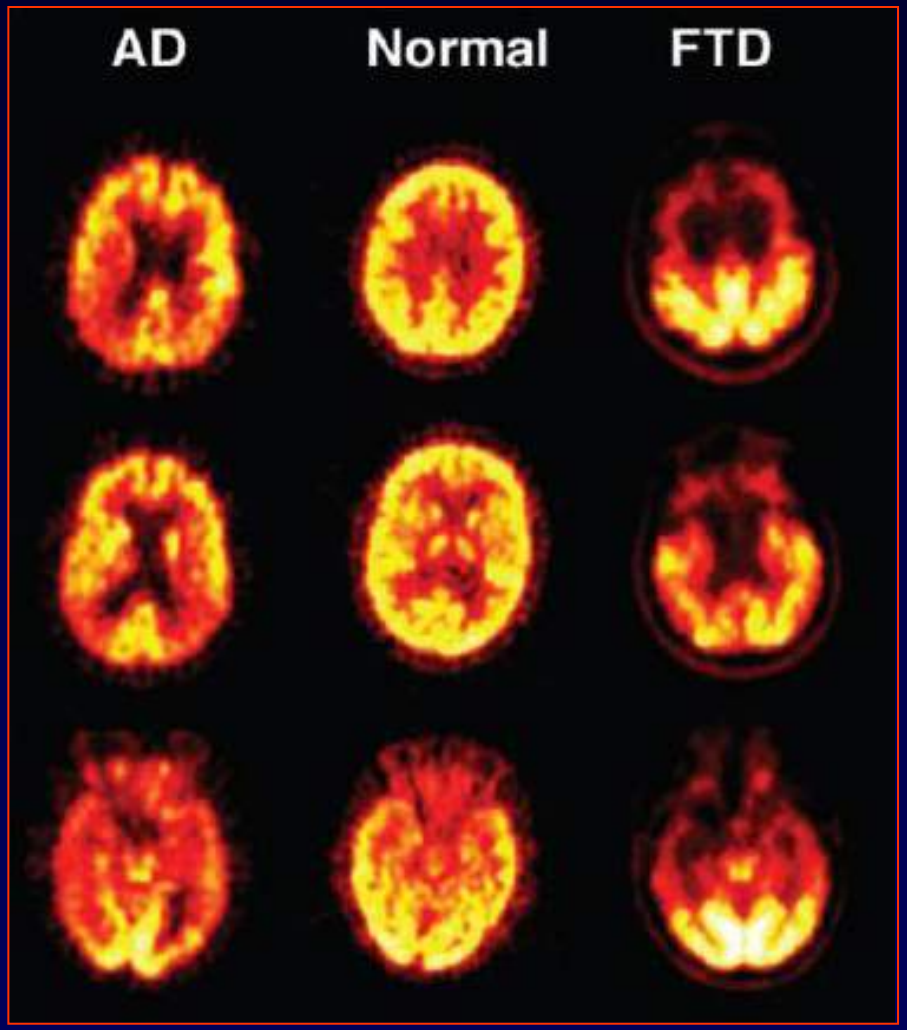
Neuroimaging





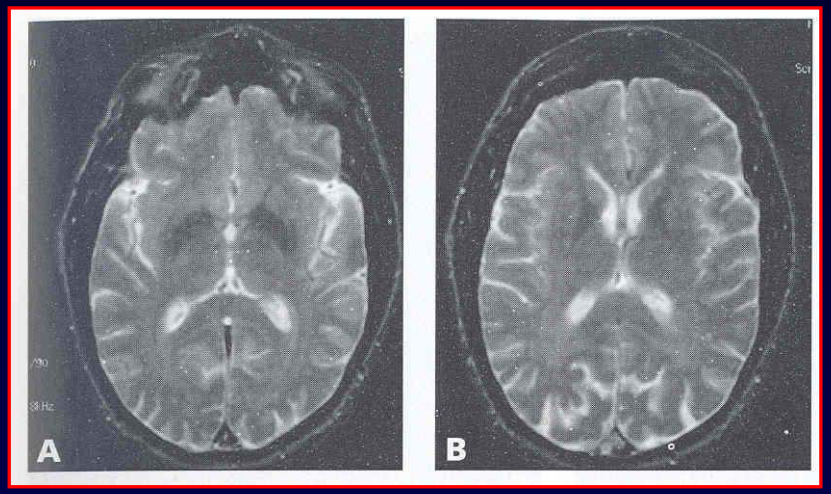
PET Molecular imaging of AD

[18F]fluorodeoxyglucose-PET

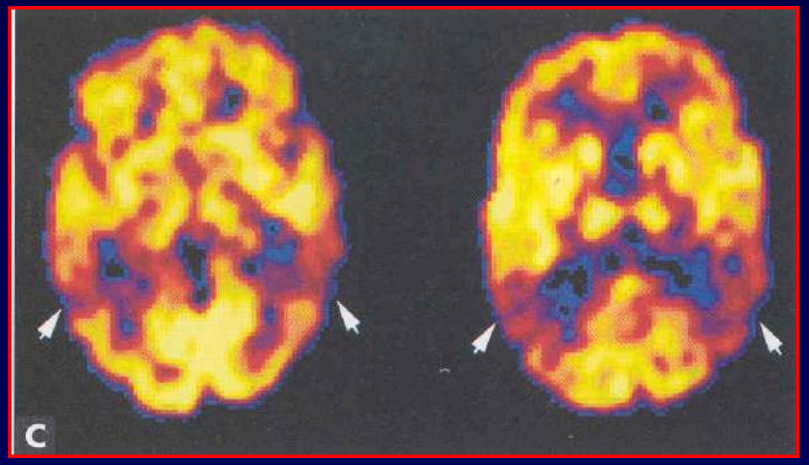


A retrospective clinical-pathological analysis using visual interpretation of PET images found 93% sensitivity and 76% specificity for the prediction of pathological AD

Silverman DH et al, JAMA 2001

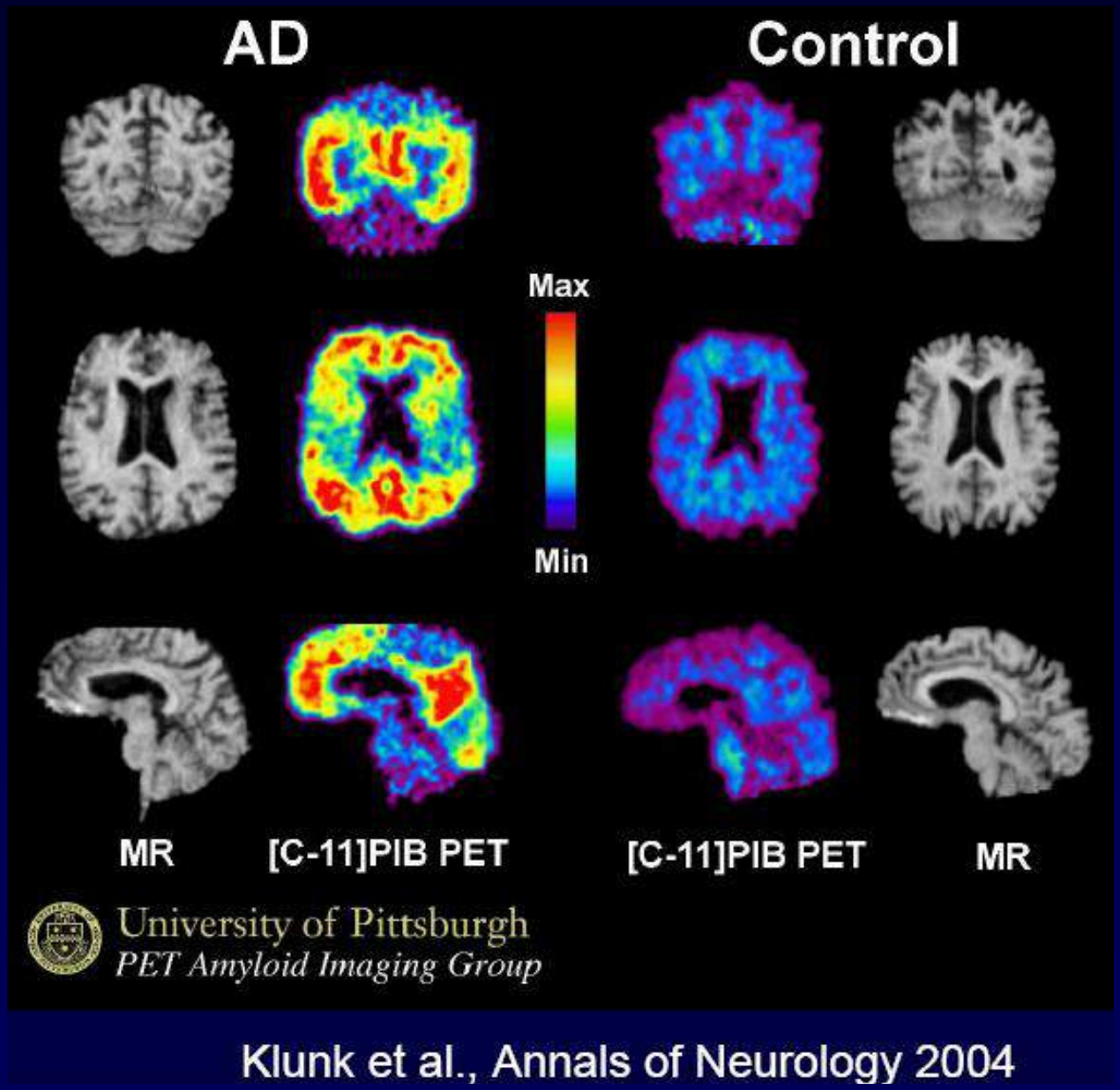


AD - RM

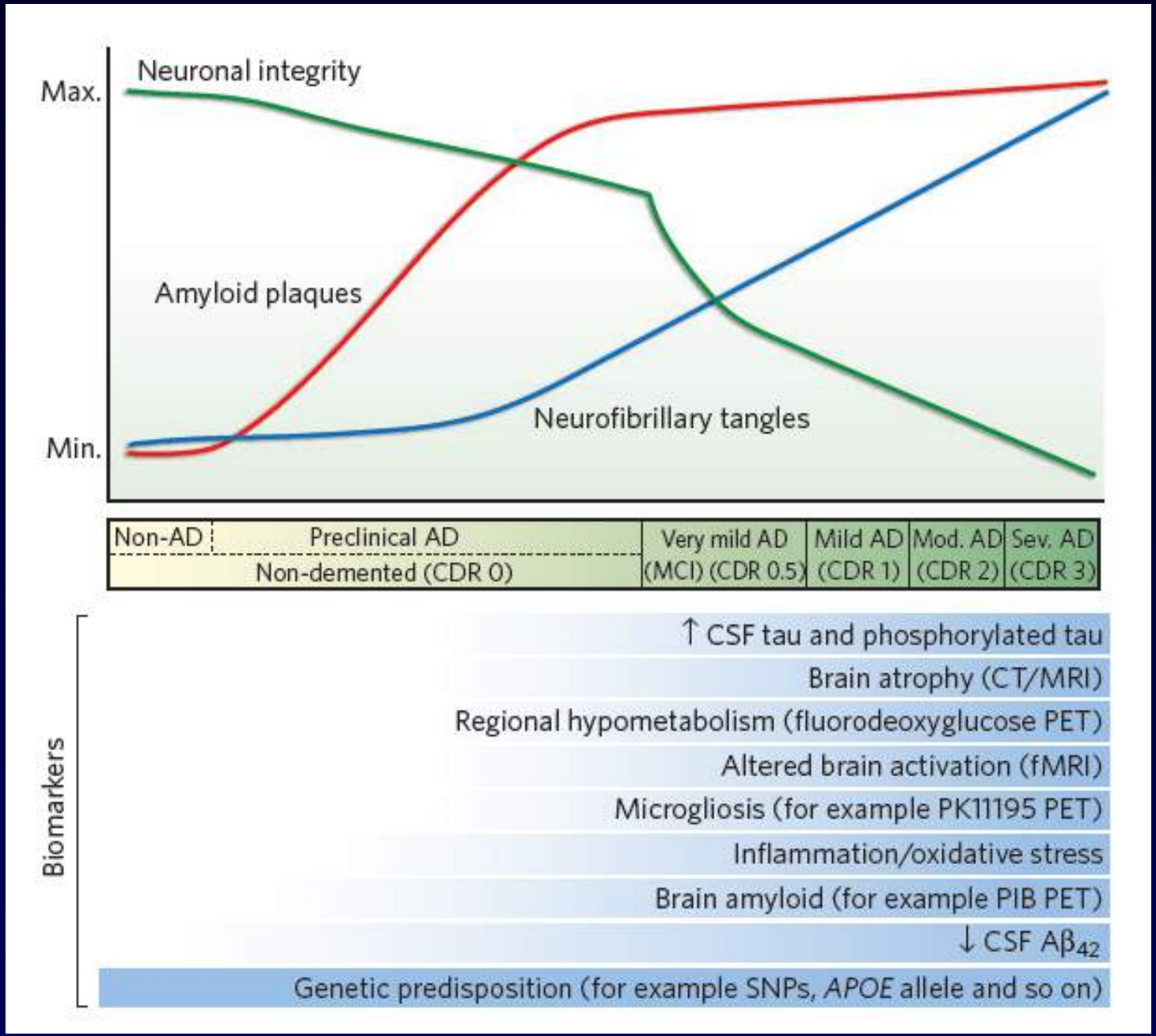


AD - PET

Pittsburgh compund P (PiB)



Klunk et al., Annals of Neurology 2004


Max.
Min.
Neuronal integrity
Amyloid plaques
Neurofibrillary tangles
Non-AD
Preclinical AD
Non-demented (CDR 0)
Very mild AD (MCI) (CDR 0.5)
Mild AD (CDR 1)
Mod. AD (CDR 2)
Sev. AD (CDR 3)
Biomarkers
↑ CSF tau and phosphorylated tau
Brain atrophy (CT/MRI)
Regional hypometabolism (fluorodeoxyglucose PET)
Altered brain activation (fMRI)
Microgliosis (for example PK11195 PET)
Inflammation/oxidative stress
Brain amyloid (for example PIB PET)
↓ CSF $A\beta_{42}$
Genetic predisposition (for example SNPs, *APOE* allele and so on)

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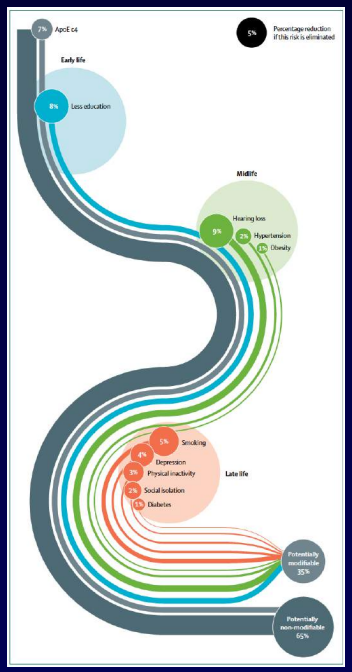
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network



> 20 anni !!

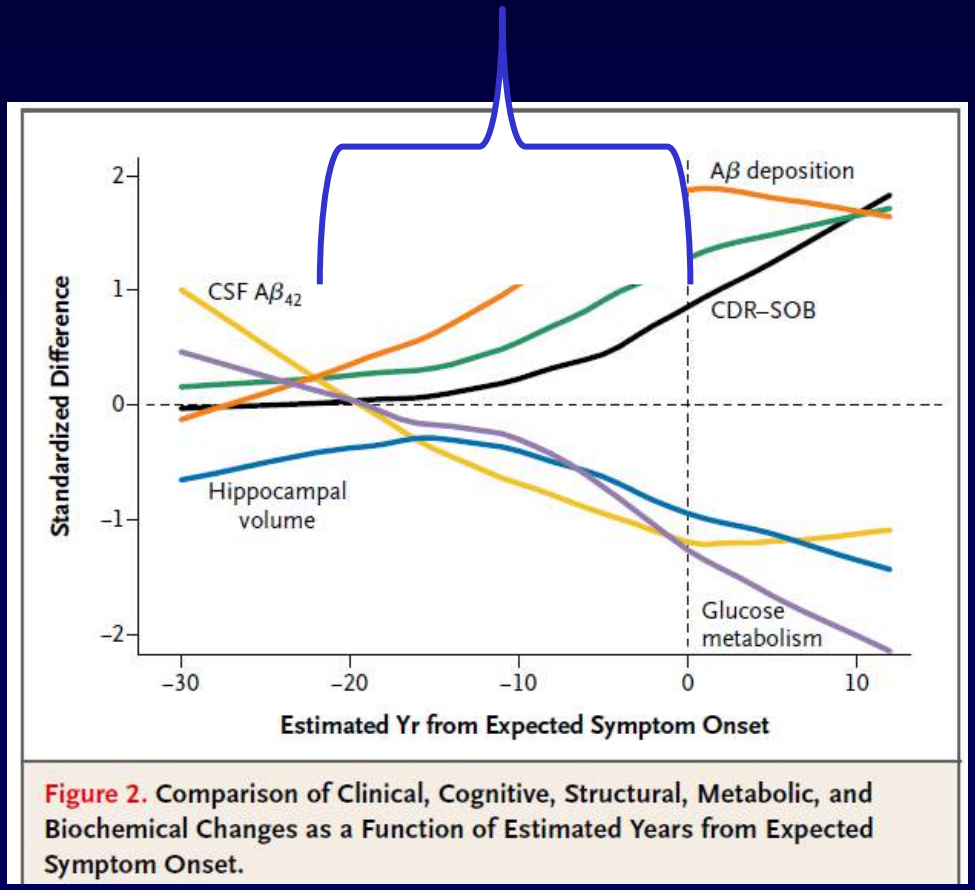
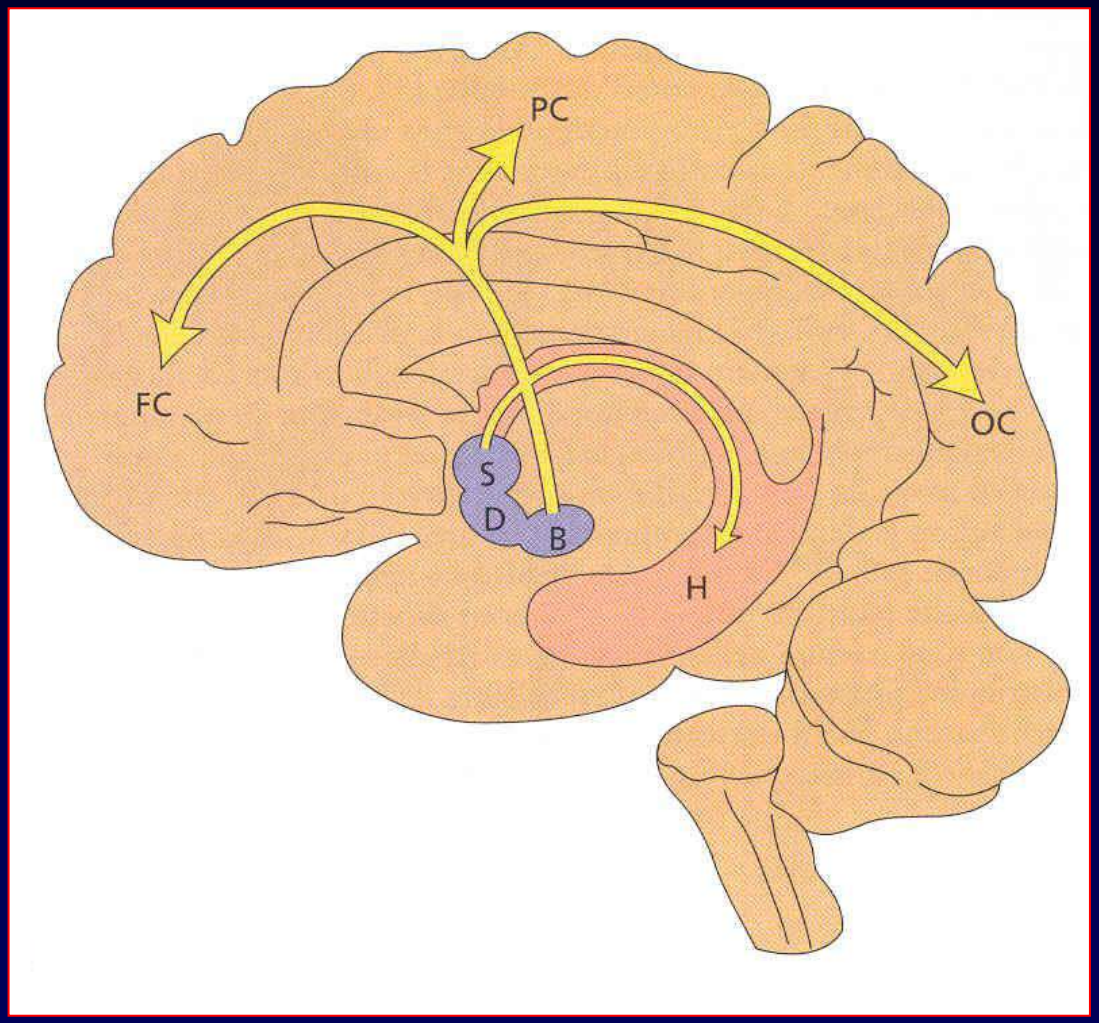


Figure 2. Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset.

AD: gestione

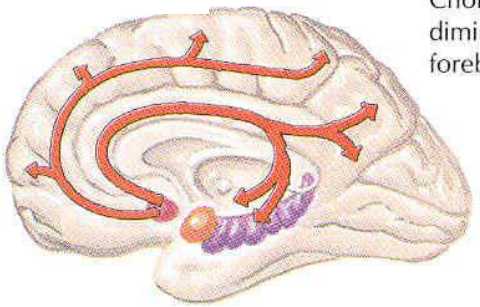
- Frequenti episodi confusionali per problemi medici intercorrenti.
- Depressione.
- Comportamenti aggressivi (neurolettivi e benzodiazepine breve emivita).
- Problemi sessuali.
- Caregiver: richiedono supporto adeguato.



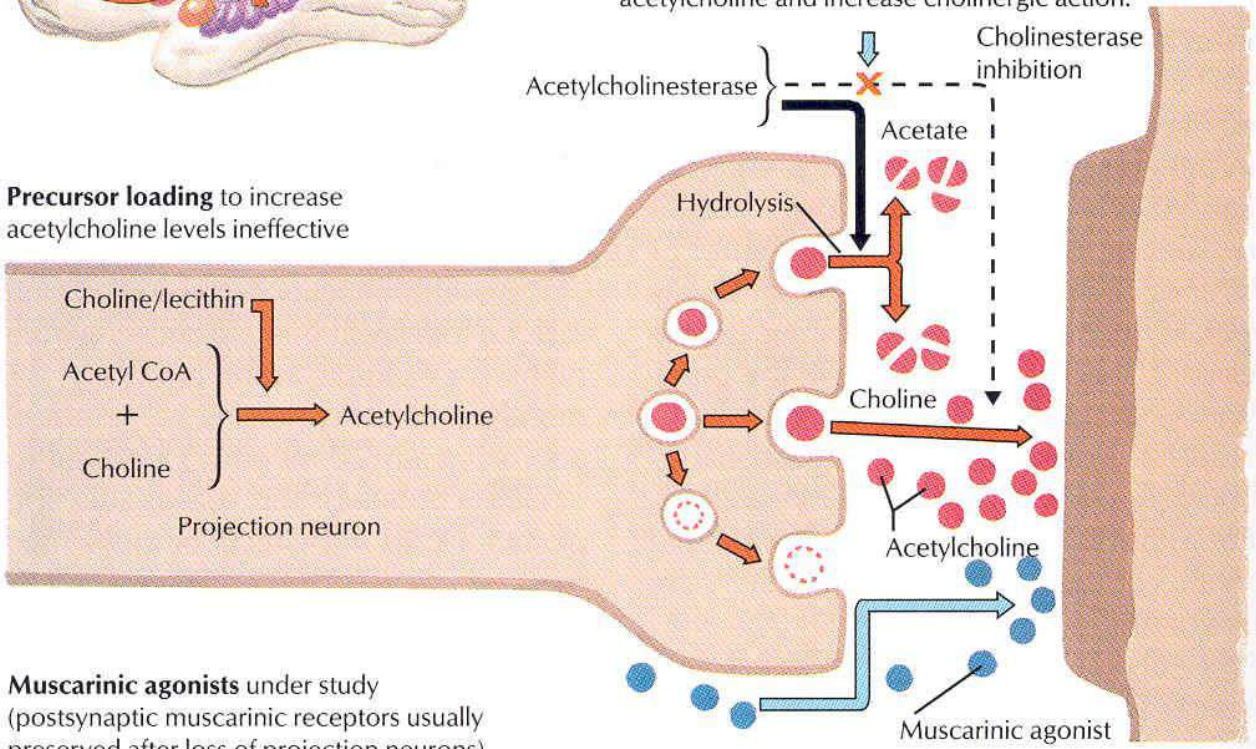
Ipotesi colinergica-taupatia (Mesulam et al, 2004)

Cholinergic approaches

Cholinergic therapies attempt to boost cholinergic function diminished by loss of cholinergic projections from basal forebrain to frontal cortex, amygdala, and hippocampus.



Cholinesterase inhibitors prevent hydrolysis of acetylcholine and increase cholinergic action.



Muscarinic agonists under study (postsynaptic muscarinic receptors usually preserved after loss of projection neurons)

AD: Terapia Farmacologica

- Trattamento con farmaci anticolinesterasici
  - Donepezil (5 - 10 mg /die)
  - Galantamina (8-24 mg /die)
  - Rivastigmina (3-12 mg/die)

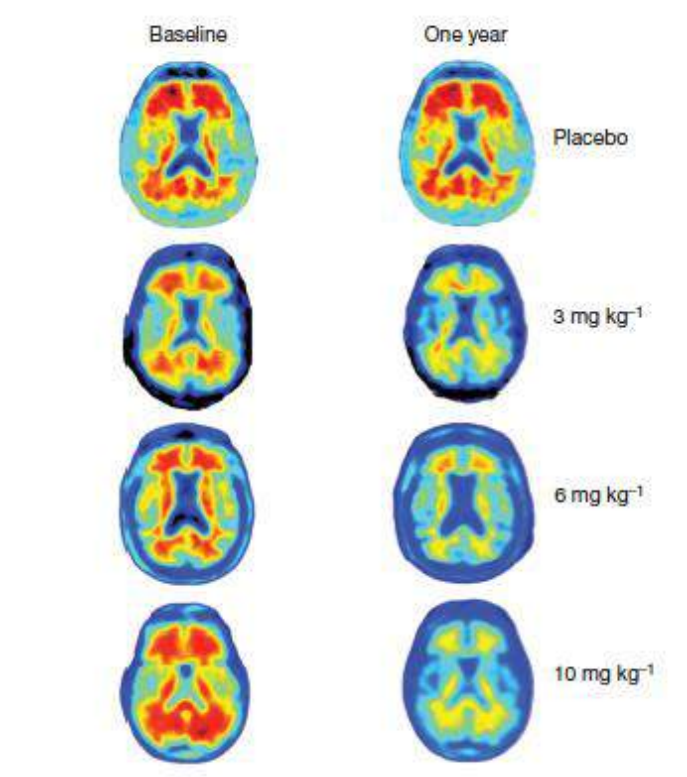
ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

2016….



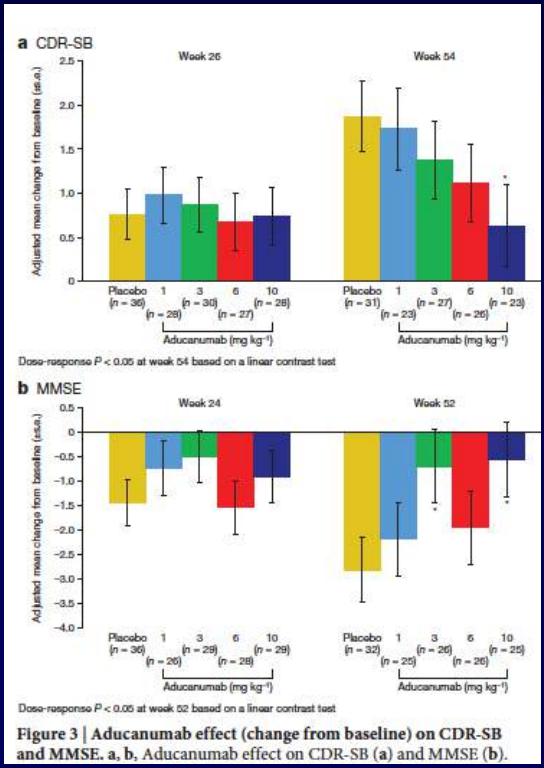


Figure 3 | Aducanumab effect (change from baseline) on CDR-SB and MMSE. a, b, Aducanumab effect on CDR-SB (**a**) and MMSE (**b**).

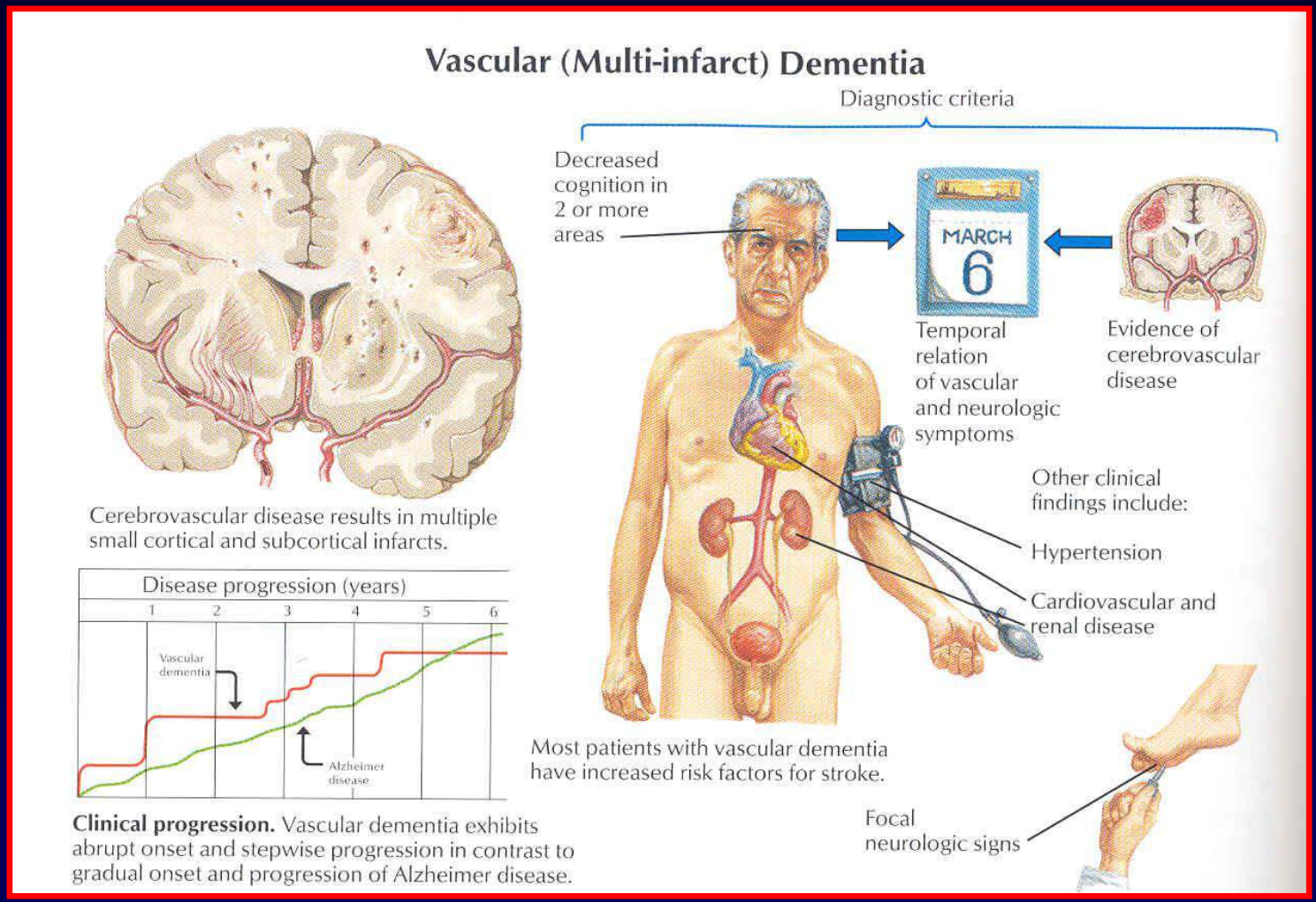
Le cure palliative

Le equipe multidisciplinari specifiche per malattia

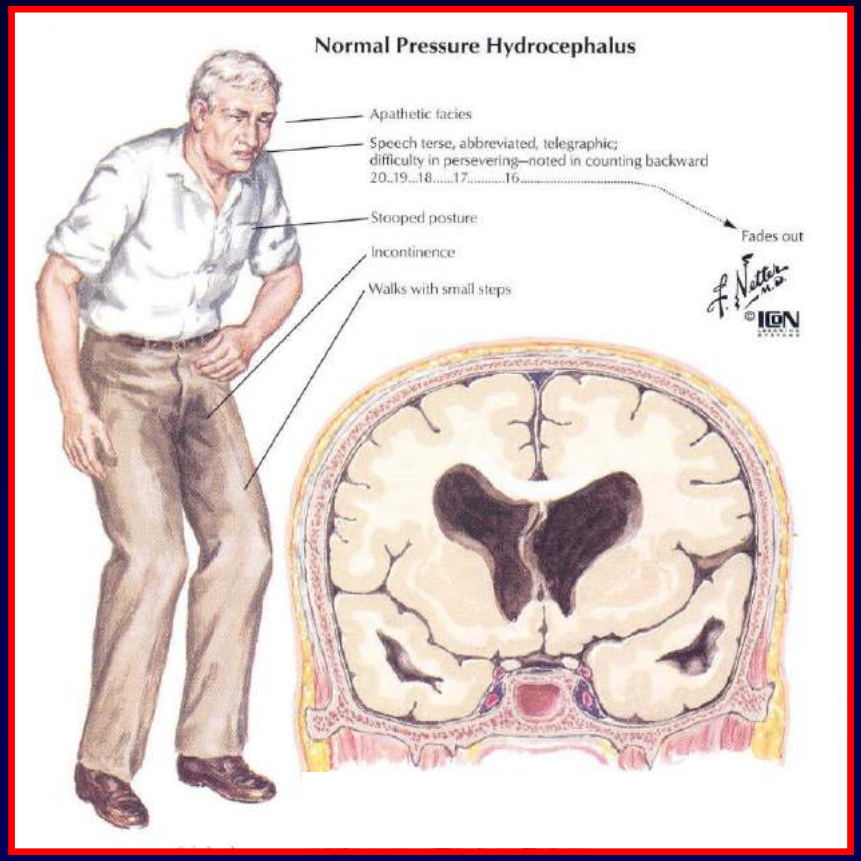
L' attenzione per il caregiver

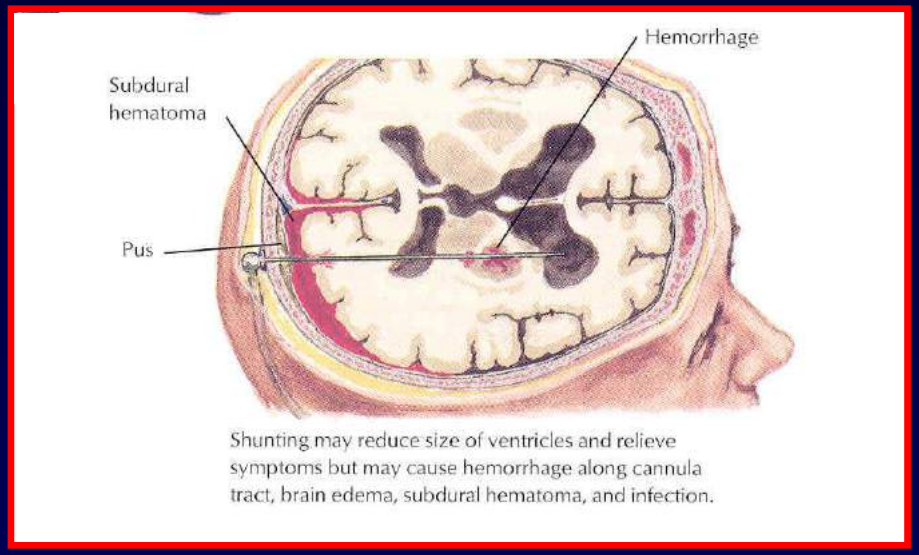
Le Associazioni dei Pazienti

Diagnosi differenziale



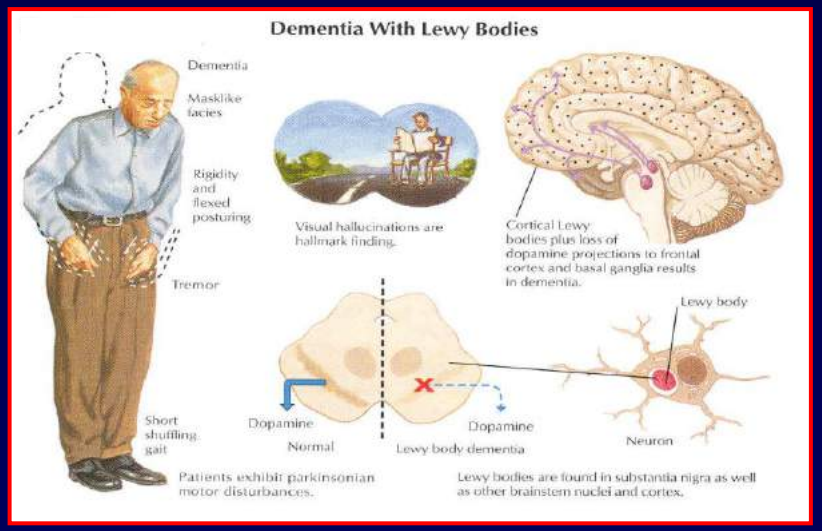
Diagnosi differenziale





Demenza con Corpi di Lewy (DLB)

- Okazaki, 1961, ritenuta erroneamente rara
- Spesso corpi di Lewy + istopatologia AD (placche senili)



DLB: clinica

- Sindrome dementigena + PDismo.
- Esordio con disturbi cognitivi seguiti da PDismo raramente asimmetrico, tremore a riposo raro.
- Disturbi cognitivi similari AD, ma funzioni visuospaziali e memoria visiva più seriamente compromesse.
- Fluttuazioni (frequenti ed improvvise) ed allucinazioni visive (persone fisse - 80%), con fasi di lucidità anche tardive.
- Marcata sensibilità ai neurolettici.
- Disturbi del sonno, cadute, episodi sincopali.
- Mioclono frequente (DD CJD).

Comparison of DLB and AD Manifestations*

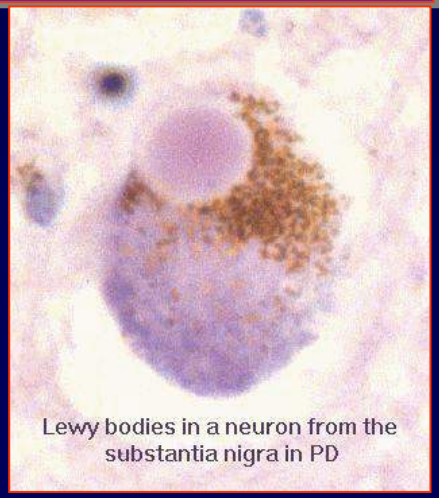
Manifestation	*DLB*	*AD*
Memory loss	Less pronounced, poor retrieval	Characteristic, poor encoding
Visuospatial and construction *skills*	Severely impaired early	Mildly impaired early
Executive function	Impaired earlier	Impaired later
Fluctuating mental status	Pronounced	Less pronounced
Psychotic features	Can be prominent early	Not typical early
Delusions	Bizarre, unrelated to impaired cognitive function	Often related to memory loss
Depression and anxiety	Common	Common
Parkinsonism	Within 1 to 2 years of dementia	Later in disease course

*AD indicates Alzheimer disease; DLB, dementia with Lewy bodies.

DLB: Indagini

- Laboratorio: non significativo
- Neuroimaging: atrofia temporo-parietale ed occipitale (scarsamente diagnostico)
- Neuropatologia: LB + grovigli neurofibrillari

Lewy bodies



Lewy bodies in a neuron from the substantia nigra in PD

Components of Lewy bodies in addition to α-synuclein

Structural proteins
Synaptic proteins: α-synuclein, synaptophysin, chromogranin A
Cytoskeletal elements: neurofilament, tau protein, MAP1, MAP2, tubulin, tropomyosin

Ubiquitin-proteasomal components
Ubiquitin, ubiquitin C-terminal hydrolase, multi-catalytic proteinase, Parkin (E3 ubiquitin ligase)

Stress-related proteins/chaperones
Chaperones: torsinA, αB-crystallin, heat shock proteins (HSP70), 14-3-3
Stress-related: p38, glutathione S-transferase, heme oxygenase, superoxide dismutase-1

Neuroinflammatory
Immunoglobulins, complement, α2-macroglobulin

Kinases
Cdk-5, calcium-calmodulin kinase, extracellular receptor kinase (ERK)

Miscellaneous
gelsolin-related amyloid protein, βAPP, calbindin, tyrosine hydroxylase, retinoblastoma protein, ubiquitin, sphingomyelin, Bcl-2

DLB: epidemiologia

- Stime di prevalenza difficili in assenza di conferma istologica
- DLB circa 15-20% casi demenza (seconda causa)
- Esistono DLB familiari non associate a mutazioni della a-synucleina

DLB: gestione

- Difficoltosa: farmaci anti-PD utili ma peggiorativi si allucinazioni e confusione.
- Neurolettici antiDa gravememnete peggiorativi di PDismo e funzioni cognitive (pericolo di morte).
- Talvolta meglio non trattare.
- Anticolinergici da evitare, anticolinesterasici?

Demenze Fronto-Temporali (FTD)

- Gruppo a varia eziologia con lobo frontale e/o temporale selettivamente interessati unitamente a degenerazione subcorticale.
- Gustafson e Brun (1990): degenerazione frontale non-AD, esordio 50-60a, con disturbi di personalità, disinibizione, perdita della parola.
- Esordio tra 50 e 60 anni, prevalenza similare alla AD, M = F,
- 50% casi familiari AD (> 30 mutazioni gene tau chr 17 (FTDP17) = TAUPATIE ma anche chr 17 non tau + chr 3 e chr 9.
- Quadro suggestivo di Pick ma senza evidenza neuropatologica.
- Perdita neuronale frontale + perdita mielinica + gliosi astrocitaria della bianca = FTD.
- La Pick è una FTD.

FTD

- Sintomi clinici = distribuzione anatomica
  - Lobo temporale bilaterale: FTD, funzioni disesecutive, comportamento inadeguato
  - Lobo frontoparietale sinistro: afasia nonfluente progressiva
  - Lobo bitemporale: demenza semantica con perdita significato della parola ed oggetti
  - Lobo temporale allargato: prosopoagnosia
  - Lobo frontale premotorio e parietale: aprassia artuale progressiva
  - Quando le espressioni locali delle sindromi degenerative focali si diffondono ai lobi frontali emerge lo spettro della FTD.
  - MND e PD si associano alla FTD.

- L' istologia non dipende dalla sindrome clinica o dalla familiarità:
  - Alterazioni microvacuolari o spongiformi
  - Gliosi con/senza corpi inclusi e neuroni ballonati (Pick)
  - Patologia MND

FTD: clinica

- Disordine neurocomportamentale dell' età media con perdita dell' insight, facile distrazione, ridotto interesse od empatia per il prossimo, labilità emotiva o disinteresse, impulsività, scarsa cura del sé, perseverazione e ridotta espressione verbale, demenza, aprassia, PD e MND.

- In generale, due quadri clinici:

  - progressivo disturbo comportamentale: con alterazioni della personalità, variazione delle funzioni esecutive e del ragionamento.

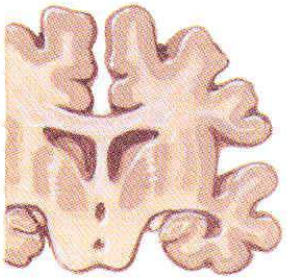
  - progressivo disturbo del linguaggio (Pick): con afasia fluente progressiva o semantica fino al mutismo seguita da disturbi di personalità.

- Circa 8 anni di malattia.

FTD: clinica

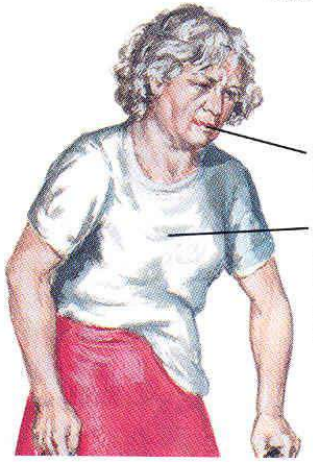
- Pazienti iperattivi, disinibilit, affacendati, fatui oppure apatici, inerti, non responsivi (spettro comportamentale relativo alle diverse aree affette =
  - Corteccia orbito-frontale: disinibizione ed iperattività
  - Corteccia frontale con regione dorso-laterale: apatia
- Alterato rapporto con il cibo (golosità, iperoralità).
- Sindrome di dipendenza ambientale.
- Comportamento di utlizzazione (bere da un bicchiere vuoto).
- Stereotipie, vagabondaggio, riduzione della produzione verbale (ecolalia, etc.) fino al mutismo.
- Memoria frammentaria con amnesia frontale.
- Segni striatali tardivi (acinesia, rigidità) o MN.

Frontotemporal dementias (FTDs)



Atrophy of frontal and/or temporal areas

Clinical features of frontal lobe variant

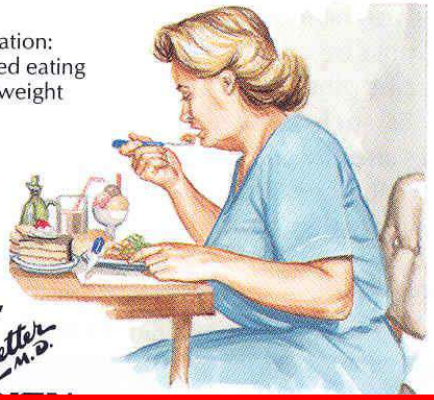


Decrease in speech

Loss of awareness of personal appearance and hygiene

Bizarre, uninhibited socially inappropriate behavior

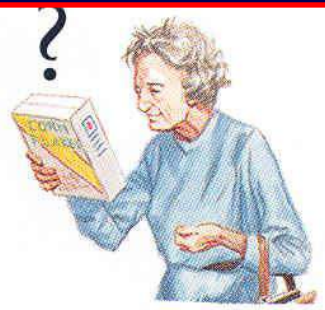
Oral fixation: increased eating causes weight gain.



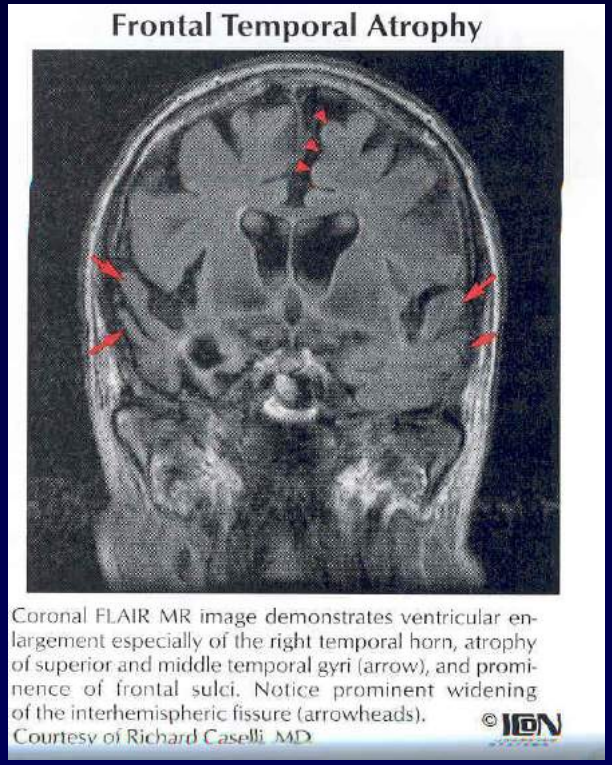
Decreased concern and empathy for others

F. Netter M.D.

Temporal lobe variant may exhibit severe naming and word comprehension deficit.



FTD: neurodiagnostica



Afasia non fluente progressiva

- Sindrome afasica non fluente con anomie, errori fonemici e semantici.
- Reperimento vocaboli e ripetizione compromessi.
- Lettura forzata e non fluente, telegrafica, con errori fonologici.
- Comprensione inizialmente conservata con consapevolezza di malattia.
- Funzioni cognitive non linguistiche (con memoria) sono conservate.

Primary progressive aphasia

"I have went to dat town."

Patients show grammatical and phonological deficit as well as deficits in reading and writing.

Afasia non fluente progressiva

- Esita in mutismo.
- Aprassia possibile (comunicazione non verbale impossibile).
- Anche a lungo il paziente mantiene una certa capacità di comprensione.
- Analogia, co-espressione con FTD.
- PET e SPECT: ipometabolismo perisilviano sinistro.

Demenze nel corso di Malattie Neurodegenerative

Malattia di Parkinson

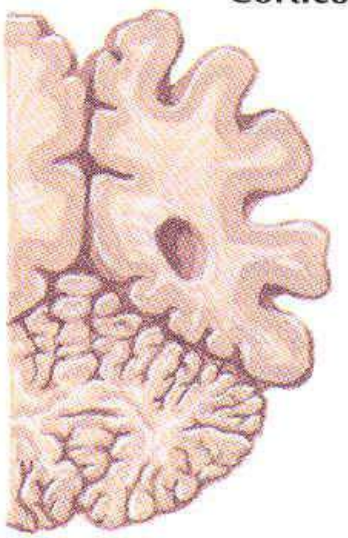
- la demenza complica frequentemente le forme avanzata (20 - 30%)
- prototipo: sindrome disesecutiva con stigmate affettivo-comportamentali
- Talvolta quadro più similare ad AD o DLB

Paralisi Sopranucleare Progressiva o PSP

- forma più comune di Pdismo dopo PD
- caratterizato da instabilità posturale, paralisi di verticalità, Pdismo bilaterale L-DOPA insensibile e paralisi pseudobulbare con disartria e disfagia
- alterazioni cognitive nel decorso di malattia: disfunzione dei lobi frontali con apatia, alterato pensiero astratto, < fluenza verbale, comportamento imitativo e segni di rilascio frontale
- tali segni sono raramente presenti nel PD
- i criteri diagnostici attuali (NINDS-SPSP) richiedono per la diagnosi di probabile PSP obbligatoriamente 3 elementi:
  - gradualità del disturbo
  - esordio dopo i 40 anni
  - oftalmoparesi sovranucleare verticale + instabilità posturale + cadute nel 1° anno

- la diagnosi diventa da probabile a possibile
  - in assenza di paralisi di verticalità dello sguardo
  - presenza del rallentamento della velocità dei saccadi verticali

Corticobasal degeneration



Contralateral assymetric atrophy of parietal lobe

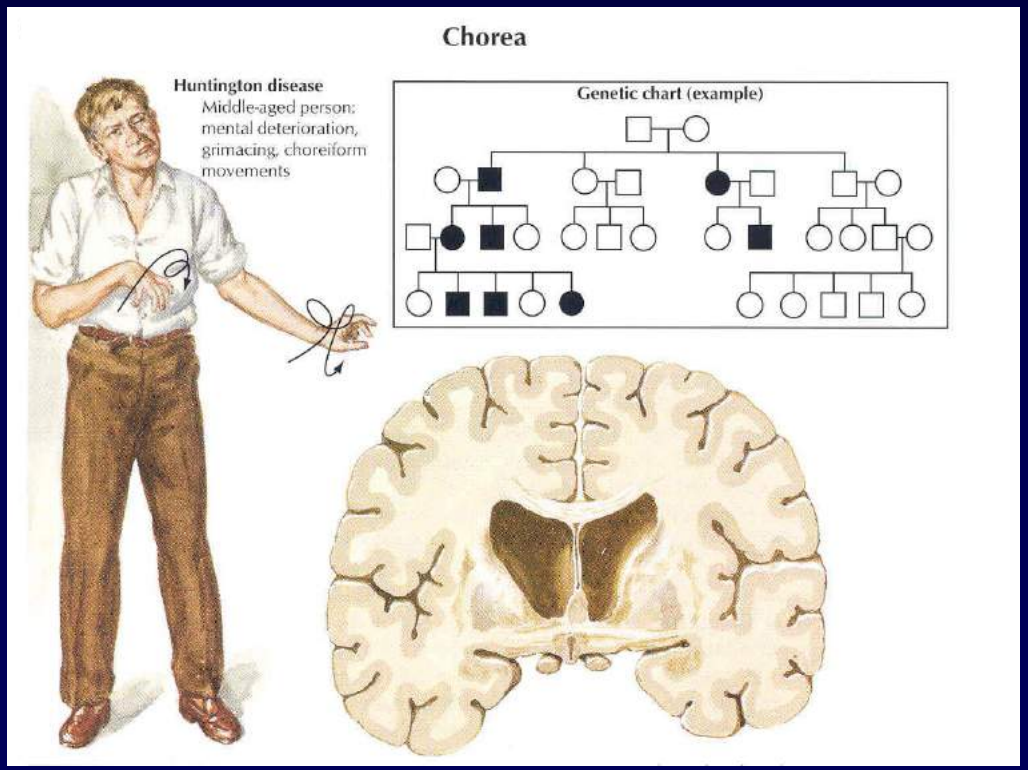
Apraxia may inhibit everyday activities such as dressing.

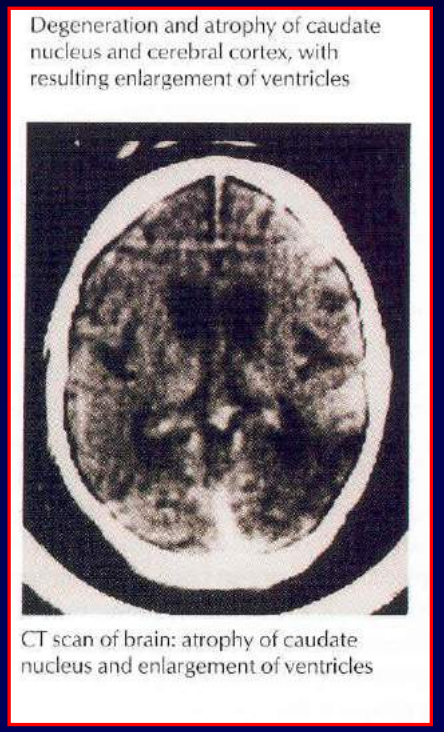
Stiff, jerky limb posturing

Patient may exhibit "alien limb" phenomenon in limb contralateral to cortical atrophy.

MALATTIA DI HUNTINGTON

- malattia ereditaria AD
- prevalgono i movimenti involontari e i sintomo psichiatrici sulla demenza che è tardiva





Altre demenze

DEMENZE TRATTABILI

- CAUSE INFETTIVE, METABOLICHE, PSICHIATRICHE, LESIONI OCCUPANTI SPAZIO, IDROCEFALO NORMOTESO (< 15%)

DEMENZA VASCOLARE (DV)

- 10-15% di tutte le demenze (seconda causa e concausa dopo AD, in 1 su 4 pazienti)
- con uno o più piccoli infarti o da grandi infarti
- lesioni vascolari sono presenti in pazienti con forme degenerative primarie

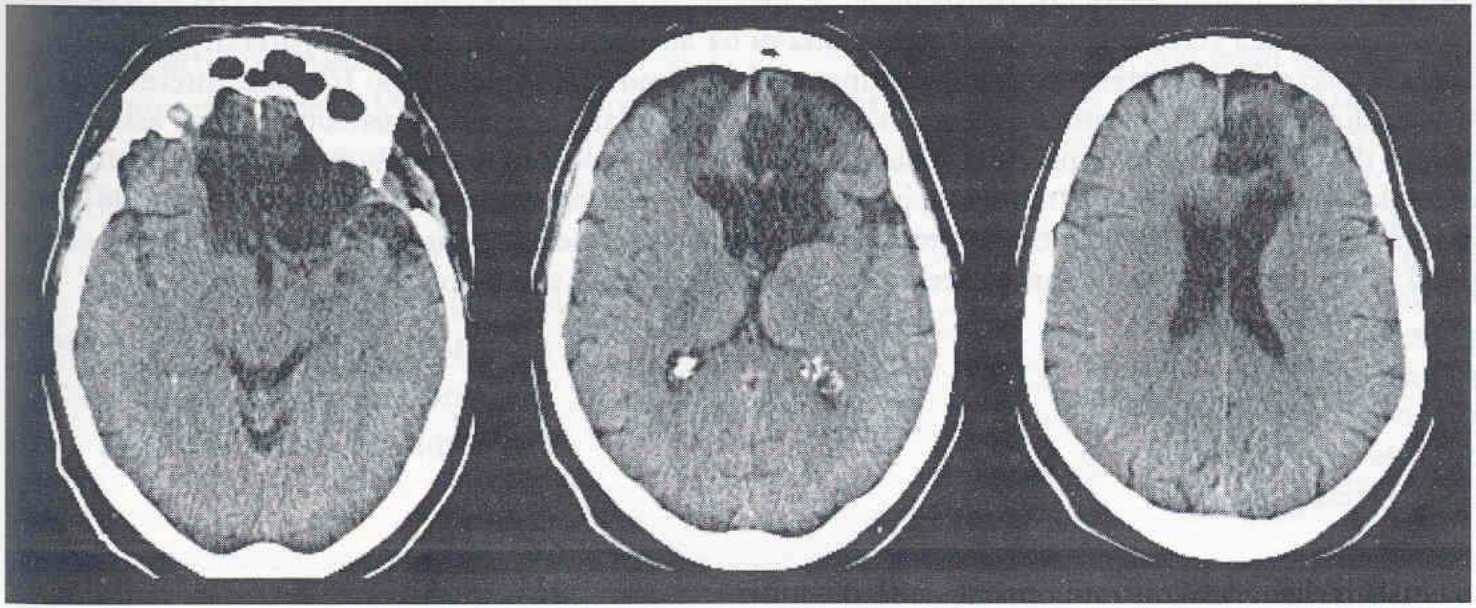
Demenze dopo lesioni cerebrali singole

ARTERIA CEREBRALE ANTERIORE

- **Apatia, indifferenza, appiattimento emotivo, perdita autocritica.**
- **Comportamento corretto dopo stimolo.**
- **Abilità cognitive intatte, deficit pensiero divergente, organizzazione temporale e pianificazione.**
- **Tendenza ad imitare ed utilizzare in automatico oggetti (comportamento di mitazione ed utilizzazione).**

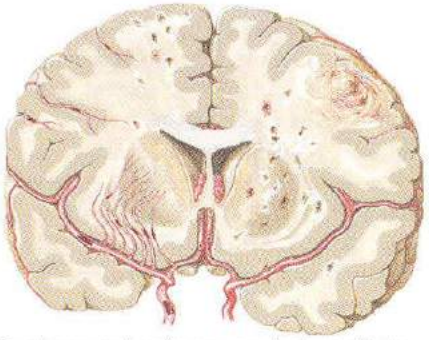
ARTERIA CEREBRALE POSTERIORE

- **Deficit capo visivo, visione colori, alessia senza agrafia.**
- **Distorsioni immagini, pseudoallucinazioni, immagini persistenti, agnosia visiva o cecità corticale, prosopagnosia.**
- **Demenza acuta (occlusione) + segni/sintomi circolo posteriore (DD Ischemia globale).**

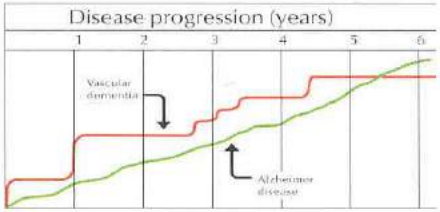


Scansione di tomografia computerizzata (TAC) di un uomo di 47 anni con una storia di demenza "ad infarto strategico".

Vascular (Multi-infarct) Dementia



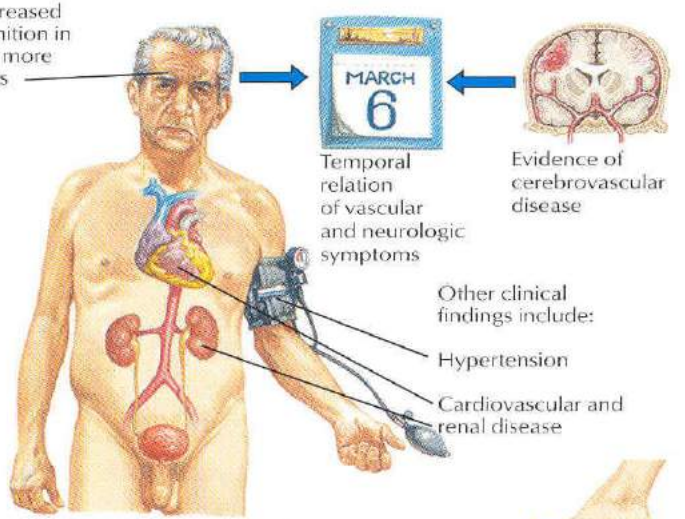
Cerebrovascular disease results in multiple small cortical and subcortical infarcts.



Clinical progression. Vascular dementia exhibits abrupt onset and stepwise progression in contrast to gradual onset and progression of Alzheimer disease.

Diagnostic criteria

Decreased cognition in 2 or more areas



Temporal relation of vascular and neurologic symptoms

Evidence of cerebrovascular disease

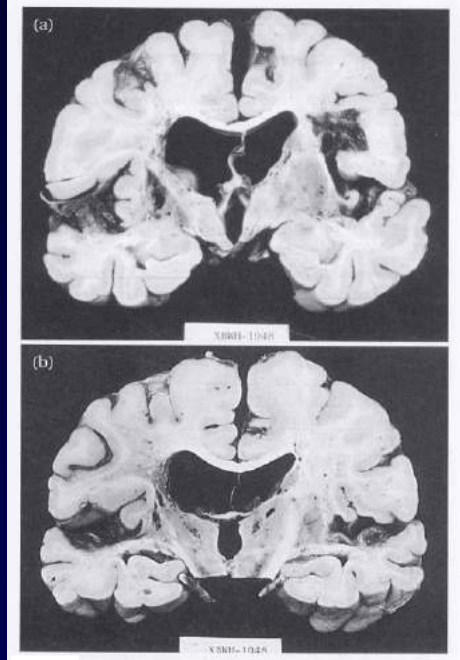
Other clinical findings include:

Hypertension

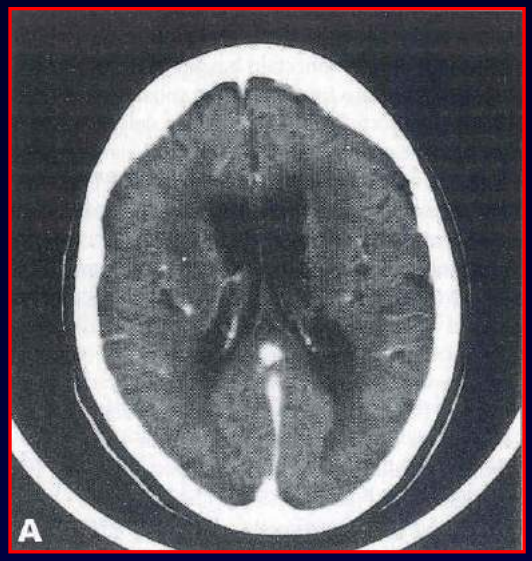
Cardiovascular and renal disease

Most patients with vascular dementia have increased risk factors for stroke.

Focal neurologic signs



Multi-infarct dementia: two adjacent brain slices from a patient with multi-infarct dementia showing the variety and severity of tissue destruction commonly seen in these patients. (*a*) In the more anterior slice there is infarction in the territories of the inferior division of both middle cerebral arteries, part of the superior division of the right middle cerebral artery and in the left caudate and putamen involving the intervening internal capsule. This damage has resulted in significant enlargement of the right lateral ventricle and third ventricle and gross enlargement of the left lateral ventricle. (*b*) In the posterior slice, there are still infarctions in both inferior divisions of the middle cerebral arteries, the left putamen and an additional extensive area of damage in the white matter of the left centrum semiovale. There are also at least three identifiable lacunes in the thalami.

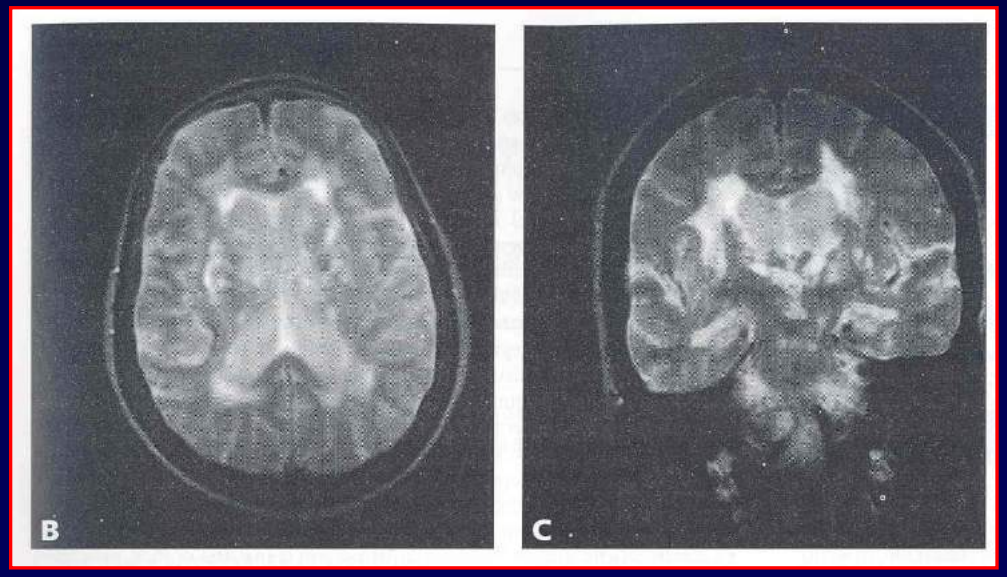


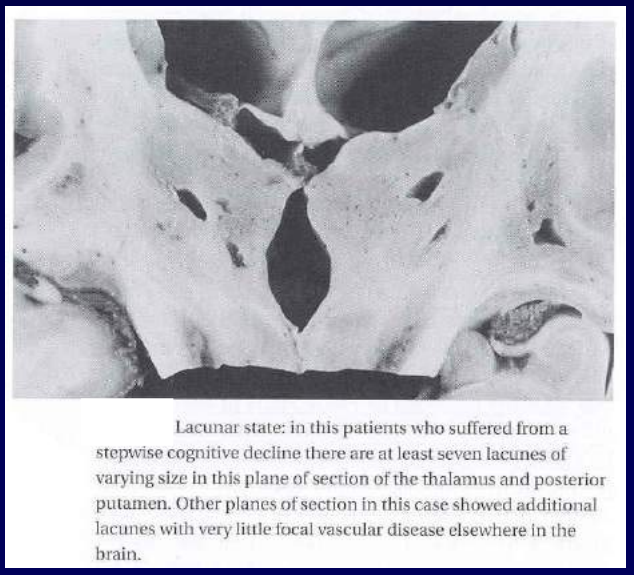
DEMENZA DA PICCOLI VASI

• Biswanger or, better, leukoaraiosis (40%)

- ipertensione
- genetica

• Stato lacunare 0.5-15 mm





Lacunar state: in this patients who suffered from a stepwise cognitive decline there are at least seven lacunes of varying size in this plane of section of the thalamus and posterior putamen. Other planes of section in this case showed additional lacunes with very little focal vascular disease elsewhere in the brain.

Forme miste

- Caratteristiche congiunte: encefalopatia cronica su base vasculo-degenerativa.
- EON: segni focali e corticali
- Diagnosi: neuroimaging (atrofia + lacune) e neuropsicologia (caratteristiche su pattern vascolare di forme dementigene strettamente primarie)

Demenze associate a disturbi infettivi: Demenza da HIV

- Dal 1980 prevalenza della HIV-D < dal 50 al 10% con HAART che ha < il rischio di svilupparla.
- La prevalenza rimane del 5-10%.
- Due entità:
  - DISORDINE HIV-1 associato con lieve disordine cognitivo /motorio che non sempre evolve a
  - DEMENZA COMPLEX associata ad HIV-1, anche a decorso fluttuante

HIV-D: quadro clinico

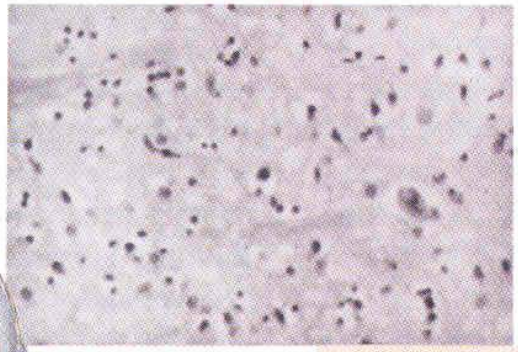
- Quadro neurologico + rallentamento psicomotorio ed anomala flessibilità mentale (demenza sottocorticale).
- Sviluppo di deficit mensici e di linguaggio fino ad un deficit globale con sopravvivenza < 1 anno prima degli HAART.
- Delirio, depressione, psicosi, mania.
- DD: neuroimaging per escludere lesioni strutturali.
- Neuropatologia: non chiaro rapporto tra HIV-D e neuropatologia.
  - HIV tende ad invadere le strutture subcorticali
  - perdita neuronale e sinaptica corticale (frontale)
  - stretto rapporto con la carica HIV

DD con malattie prionali

Transmissible Spongiform Encephalopathy

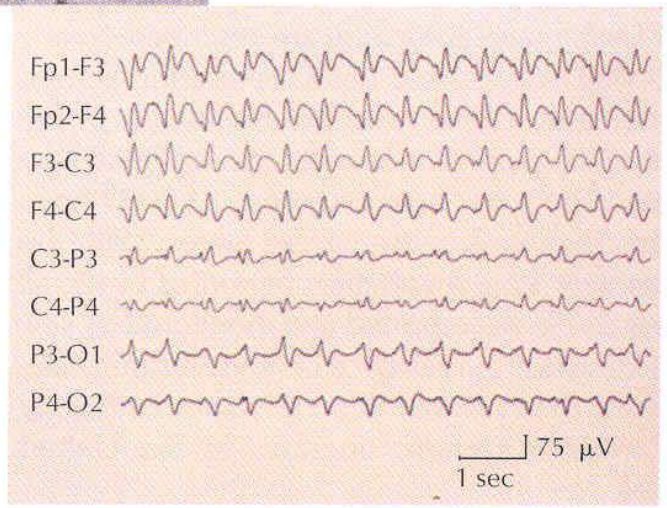
Creutzfeldt-Jakob disease

Demented patitent exhibiting myoclonus



Section from putamen showing extensive loss of neurons and spongiform brain tissue. Spinal cord usually shows similar loss of motor neurons.

EEG showing characteristic diffuse periodic wave pattern



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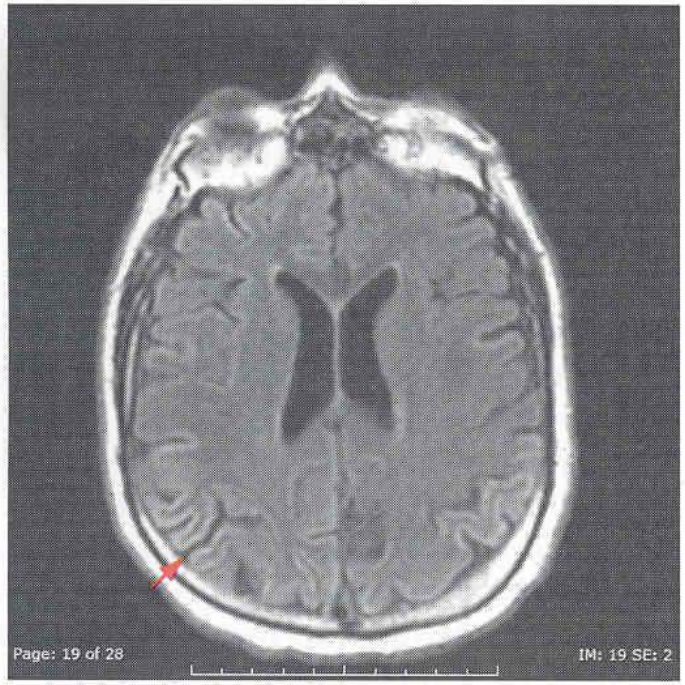
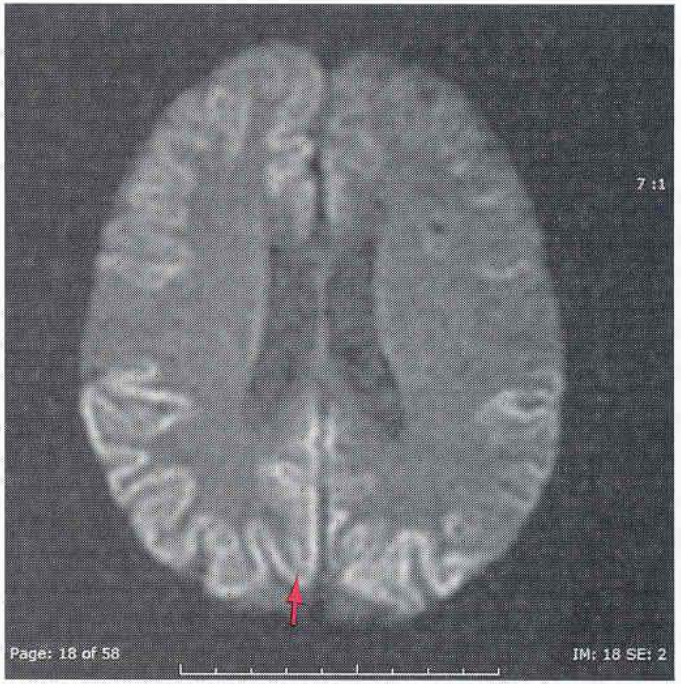
Spongiform Encephalopathy: Early Cortical Involvement



A



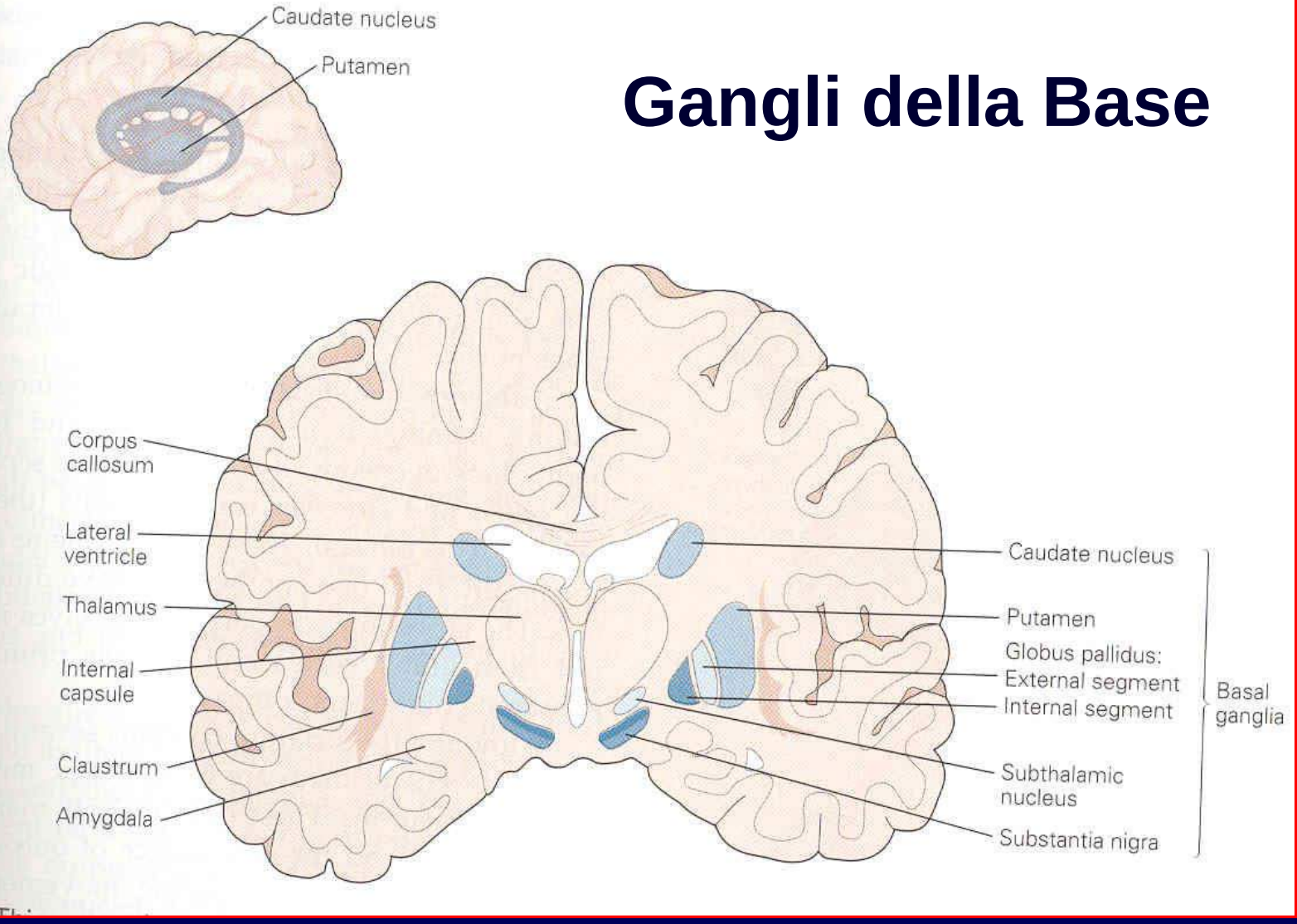
B

(**A**) FLAIR image shows increased intensity in frontal and parietal cortical gray matter. (**B**) Diffusion mimics the subtle restriction of diffusion in similar cortical regions.

REGOLE: utili 4 quesiti

- Il paziente è demente?
- Se lo è, la perdita di funzione ha un pattern caratteristico?
- Il pattern della demenza ha caratteristiche specifiche?
- Quale è il processo più verosimilmente causa della demenza?
- La conoscenza delle funzioni cognitive e dei correlati anatomici è necessaria per definire le aree cerebrali affette.

Gangli della Base



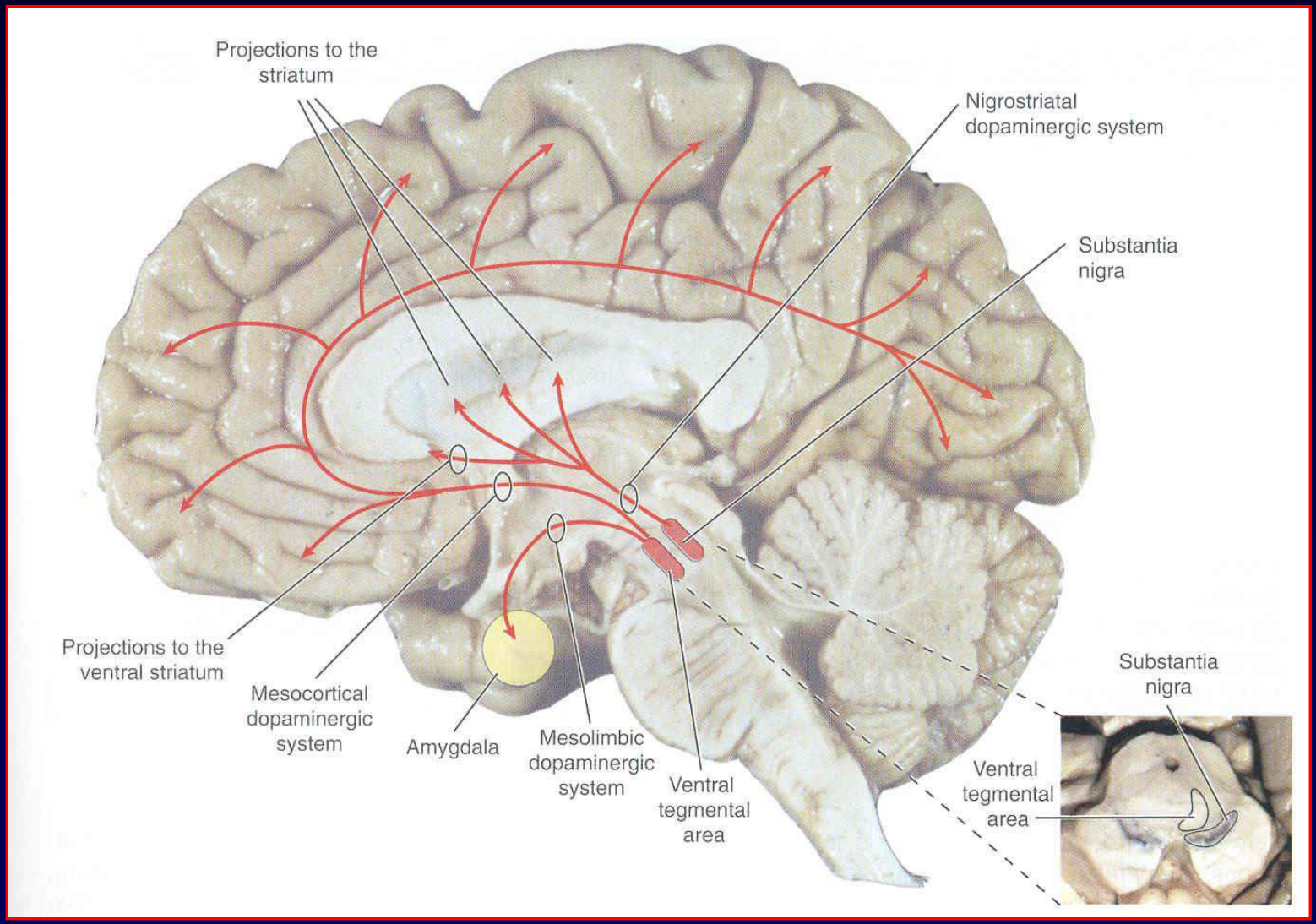
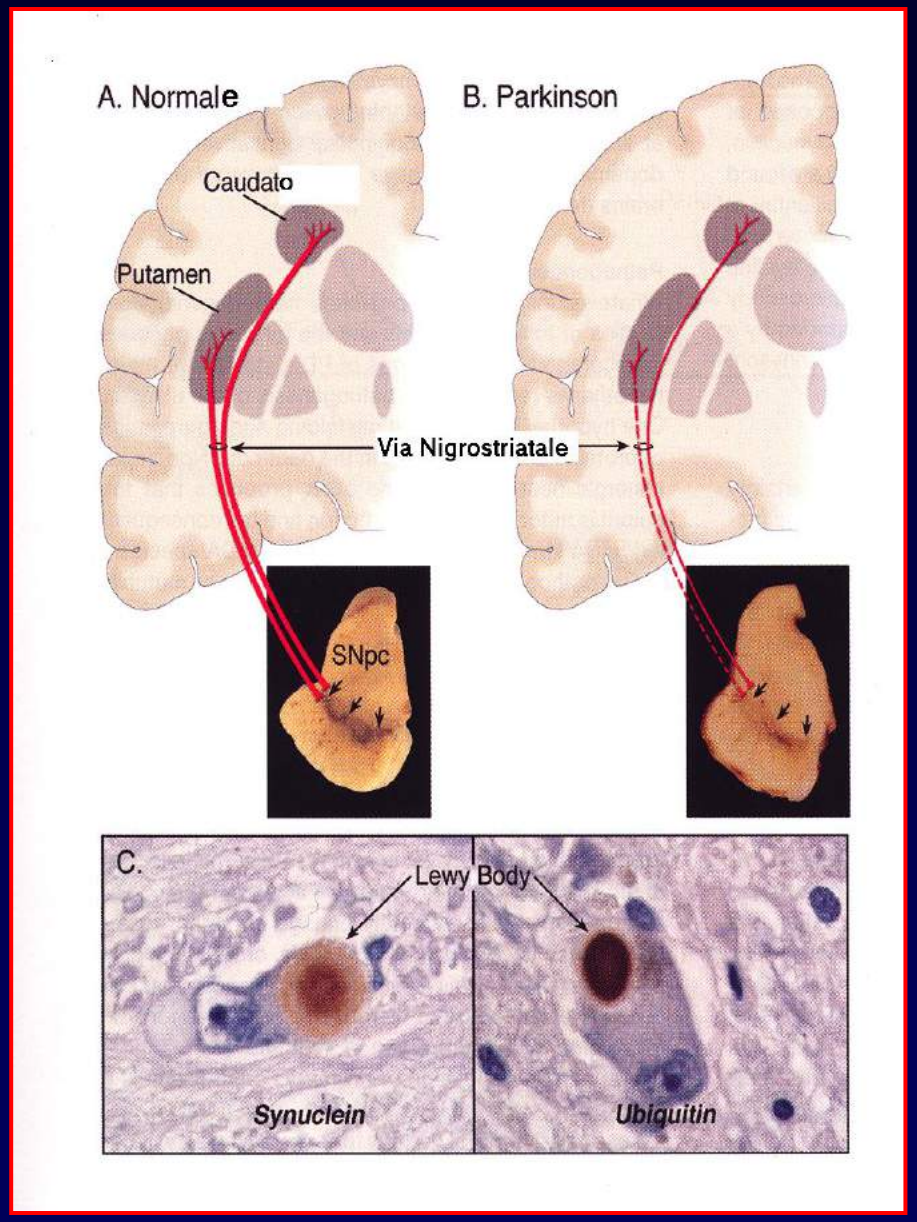

Projections to the striatum
Nigrostriatal dopaminergic system
Substantia nigra
Projections to the ventral striatum
Mesocortical dopaminergic system
Amygdala
Mesolimbic dopaminergic system
Ventral tegmental area
Substantia nigra
Ventral tegmental area

TABLE 6-8 Summary of Major Movements Disorders Stemming from Lesions of the Basal Ganglia

Movement Disorder	Characteristics	Structure Implicated	Diseases Responsible
Akinesia	Difficulty initiating movement	Head of caudate (dopamine deficiency)	Parkinson's disease
Bradykinesia	Slowness of movement		
Hypokinesia, rigidity, pill-rolling tremor	Small movements	Putamen (dopamine deficiency)	Parkinson's disease
Chorea	Small, quick, involuntary movements of fingers, hands, occasionally head, arms and legs. Lilting, dance-like gait	Putamen (intrinsic pathology)	Huntington's disease
Athetosis	Nearly constant, slow, sinuous, writhing movements	Putamen, globus pallidus (intrinsic pathology)	Hypoxia, carbon monoxide poisoning, Wilson's disease (an autosomal recessive disease causing tissue copper deposition)
Ballism	Violent, flinging movements, usually involving an entire arm	Subthalamic nucleus	Stroke

Mlattia di Parkinson's Disease



SINDROMI PARKINSONIANE

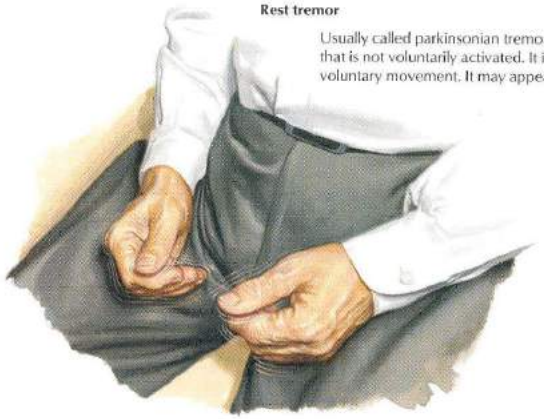
- **Primary Parkinsonism**
  - Parkinson disease or PD (sporadic or familial)
- **Secondary Parkinsonism**
  - Drug-induced: dopamine antagonist and depletors
  - Hemiatrophy-hemiparkinsonism
  - Hydrocephalus: normal pressure hydrocephalus
  - Hypoxia
  - Infectious: postencephalitic
  - Metabolic: parathyroid dysfunction
  - Toxin: MN, CO, MPTP, cyanide
  - Trauma
  - Tumor
  - Vascular: multiinfarct state
- **Parkinson-plus Syndromes**
  - Cortico-basal ganglionic degeneration
  - Dementia syndromes: Alzheimer disease, diffuse Lewy body disease
  - frontotemporal dementia
  - Lytico-Bodig (Guamanian Parkinson-dementia-ALS)
  - Multiple system atrophy syndromes: striatonigral degeneration, Shy- Drager syndrome, sporadic olivopontocerebellar degeneration (OPCA), motor neuron disease-parkinsonism
  - Progressive pallidal atrophy
  - Progressive sopanuclear palsy
- **Familial Neurodegenerative Diseases**
  - Hallervorden-Spatz disease
  - Huntington's disease
  - Lubag (X-linked dystonia-parkinsonism)
  - Mitochondrial cytopathies with striatal necrosis
  - Neuroacanthocytosis
  - Wilson disease

Parkinsonian posture.

Tremor

Rest tremor

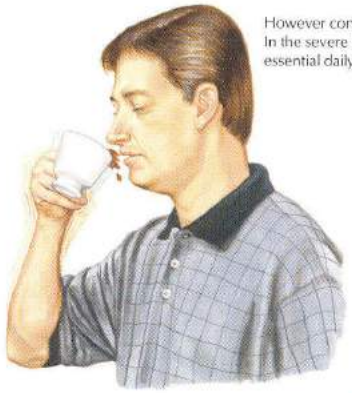
Usually called parkinsonian tremor, occurs in a limb that is not voluntarily activated. It is suppressed with voluntary movement. It may appear as "pill rolling."

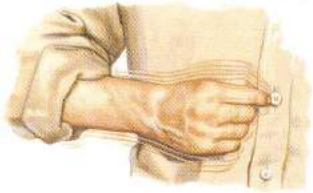


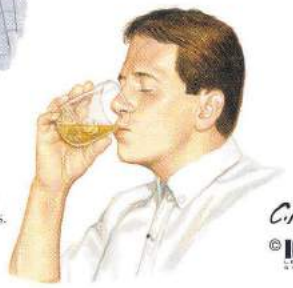
Action tremor (example: essential tremor)

Typically bilateral, this movement disorder is the most common. It may be accentuated with goal-directed movement of the limbs. Essential tremor affects the hands and facial musculature (in this order of prevalence). Most common presentation is the association of hand tremor and tremor in cranial musculature.

However considered benign, it can become incapacitating. In the severe forms the patient may not be able to perform essential daily activities, such as drinking from a cup or dressing.







A useful clinical clue is that alcohol temporarily alleviates the symptoms.

C. Machado M.D.

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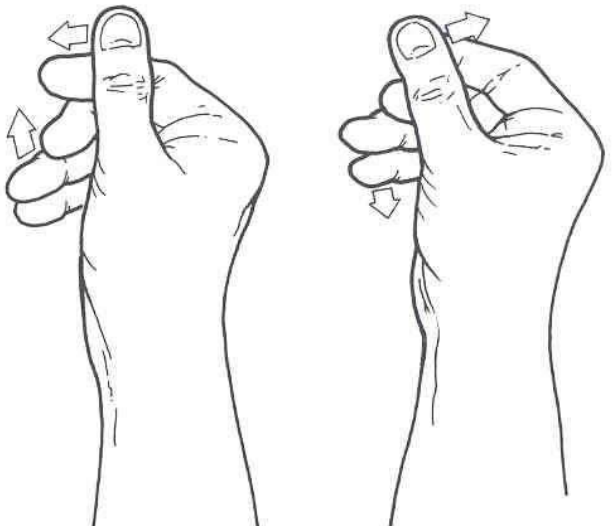
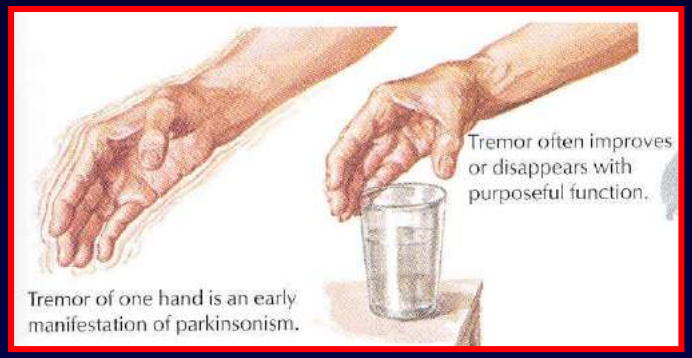
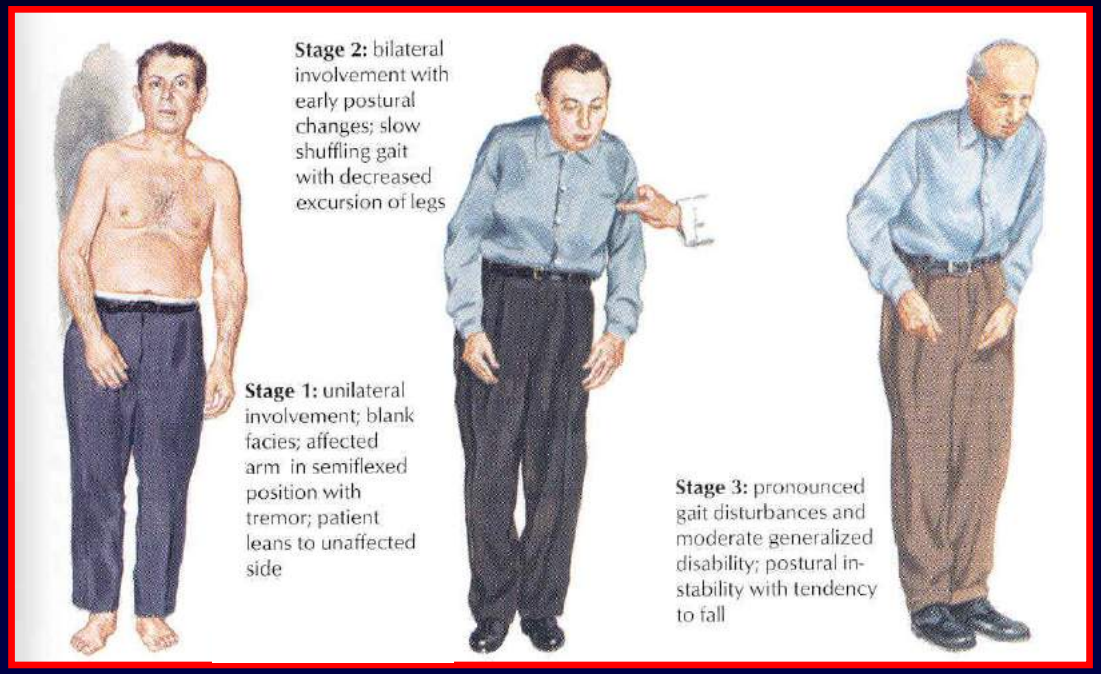


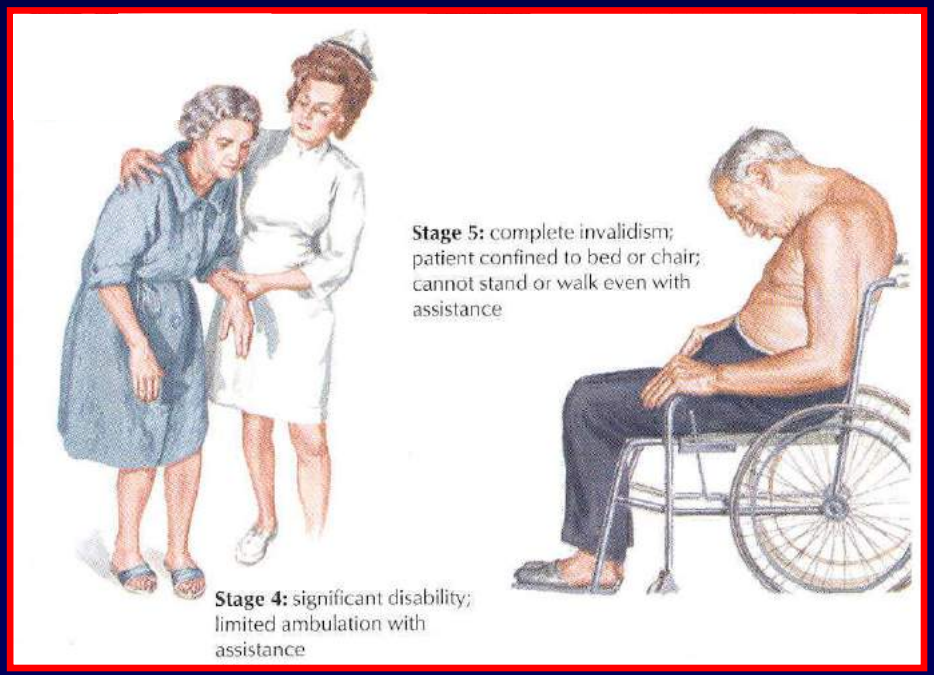
Il contar monete

Malattia di Parkinson: segni e sintomi

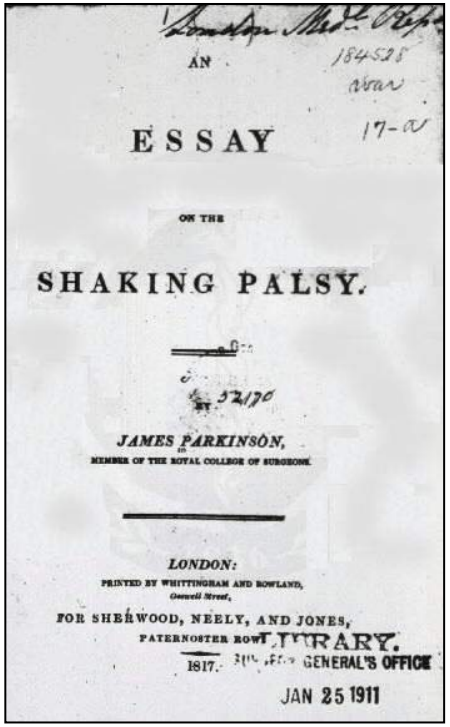
- bradicinesia
- ipertono plastico
- tremore a riposo
- instabilità posturale




Stage 2: bilateral involvement with early postural changes; slow shuffling gait with decreased excursion of legs
Stage 1: unilateral involvement; blank facies; affected arm in semiflexed position with tremor; patient leans to unaffected side
Stage 3: pronounced gait disturbances and moderate generalized disability; postural instability with tendency to fall


Stage 5: complete invalidism; patient confined to bed or chair; cannot stand or walk even with assistance
Stage 4: significant disability; limited ambulation with assistance

Malattia di Parkinson (PD)


AN

ESSAY

ON THE

SHAKING PALSY.

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

FOR SHERWOOD, NEELY, AND JONES,

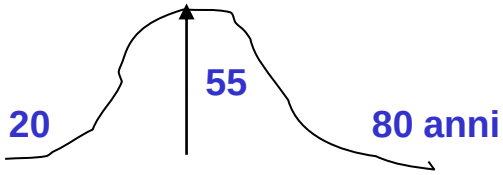
1817.

PARKINSONISMO PRIMARIO

- ⇨ malattia neurologica progressiva con una distinta patologia: degenerazione dei neuroni della Sostanza Nera e del Locus Ceruleus

PD – Epidemiologia e Fattori di Rischio

- Incidenza: 20/100.000
- Prevalenza: 160/100.000 (x 4 volte >70 aa)
- M:F = 3:2



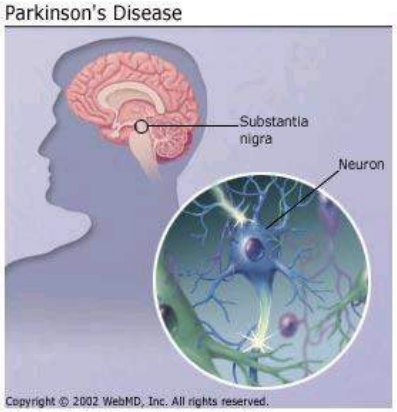
- 20-40 anni: PD ad esordio in giovane età
- < 20 anni: PD giovanile → solitamente familiare
- Aumentato rischio associato alla storia familiare di PD, insetticidi, aree rurali
- Minor frequenza di PD nei fumatori (controverso)

PD – Aspetti Clinici

- **Tremore**
  - 1° sintomo nel 70%, unilaterale → bilaterale
  - a riposo (4-5 Hz), all'estremità
  - scompare all'attivazione
  - stress
- **Rigidità**
  - elicitata dai movimenti passivi
  - resistenze in tutte le direzioni
  - *ruota dentata*
- **Postura in flessione**
  - capo flesso
  - torace flesso, schiena cifotica
  - arti flessi
- **Acinesia**
  - sintomo più comune
  - deambulazione lenta, pendolarismo assente, ipomimia facciale
  - bradicinesia: movimenti lenti; inizio; ROT ↓
  - ipocinesia: ridotta escursione del movimento, micrografia
- **Perdita dei riflessi posturale**
  - *festinatio*
  - propulsione e retropulsione (cadute)
- **Fenomeno del *freezing***
  - blocco motorio: inabilità a compiere movimenti attivi
  - pause → barriere
  - aprassia palpebrale

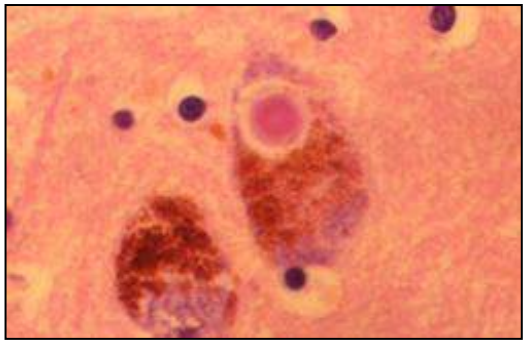
PD – altri Apetti Clinici

- **Acatisia**
- **Segni comportamentali**: - attenzione ridotta
  - diminuita capacità visuospaziale
- **Cambiamenti di personalità**: - dipendente, pauroso, indeciso, passivo
  - depressione (1/3 dei pazienti)
- **Declino cognitivo**: - bradifrenia (rispondono lentamente)
  - 20% → simile AD (diffusi corpi di Lewi)
- **Disturbi autonomici**: - cute fredda
  - stitichezza
  - alterato svuotamento vescicale
  - difficoltà erettive
  - anomalie pressorie (↓)
- **Riflessi di liberazione corticale**: glabella + , r. palmomentoniero **+**



PD – Patogenesi

- Depigmentazione e perdita neuronale nella Substantia Nigra (SN)
- Lewy bodies (inclusioni eosinofile) →



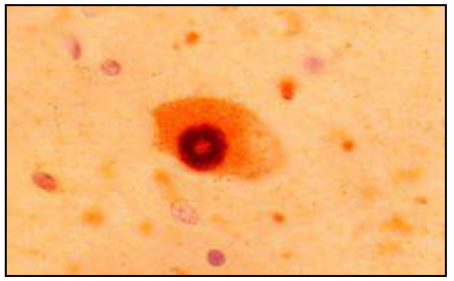
- Pars compacta della SN (SNc) è la prima colpita: proietta al Putamen
- Perdita di dopamina (DA)
- Dal 60 all' 85 % di perdita dei neuroni nigro-striatali prima dei sintomi
- Altri neurotrasmettitori coinvolti: acetilcolina, norepinefrina

  (modificazioni nel locus ceruleus) e serotonina (nel rafe dorsale)
- Meccanismo patogenetico non è noto

PD – Patogenesi

- Nessuna causa specifica identificata
- Gli studi si sono concentrati su:
  - Tossine esogene: - agente chimico → **MPTP**
    - nessun fattore ambientale
  - Tossine endogene: - reazioni ossidative cellulari → **incremento di radicali liberi** nei neuroni dopaminergici → danno da stress ossidativo
  - Fattori genetici: - studi sui gemelli → **predisposizione genetica**

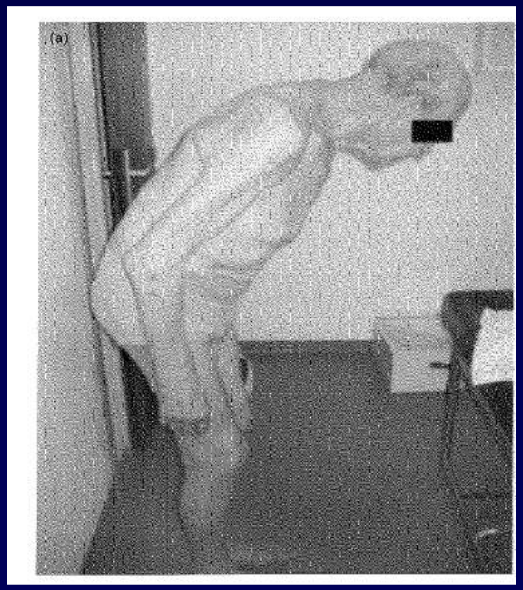
PD – Geni associati



• PARK 1	4q21	Dominante	*α-sinuclein* (sinapsi, nuclei, corpi di Lewi)	> 40	
• PARK 2	6q25	Recessivo	*parkin* (SN)	20-40	
• PARK 3	2p13	Dominante	sconosciuta	tipico PD	
• PARK 4	4q21	Dominante	triplicazione *α-sinuclein*	~ 30	
• PARK 5	4	Dominante	*ubiquitin ligasi*		
• PARK 6	1	Recessivo	pink-1 (mitoc.)	{ esordio	
• PARK 7	1	Recessivo	DJ-1 (?)	{ precoce	
• PARK 8	12	Dominante	LRRK 2 (dardarina)		
• . . .					
• . . .					
• PARK 11					

Cadute e Deformità assiali

- CAPTOCORMIA: tipica manifestazione di distonia, anteroflessione del tronco che recede al raddrizzamento al muro, non L-DOPA sensibile, generalmente tardiva, associata ad alterazioni spondilotiche, associata a dolore, patogenesi ignota (distonia focale d' azione centrale vs disordine muscolare periferico con miopatia m. docce dorsali e risposta agli steroidi), farmaci inefficaci ad eccezioie di botox, DBS ?



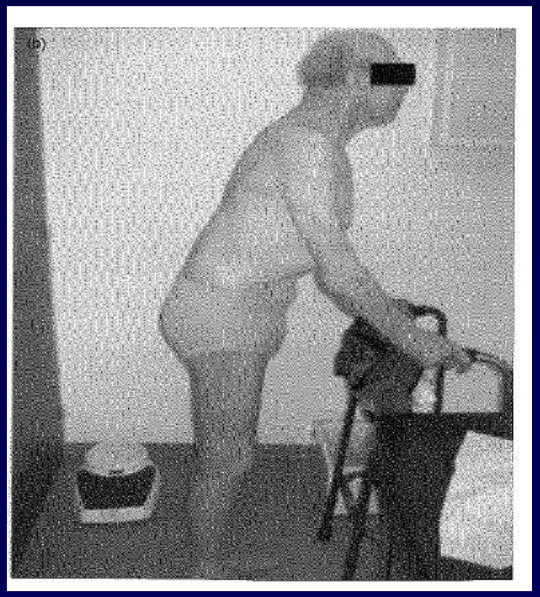


Table 33.2 Differential diagnosis of spinal deformities in PD.

Camptocormia

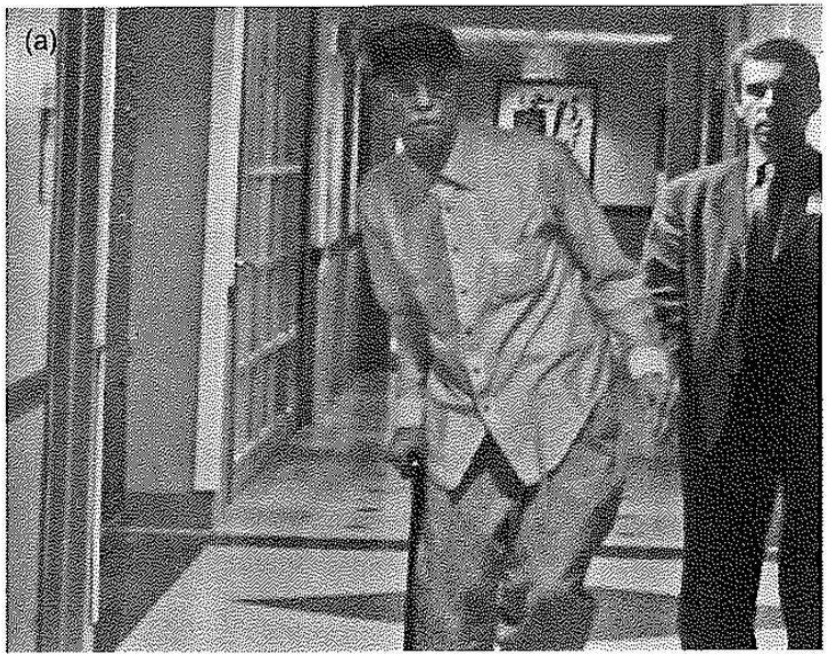
- Idiopathic
- Parkinsonism
  - Idiopathic Parkinson disease
  - Multiple system atrophy
  - Autosomal recessive juvenile parkinsonism (parkin mutation)
  - Postencephalitic parkinsonism
  - Atypical parkinsonism
- Dystonia
  - Primary
  - Secondary associated with parkinsonism
  - Secondary dystonia associated with structural lesions in the brain or spinal cord
- Spine deformities
- Stroke
- Neuromuscular
  - Focal myopathy
  - Amyotrophic lateral sclerosis
  - Inclusion body myositis
  - Nemaline myopathy
- Psychogenic
- Miscellaneous
  - Drug-induced
  - Grave's disease
  - Paraneoplastic
  - Tourette's syndrome

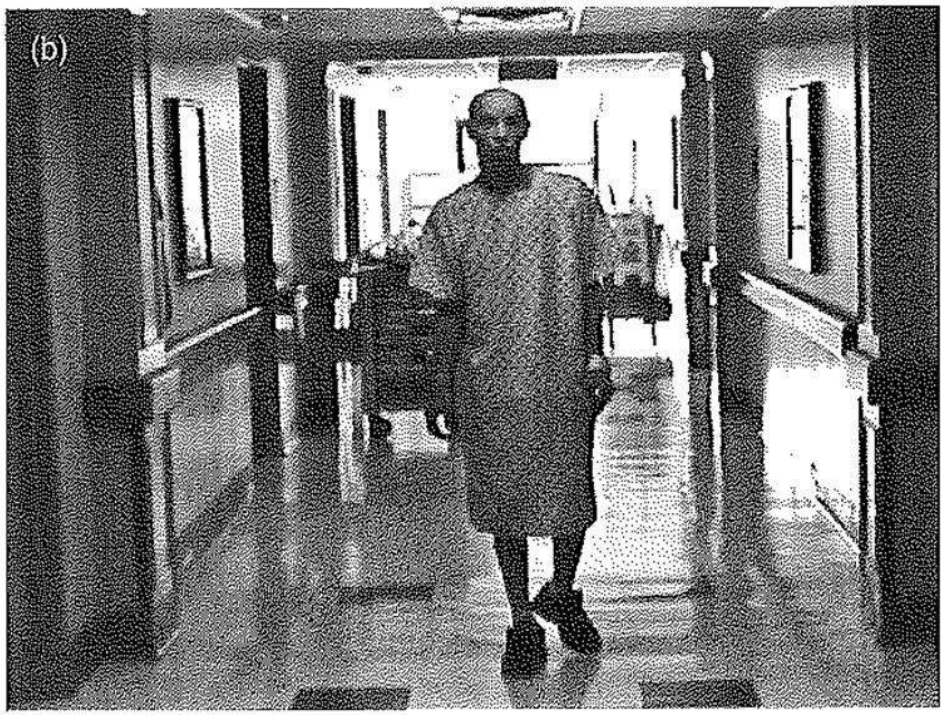
Deformità assiali

- SCOLIOSI e SINDROME DI PISA: flessione laterale controlaterale al sito di esordio, negli stadi avanzati, 80% casi, > donne ?, con presentazione cronica o subacuta

  Talvolta similare alla SINDROME DI PISA: distonia assiale rara legata a terapia antipsicotica.

  Paziente spesso inconsapevole (legata a sbilanciamento farmacologico striatale), scarsamente rispondente alla L-DOPA: prevenzione della contrazione ipertonica anomala paraspinale. DBS? Chirurgia non risolutiva ma sospensione di possibili terapie causali


(a)


(b)

PD – Diagnosi Differenziale

PARKINSONISMI EREDODEGENERATIVI

Distonia-parkinsonismo giovanile ereditario

Malattia dei Corpi di Lewi (autosomica dominante)

Malattia di Huntington (HD)

Malattia di Wilson (WD)

Deficienza ereditaria di Ceruloplasmina

Malattia di Hallervorden-Spatz (HSD)

Degenerazione Olivopontocerebellare e Spinocerebellare (OPCA/SCA)

Amiotrofia-demenzia-parkinsonismo familiare

Complesso disinibizione-demenzia-parkinsonismo-amiotrofia

Malattia di Gerstmann-Strausler-Scheinker

Gliosi subcorticale progressiva familiare

Lubag (distonia-parkinsonismo legata al cromosoma X)

Calcificazione dei gangli basali familiare

Citopatia mitocondriale con necrosi striatale

Lipofuscinosi da ceroidi

Parkinsonismo familiare con neuropatia periferica

Sindome parkinsoniana-piramidale

Neuroacantocitosi (NA)

Emocromatosi ereditaria

Parkinsonismi-Plus

Malattie Neurodegenerative caratterizzate da:

- ⇨ aspetti clinici simili al PD
  segni / sintomi aggiuntivi non tipici
  in generale una prognosi peggiore
  scarsa risposta alla terapia anti-PD

PD – Diagnosi Differenziale

DEGENERAZIONI MULTISISTEMICHE (Sindromi Parkinson-Plus): 12%

- Paralisi Sopranucleare Progressiva (PSP)
- Atrofia Multisistemica
  - Degenerazione Striatonigrale (SND)
  - Atrofia Olivopontocerebellare (OPCA)
  - Sindrome di Shy-Drager (SDS)
- PD-dementia-ALS complex di Guam
- Degenerazione Cortico-basale
- Atrofia Progressiva Pallidale

PD – Diagnosi Differenziale

DEGENERAZIONI MULTISISTEMICHE (Sindromi Parkinson-Plus): 12%

Paralisi Sopranucleare Progressiva (PSP)

Atrofia Multisistemica

Degenerazione S

Atrofia Olivopont

Sindrome di Shy

PD-dementia-ALS comp

Degenerazione Cortico-

Atrofia Progressiva Palli

- la più comune PD-Plus
- tremore raro
- rigidità assiale / acinetico
- instabilità posturale
- frequenti cadute
- *freezing* prominente
- paralisi nella verticalità di sguardo
- demenza sottocorticale

- T: rara risposta alla L-dopa

PD – Diagnosi Differenziale

DEGENERAZIONI MULTISISTEMICHE (Sindromi Parkinson-Plus): 12%

- Paralisi Sopranucleare Progressiva (PSP)
- Atrofia Multisistemica
  - Degenerazione Striatonigrale
  - Atrofia Olivopontocerebellare
  - Sindrome di Shy-Drager (SDS
- PD-dementia-ALS complex di Guam
- Degenerazione Cortico-basale
- Atrofia Progressiva Pallidale

Vari gradi di disfunzione
- piramidale (+ anterocollo)
- cerebellare (atassia)
- atonomica (ipotensione ortostatica, postprandiale; anidrosi; impotenza; costipazione; alterazioni vescicali, etc)

- no tremore

- T: rara risposta alla L-dopa

PD – Diagnosi Differenziale

DEGENERAZIONI MULTISISTEMICHE (Sindromi Parkinson-Plus): 12%

- Paralisi Sopranucleare Progressiva (PSP)
- Atrofia Multisistemica
  - Degenerazione Striatonigrale (SND)
  - Atrofia Olivopontocerebellare (OPCA)
  - Sindrome di Shy-Drager (SDS)
- PD-demenza-ALS complex di Guam — Semi di Cicas circinalis
- Degenerazione Cortico-basale
- Atrofia Progressiva Pallidale

PD – Diagnosi Differenziale

DEGENERAZIONI MULTISISTEMICHE (Sindromi Parkinson-Plus): 12%

Paralisi Sopranucleare Progres

Atrofia Multisistemica

Degenerazione Striatoni

Atrofia Olivopontocerebe

Sindrome di Shy-Drager

PD-dementia-ALS complex di G

Degenerazione Cortico-basale

Atrofia Progressiva Pallidale

- Acromaticità dei neuroni corticali frontoparietali (atrofia), degenerazione nigrale e striatale (no corpi Lewi)
- PD + specifici segni corticali
- > 60 anni
- rigidità focale, asimmetrica
- bradicinesia
- tremore posturale e d'azione
- distonia (in un arto sup.)
- aprassia (arto alieno): 50%

- T: L-dopa o DA agonisti poco attivi

PD – Diagnosi Differenziale

DEGENERAZIONI MULTISISTEMICHE (Sindromi Parkinson-Plus): 12%

Paralisi Sopranucleare Progressiva (PSP)

Atrofia Multisistemica

Degenerazione S

Atrofia Olivopont

Sindrome di Shy-

PD-dementia-ALS compl

Atrofia Progressiva Pallid

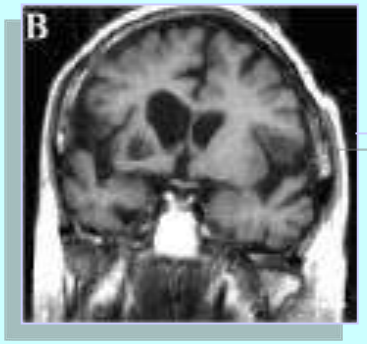
- Demenza progressiva con prominenti deficit attentivi e visuospaziali
- Allucinazioni visive + Parkinsonismo
- Degenerazione neocorticale e limbica con corpi di Lewi, anche nel tronco encefalico
- Spettro: LB dementia – PD dementia

Malattia da Corpi di Lewi diffusi (DLBD)

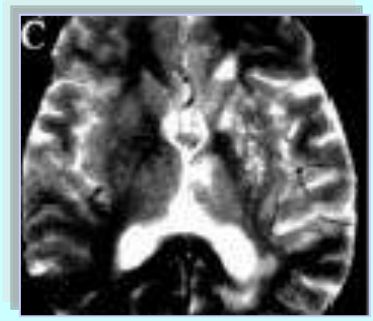
PD – Diagnosi Differenziale

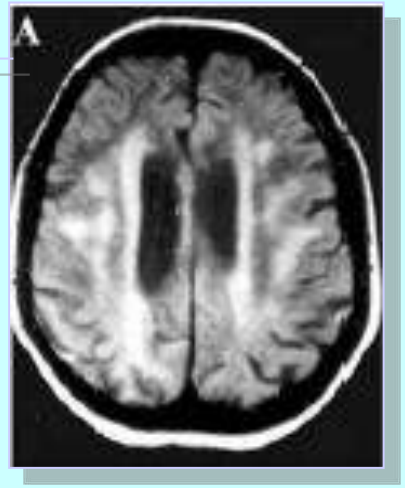
PARKINSONISMO SECONDARIO (acquisito): 8%

- **VASCOLARE**: - lacune (infarti) multiple nei gangli della base (BG)



- malattia di Binswanger
- infarti più ampi ai BG o nel territorio dell'a. cerebr. ant
- stato cribriforme (nello striato)

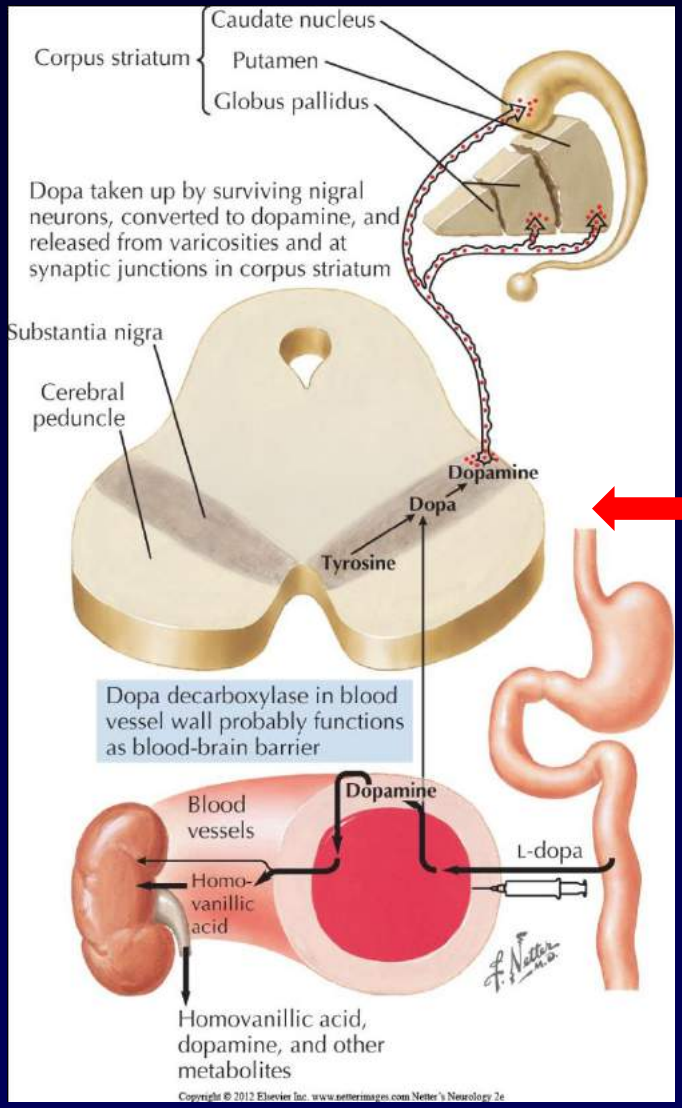




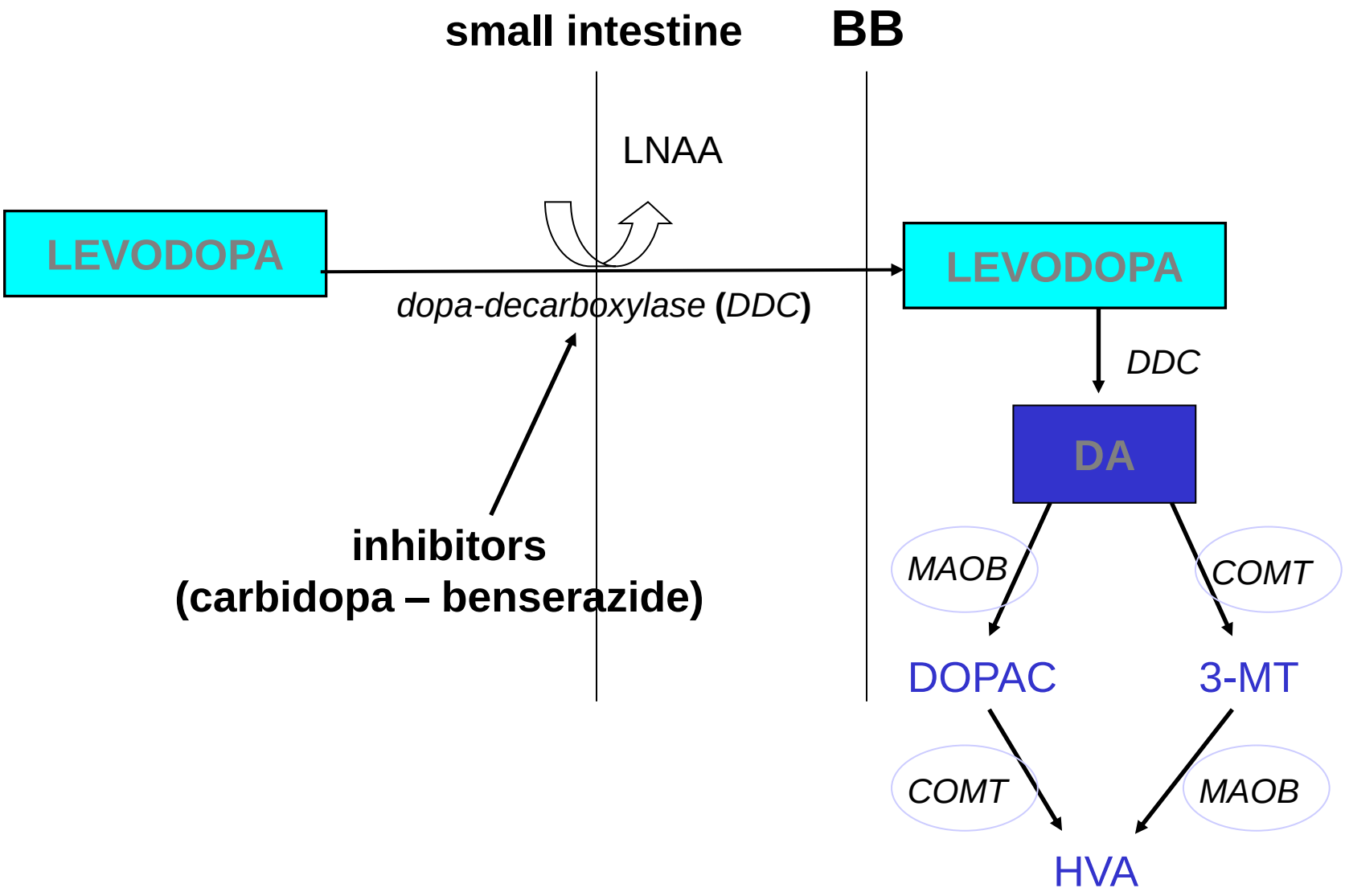
PD : Finalità del trattamento

RIPRISTINARE LA CARENZA DI DA

Malattia di Parkinson: l' esempio più felice, ma pur sempre una terapia sintomatica!



L-dopa


small intestine
BB
LNAA
LEVODOPA
dopa-decarboxylase (DDC)
LEVODOPA
DDC
DA
inhibitors
(carbidopa – benserazide)
MAOB
COMT
DOPAC
3-MT
COMT
MAOB
HVA

PD - Terapia

- Levo-dopa: il trattamento più efficace
- L'uso cronico è complicato da 2 problemi motori:
  - Fluttuazioni: irregolari, imprevedibili
  - Discinesie: involontarie, solitamente coreiche, distoniche
- Nelle fasi iniziali le fluttuazioni bene correlano con i livelli plasmatici di levo-dopa (*wearing off*, *end-of-dose*, *peak dose dyskinesia*)
- Nelle fasi più avanzate, fluttuazioni motorie "on-off"

PD – Terapia

Farmaci Dopaminergici
- Levodopa
- Carbiodopa/Levodopa
- Levodopa Controlled Release

Dopamino-agonisti
- Bromocriptine
- Pergolide
- Pramipexole
- Ropinirole
- Aphomorphine

Inibitori della Monoamino oxidasi B
- Selegiline

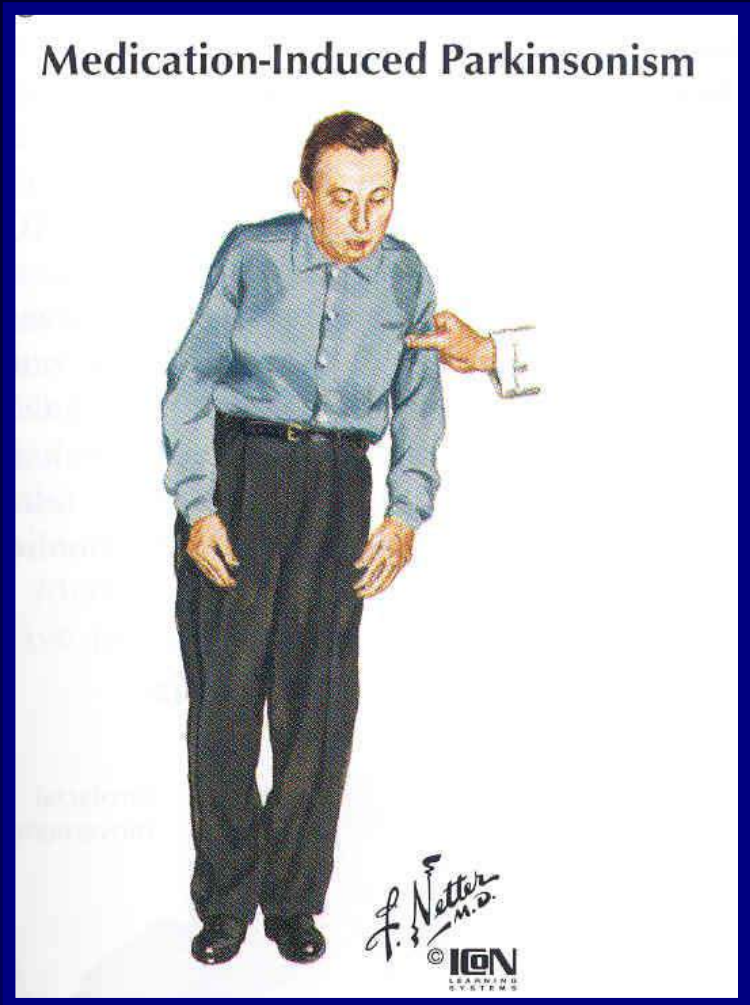
Agonisti indiretti
- Amantadine

PD – Terapia

Inibitori della Catecolamina-O-metil transferasi
- Tolcapone
- Entacopone

Altre classi di farmaci
- Anticolinergici
  - Trihexiphenidyl
  - Biperidin
- Nuovi neurolettici
  - Clozapine
- Miscellanea
  - Amitriptilina (per la frammentazione del sonno)
  - Baclofene (per crampi distonici)

Differential Diagnoses of Parkinson Disease
1. Drug induced
2. Familial
3. Toxic
4. Young onset
5. Metabolic
6. Parkinsonism diagnosable by imaging studies
7. Infectious or postinfectious
8. Miscellaneous causes
9. Degenerative diseases causing parkinsonism



CEREBRAL VASCULAR DISORDERS

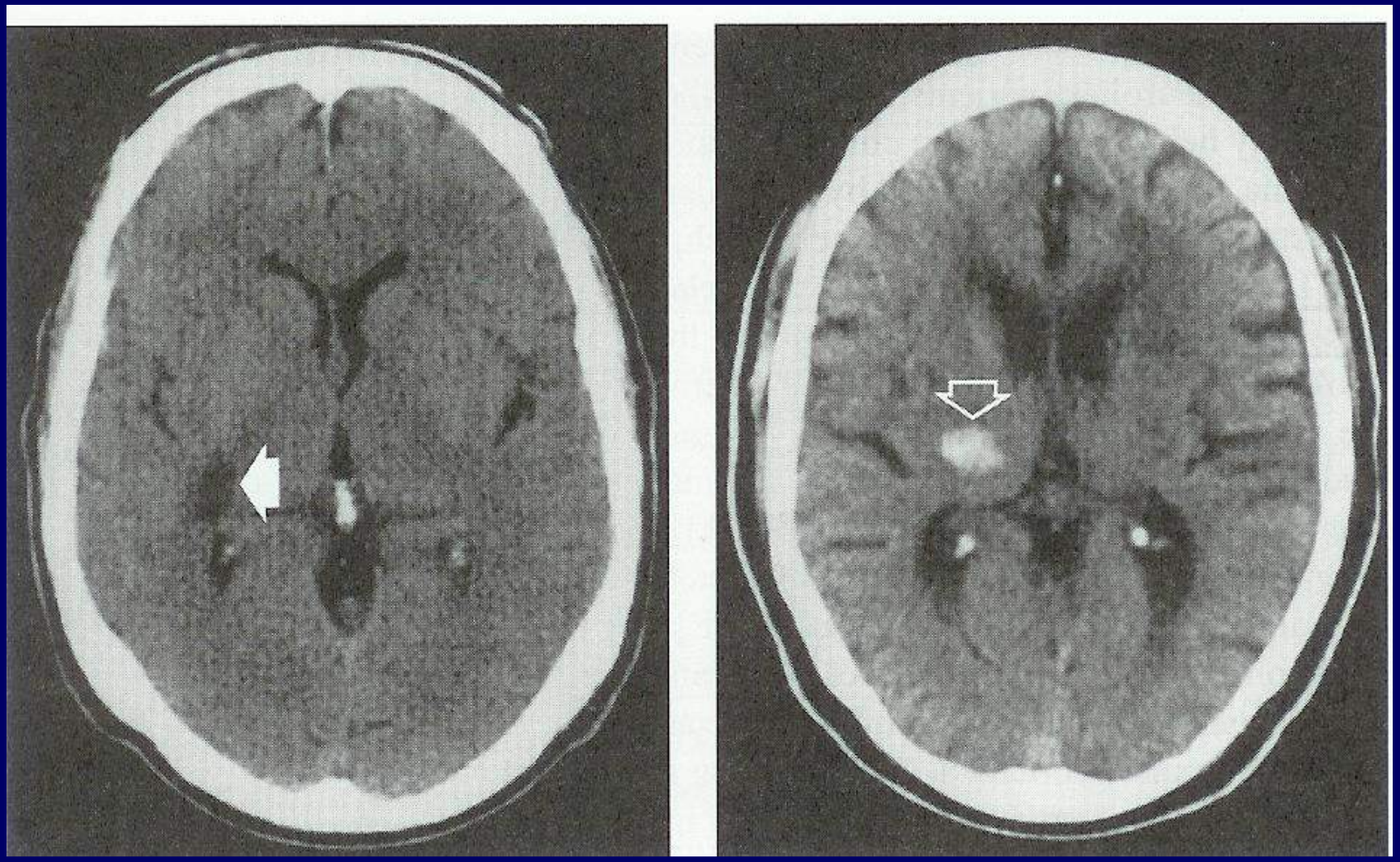
STROKE = BRAIN ATTACK = REQUIRE IMMEDIATE MEDICAL ATTENTION

PRIMARY ISCHEMIC STROKE vs PRIMARY HEMORRHAGIC STROKE

“TIME IS BRAIN”

OFTEN A CASCADE EVENT (STROKE IN EVOLUTION)

Diverse forme ictali



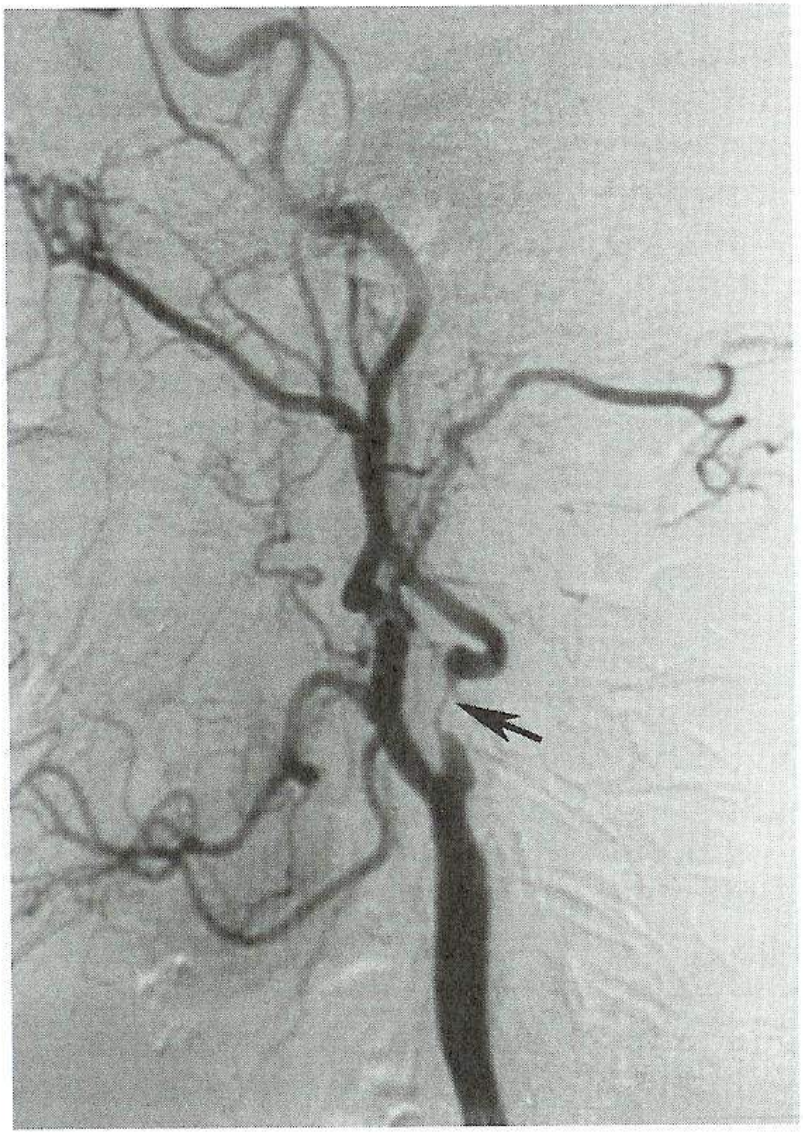


FIG. 2-2. High-grade internal carotid artery stenosis (*arrow*) as demonstrated on a routine cerebral arteriogram.

Ictus

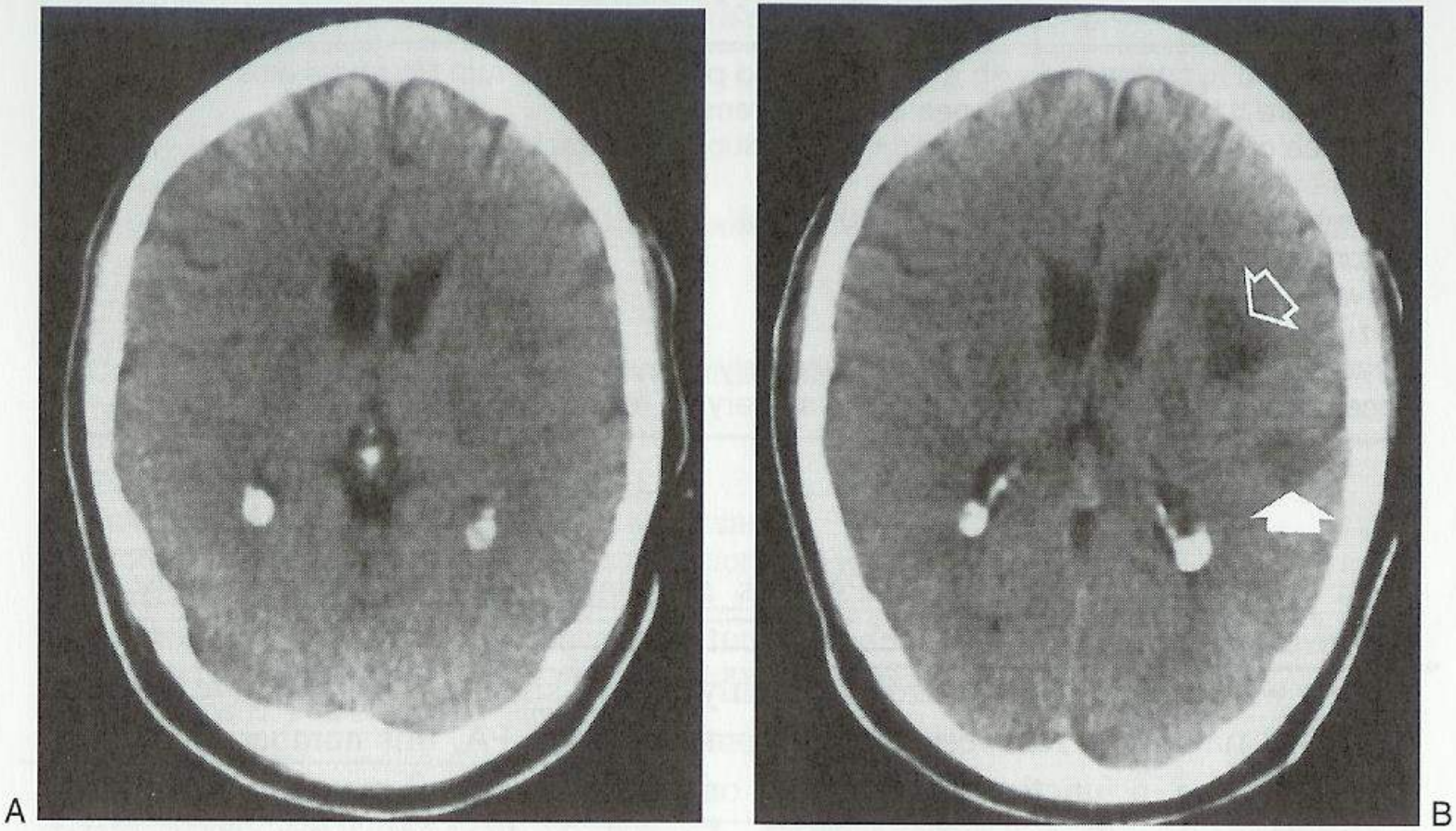
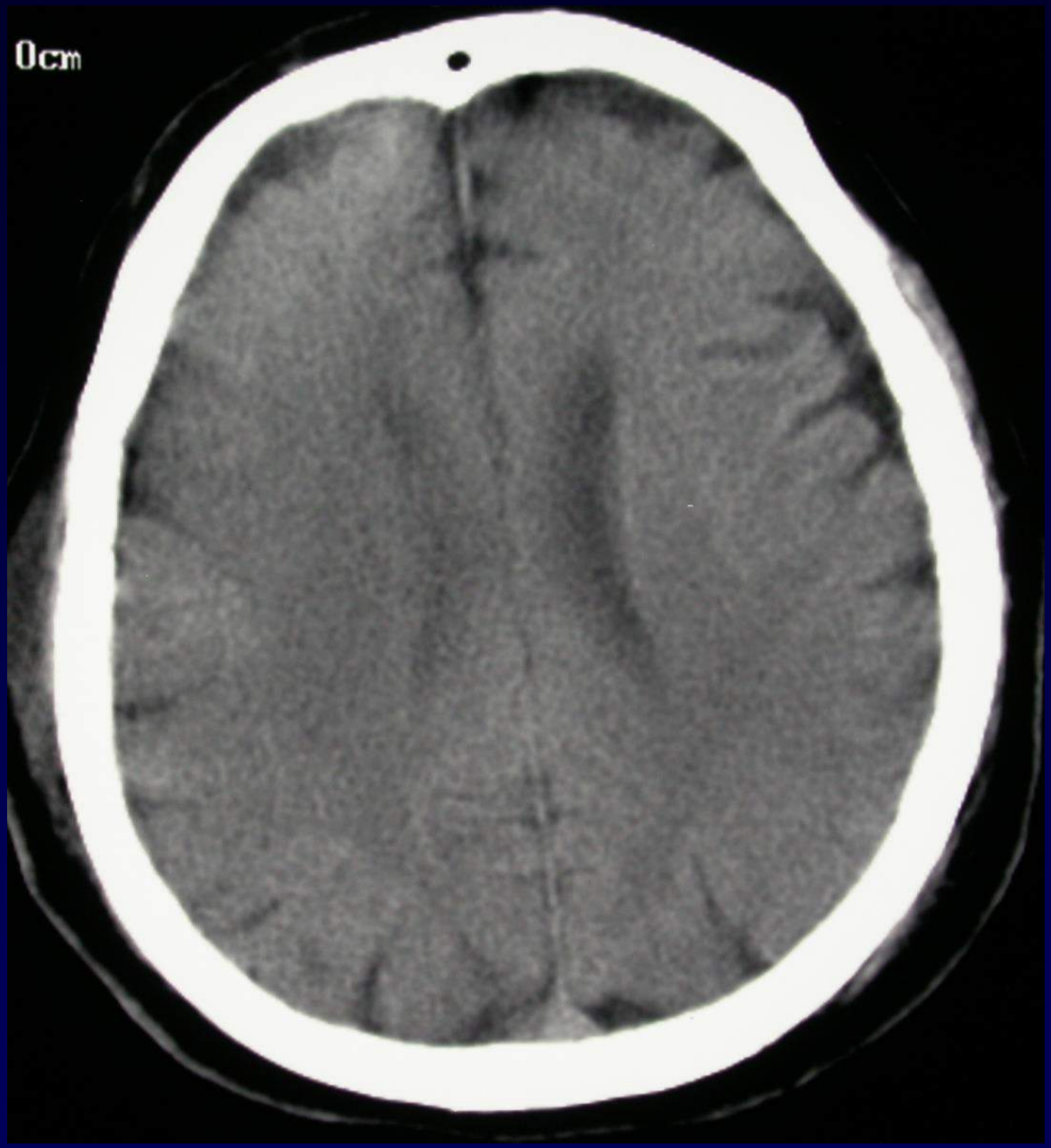


FIG. 2-6. A: Normal noncontrast computed tomography (CT) brain scan in a patient presenting with global aphasia but no associated weakness. **B:** Follow-up CT brain scan, 3 days later, which demonstrates an infarct in the distribution of the superior division of the left middle cerebral artery (*open arrow*) and an infarct in the distribution of the inferior division of the left middle cerebral artery (*closed arrow*). This is most compatible with two separate embolic events.

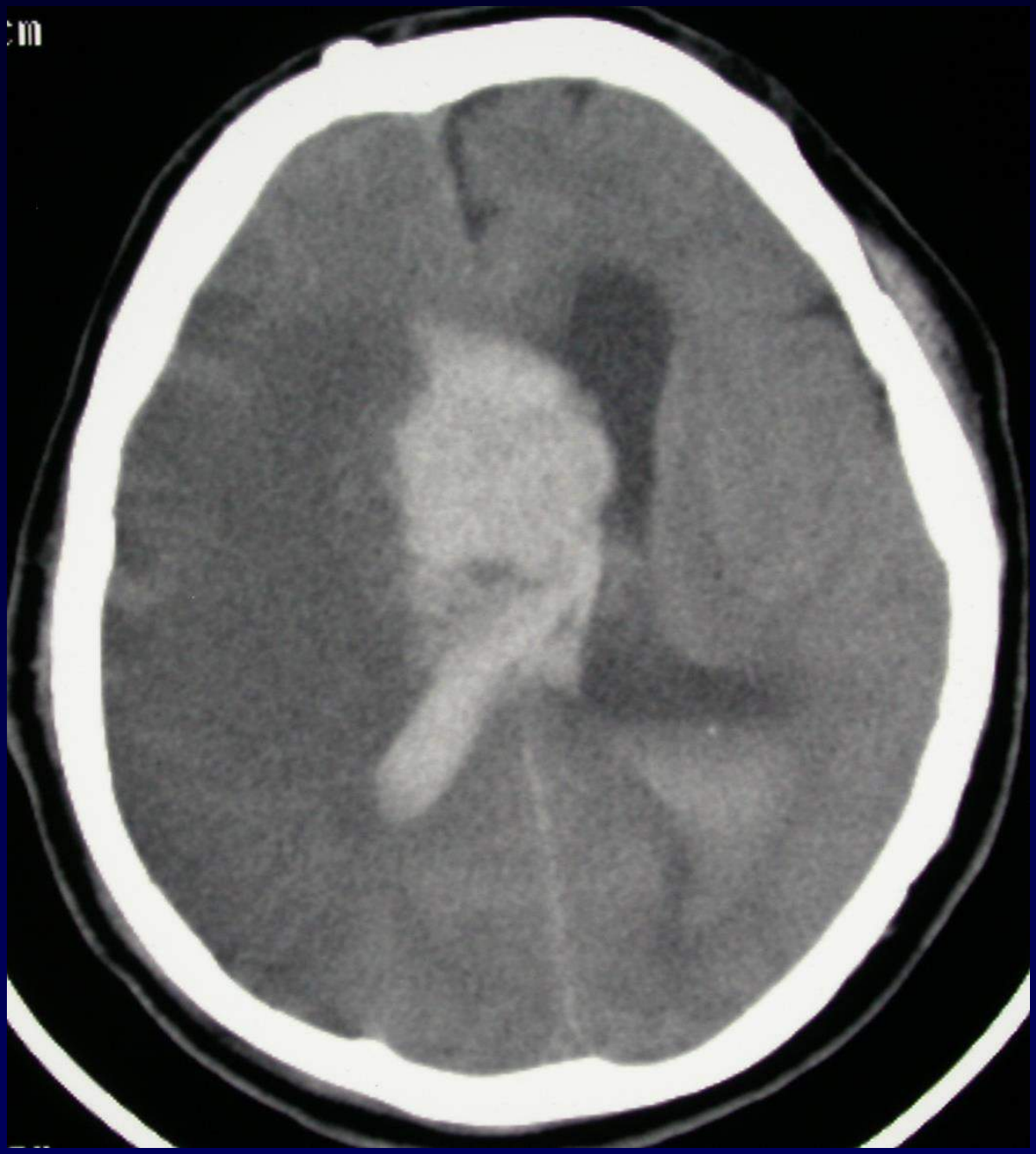
TAC encefalo di base

(eseguita in PS)



TAC encefalo di base

(eseguita dopo 2 gg)



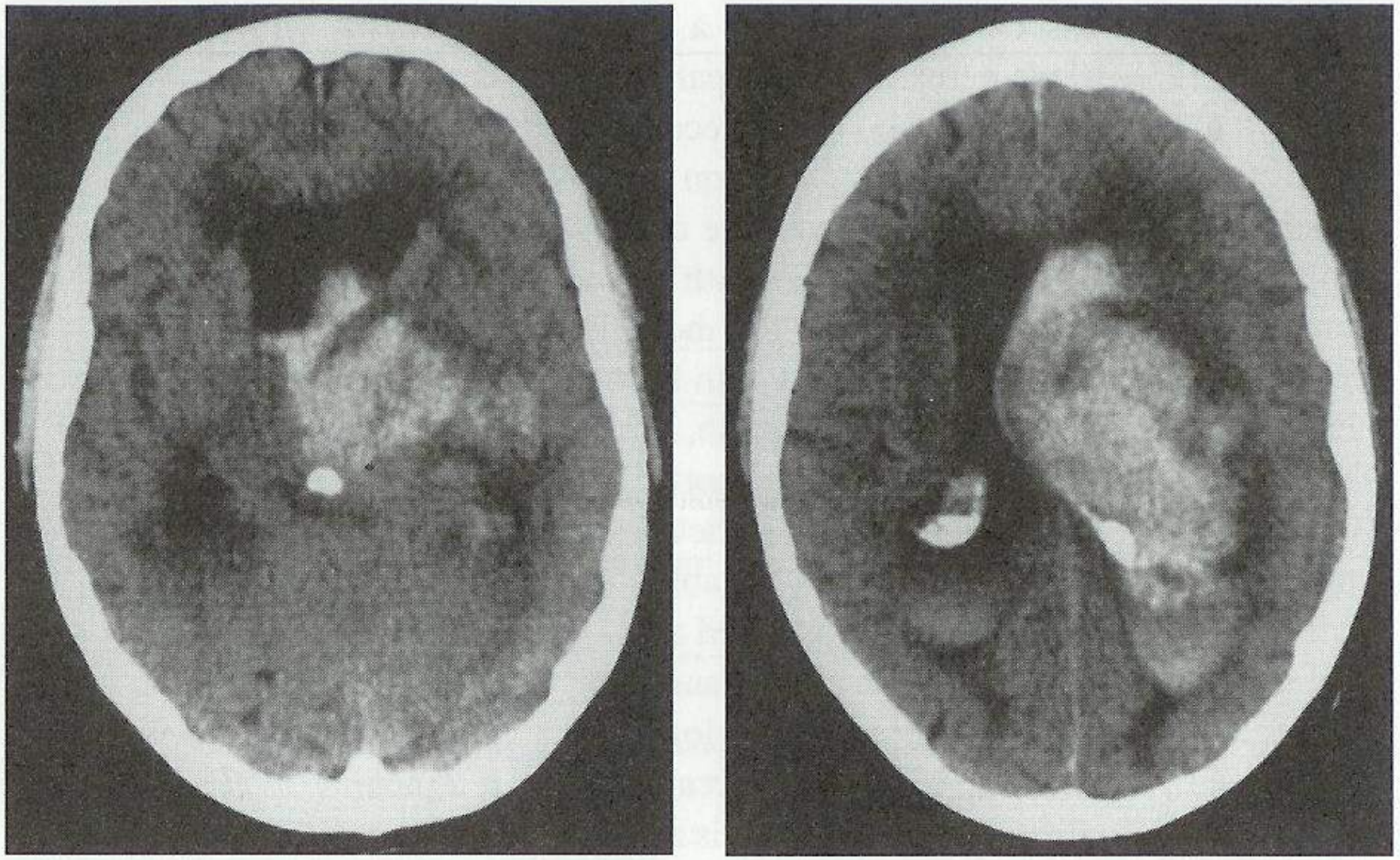


FIG. 2-7. Massive right putaminal (intracerebral) hemorrhage seen on two planes of the non-contrast computed tomography brain scan. There is associated intraventricular extension. The size of the hematoma and the ventricular extension are both poor prognostic signs.

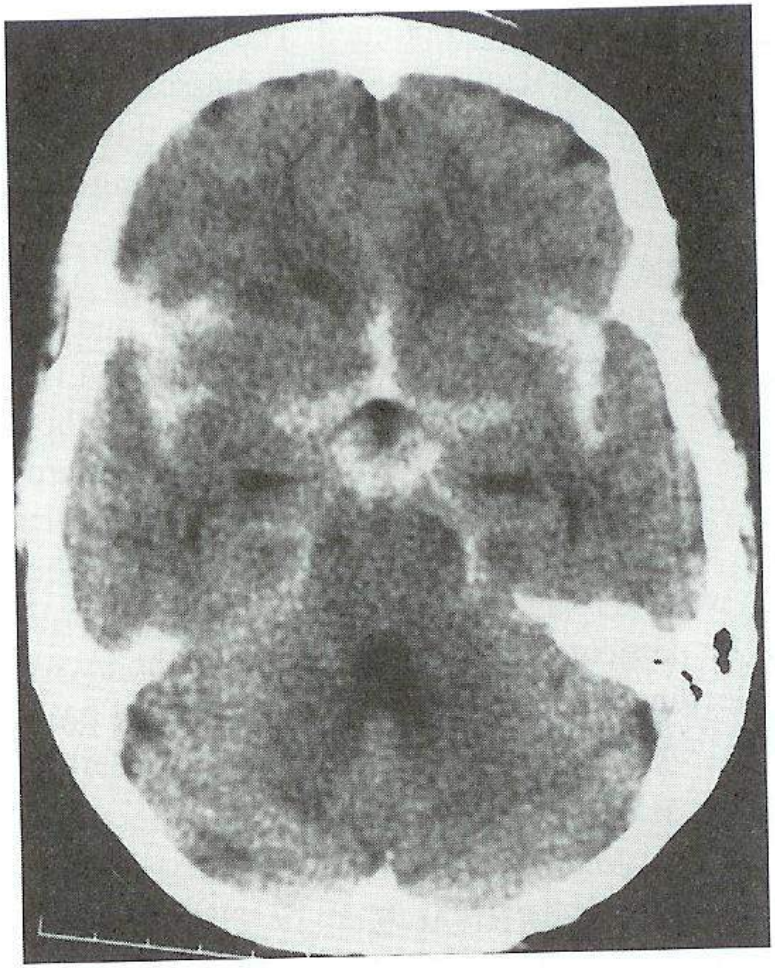


FIG. 2-8. Diffuse subarachnoid blood seen on a noncontrast computed tomography brain scan. This patient had a rupture of a right middle cerebral artery aneurysm.

Major mechanisms of acute stroke

ischemic (85%)	*hemorrhagic (15%)*
Thrombotic	**Intracerebral hemorrhage**
Larger artery	**Hypertensive**
Small artery (lacunar)	**Vascular anomalies**
Sinovenous	**Bleeding diatheses**
Embolic	**Neoplastic**
Cardiogenic	**Infectious**
Paradoxical (peripheral sources with interatrial defect)	**Iatrogenic**
	Amyloid angiopathy
Artery-to-artery (e.g., aortic arch, carotid, vertebral to intracranial)	
Hemodynamic	**SAH**
Hypotensive (e.g., watershed-type infarcts)	**Aneurysmal rupture**
Mechanical obstruction	**AV malformations**
Vascular dissection	
Hematologic (polycythemia, thrombocytosis, hyperviscosity syndromes, hypercoaghulable states)	

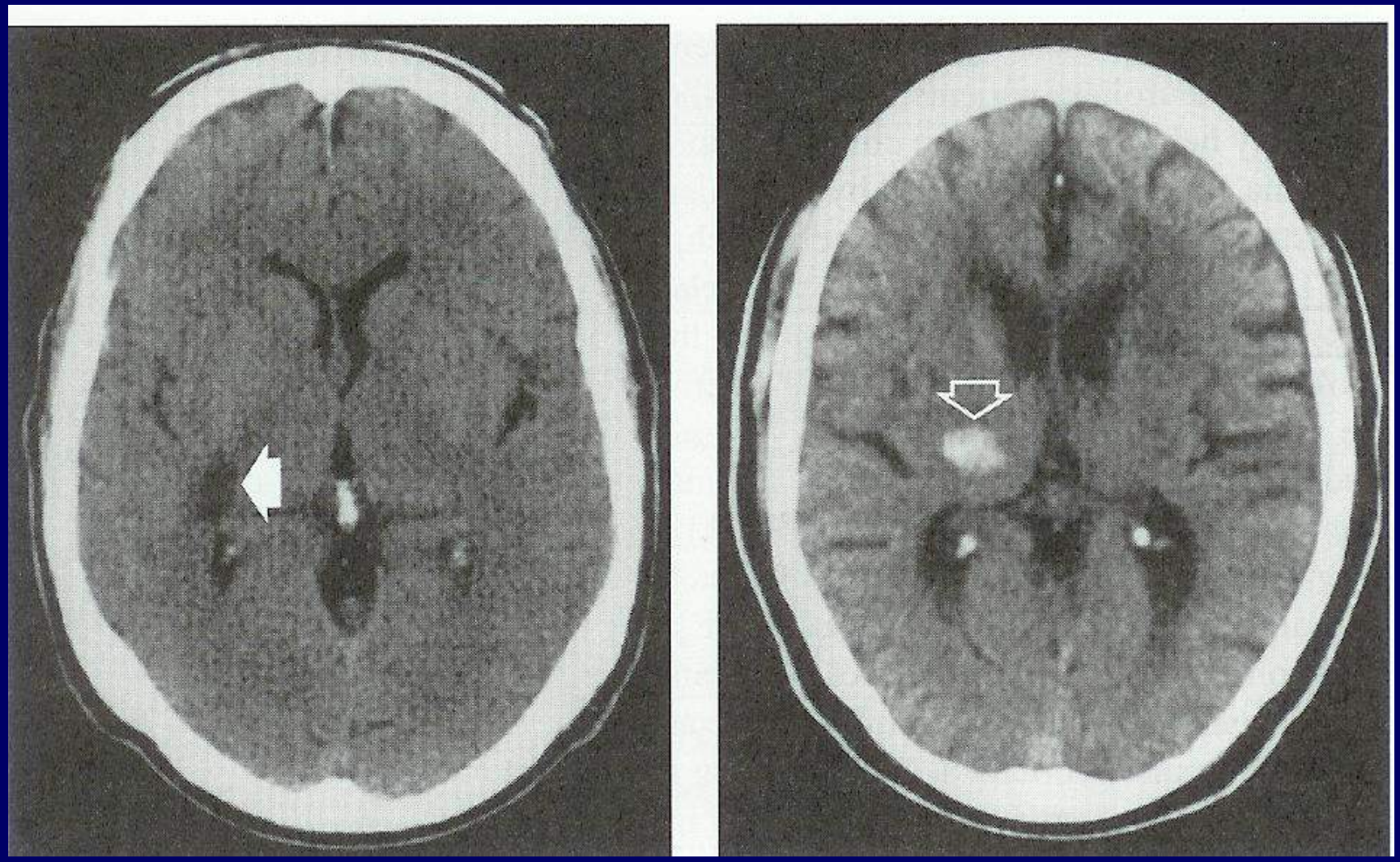
NEUROIMAGING NEEDED TO DISTINGUISH!

TIA

- A NEUROLOGICAL EMERGENCY (RIND as well)
- TIA OFFERS OPPORTUNITY TO PROVIDE PROTECTION AGAINST AN ISCHEMIC STROKE
- 12% TIA PATIENTS GO ON TO HAVE A STROKE IN 1 YEAR, 1/3 TO ½ IN 5 YEARS
- SEIZURES NOT IN ITSELF A POOR PROGNOSTIC SIGN
- DIFFERENT POTENTIAL MECHANISMS, CT SCAN NEGATIVE
- THROMBOTIC, EMBOLIC (ICA, HEART, PROXIMAL AORTIC ARCH) OR HEMODYNAMIC MECHANISM
- MIMICKING CAUSES : BRAIN ASCESSES, SUBDURAL HEMATOMA, FOCAL MOTOR OR SENSORY SEIZURE, MIGRAINE WITH FOCAL SIGNS

ISCHEMIC STROKE

- BRAIN ATTACK, “TIME IS BRAIN”
- NO ACCURATE NEUROLOGICAL EXAM, BUT SCALES (NIH)
- MECHANISM OF STROKE?
- EMBOLIC VS THROMBOTIC VS LACUNAR-TYPE STROKE (NO CORTICAL DISTURBANCES)
- DD EMBOLIC STROKE vs LARGER-ARTERY THROMBOTIC STROKE
- ISCHEMIC STROKE SECONDARY TO CEREBROVASCULAR DISSECTION with trauma/pain, trivial
- CEREBRAL VENOUS THROMBOSIS in pregnancy, oral contraceptive, infections, prothrombotic state
- SPINAL CORD INFARCTIONS: MIDTHORACIC REGION



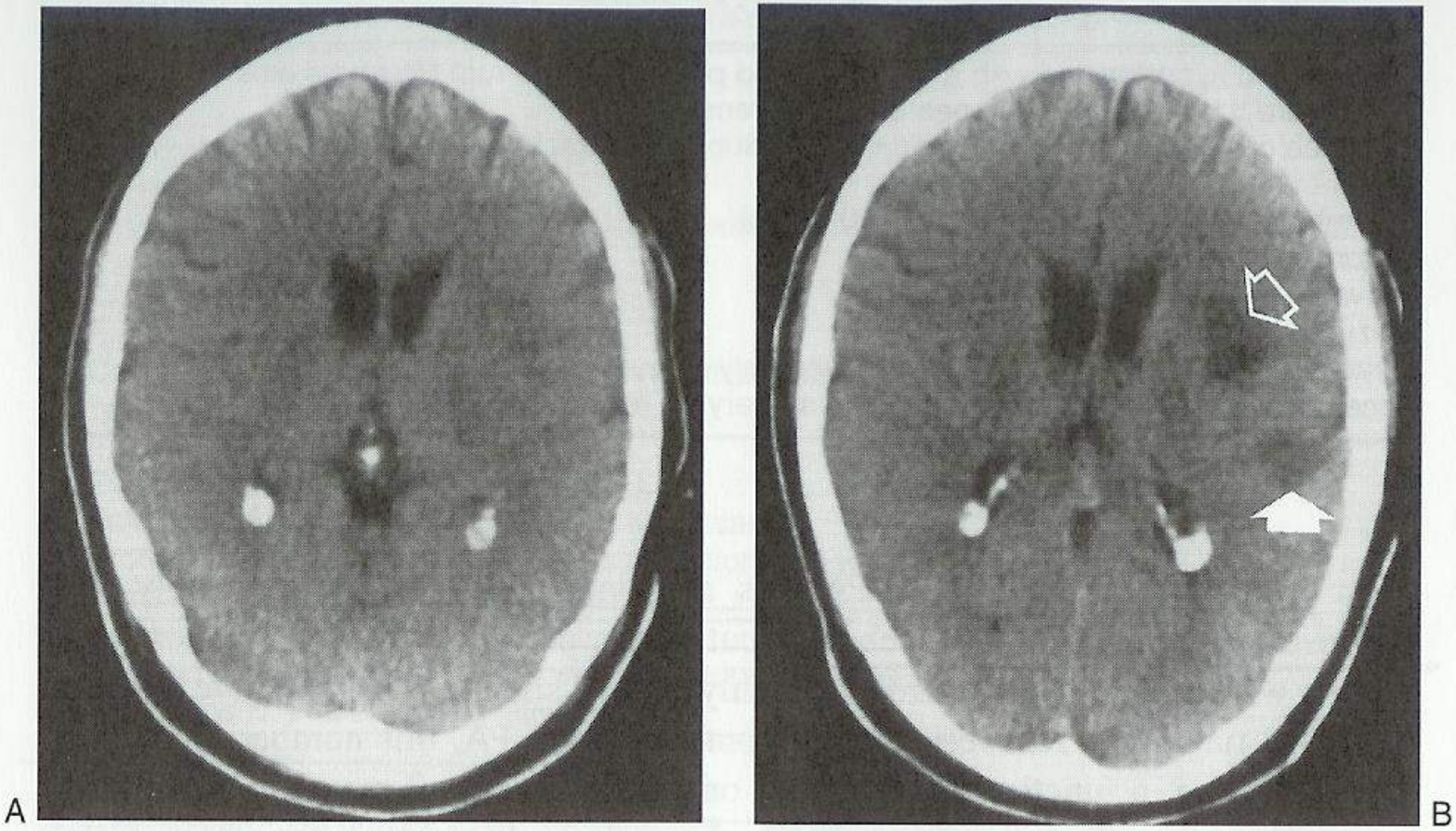
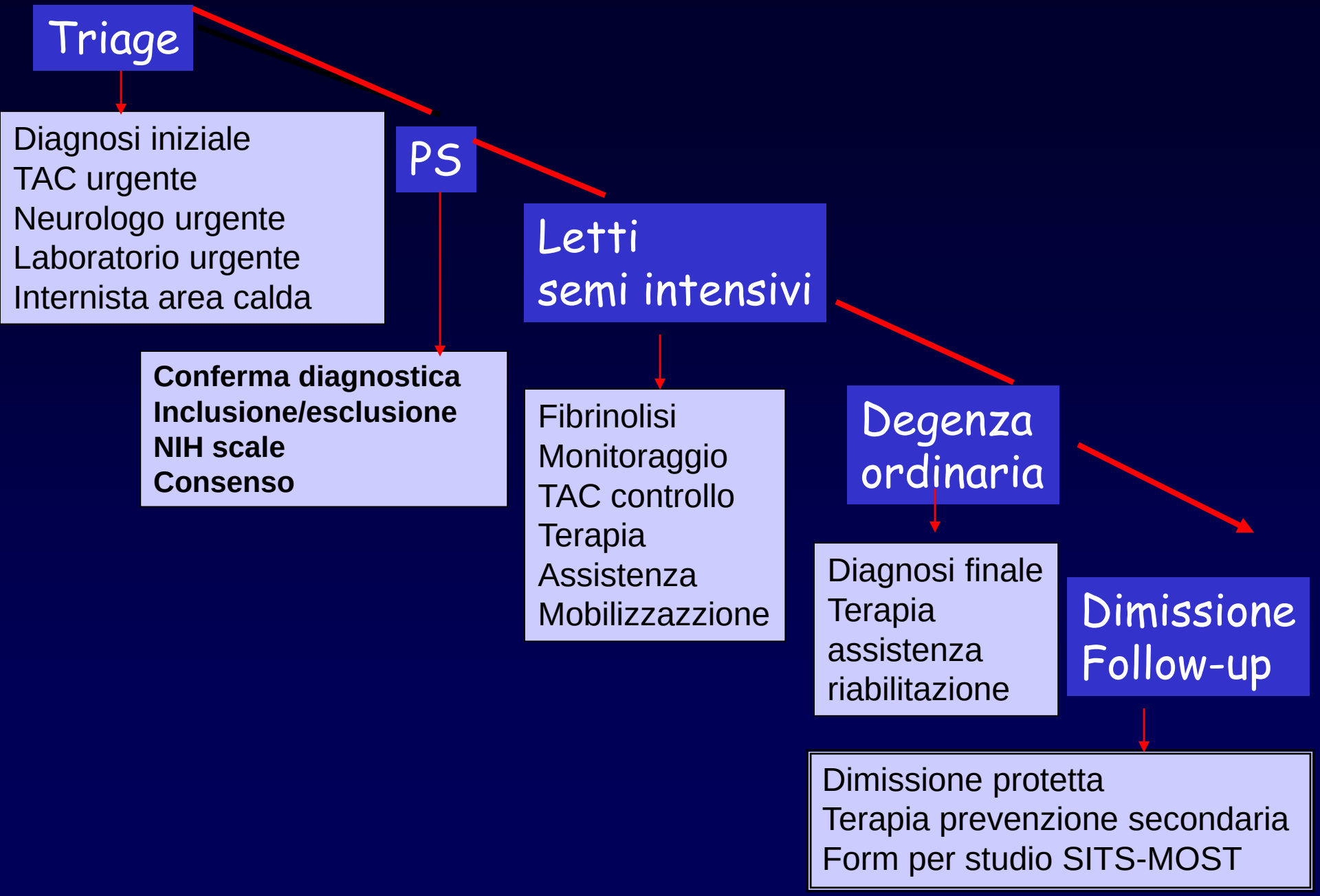


FIG. 2-6. A: Normal noncontrast computed tomography (CT) brain scan in a patient presenting with global aphasia but no associated weakness. **B:** Follow-up CT brain scan, 3 days later, which demonstrates an infarct in the distribution of the superior division of the left middle cerebral artery (*open arrow*) and an infarct in the distribution of the inferior division of the left middle cerebral artery (*closed arrow*). This is most compatible with two separate embolic events.

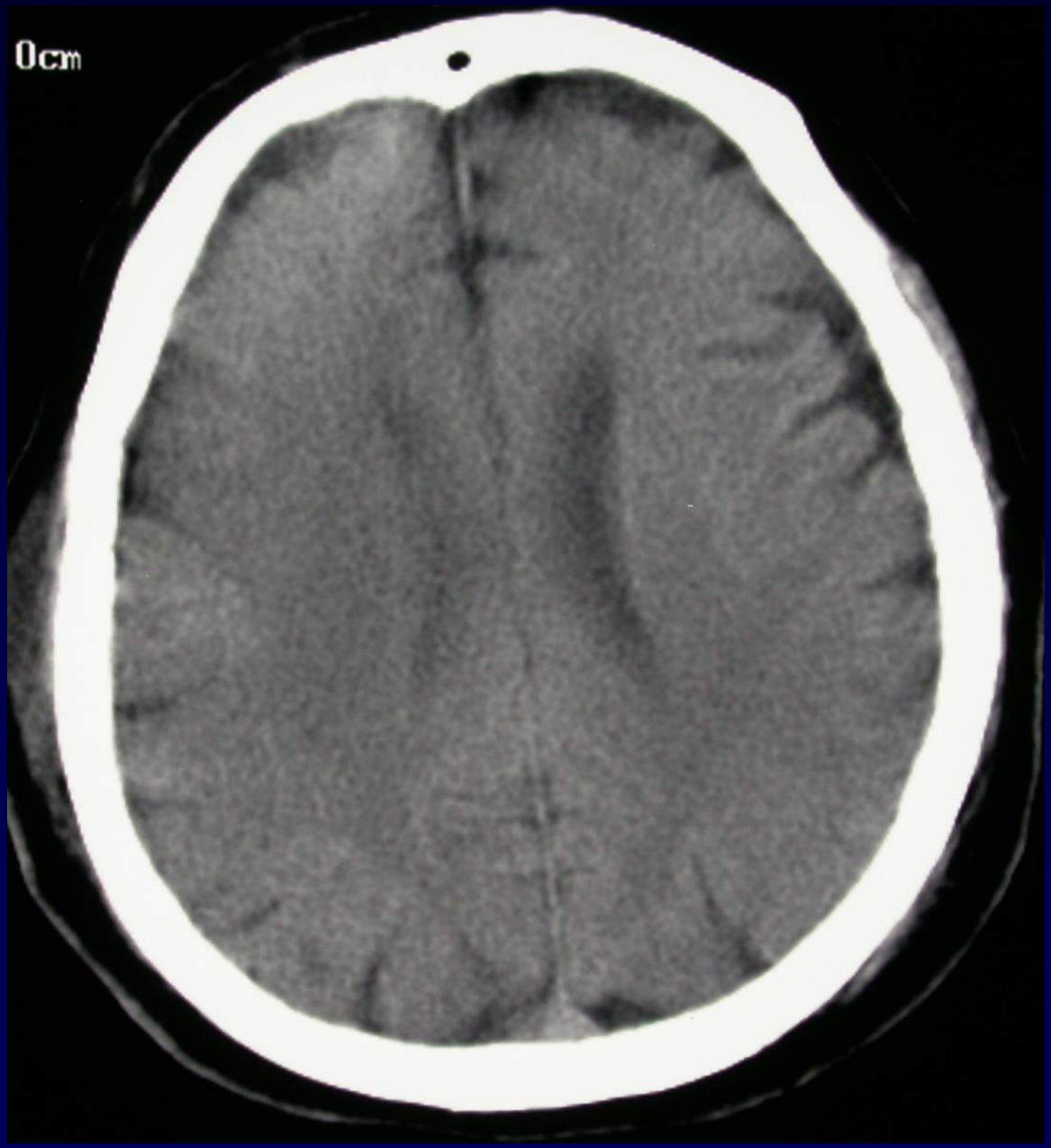
Emiparesi

FIG. 23–8. Left hemiparesis of 15 years' duration. The patient circumducts his left leg as he begins walking.


Triage
Diagnosi iniziale
TAC urgente
Neurologo urgente
Laboratorio urgente
Internista area calda
PS
Conferma diagnostica
Inclusione/esclusione
NIH scale
Consenso
Letti
semi intensivi
Fibrinolisi
Monitoraggio
TAC controllo
Terapia
Assistenza
Mobilizzazzione
Degenza
ordinaria
Diagnosi finale
Terapia
assistenza
riabilitazione
Dimissione
Follow-up
Dimissione protetta
Terapia prevenzione secondaria
Form per studio SITS-MOST

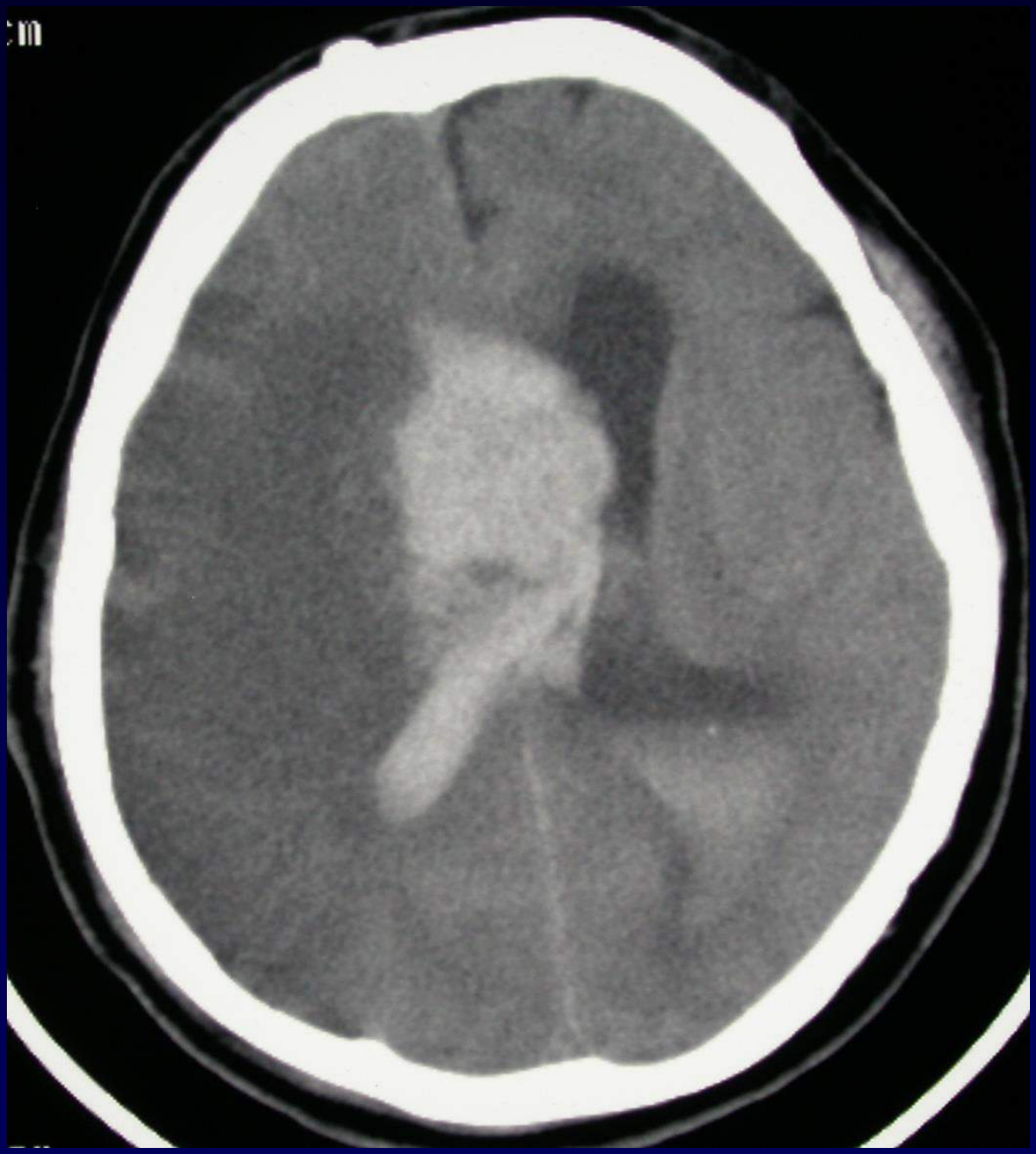
TAC encefalo di base

(eseguita in PS)



TAC encefalo di base

(eseguita dopo 2 gg)



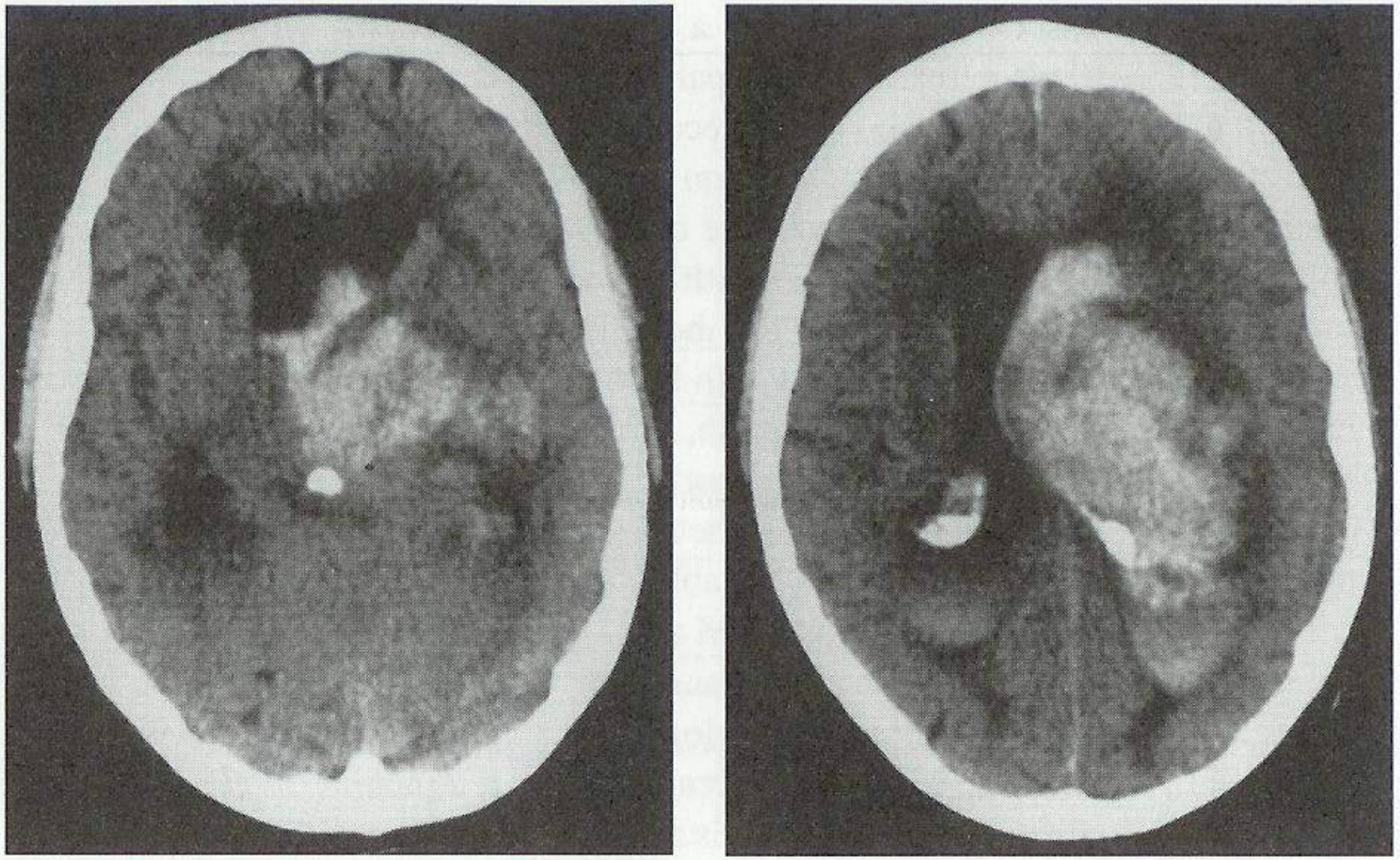


FIG. 2-7. Massive right putaminal (intracerebral) hemorrhage seen on two planes of the non-contrast computed tomography brain scan. There is associated intraventricular extension. The size of the hematoma and the ventricular extension are both poor prognostic signs.

SUBARACHNOID HEMORRHAGE

- **10% OF ALL STROKE**
- **CT DIAGNOSTIC (89% CASES), LUMBAR PUNCTURE MANDATORY IN SOME CASES (CT NEGATIVE)**
- **CEREBRAL ARTERIOGRAM MANDATORY (REPEATED or *CRYPTIC AVM*)**
- **SPIRAL CT ANGIOGRAPHY**
- **MRA AS A SCREENING (5 mm diameter)**

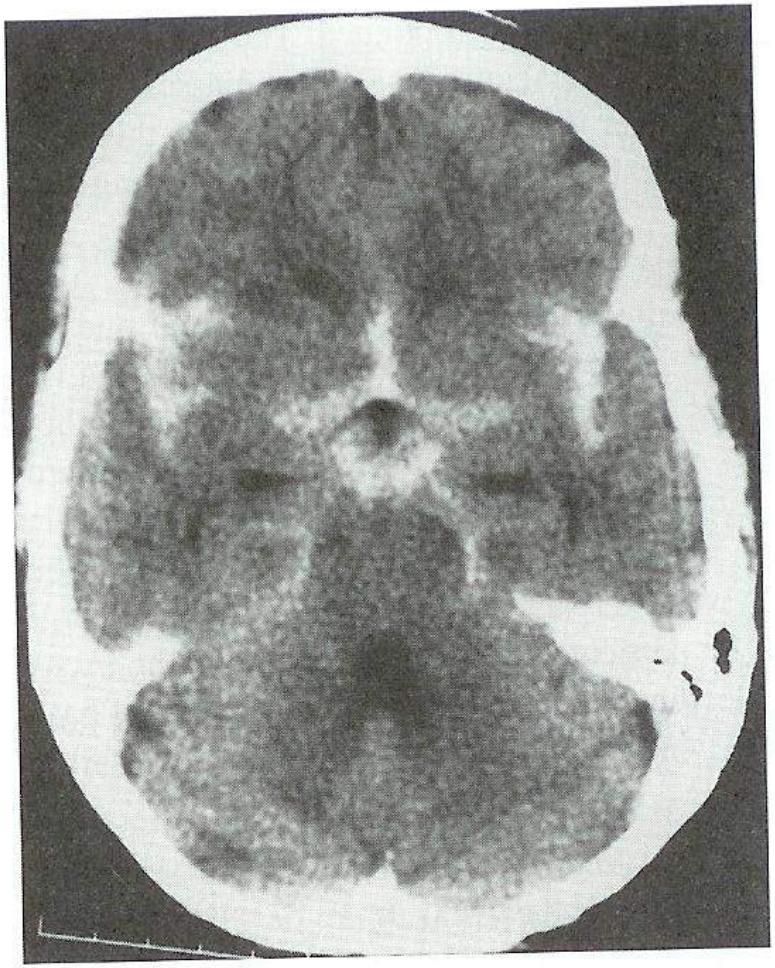
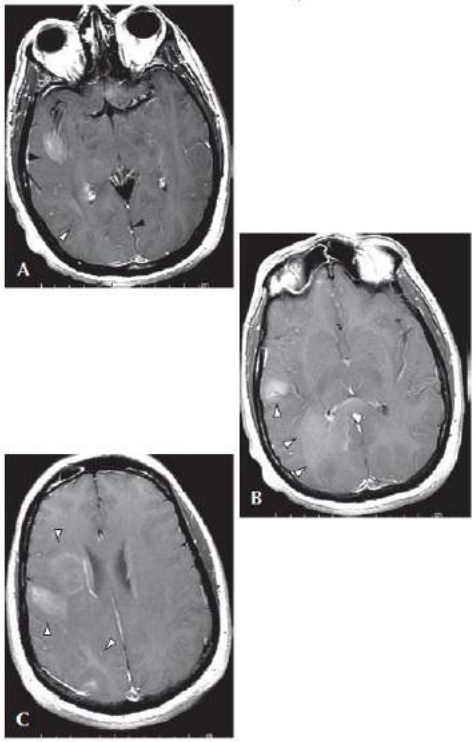


FIG. 2-8. Diffuse subarachnoid blood seen on a noncontrast computed tomography brain scan. This patient had a rupture of a right middle cerebral artery aneurysm.

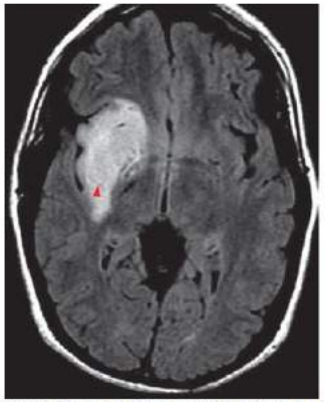
Tumori Primitivi

Gliomatosis cerebri in 46-year-old with 3-day history of headache and left facial droop

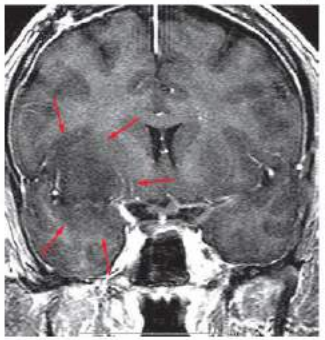


A.-C. Multiple axial post–gadolinium-enhanced T1-weighted fast spin echoes images demonstrate multiple areas of subtle enhancement involving white matter with extension into cortex. These same regions were subtly T2 bright on FLAIR (arrowheads).

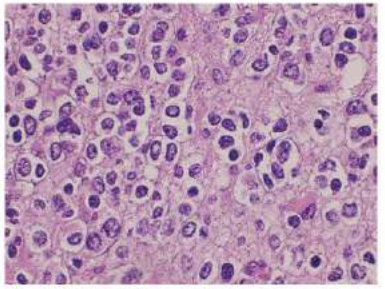
Oligodendroglioma in a 34-year-old woman with recent uncinate seizures



A. Axial FLAIR MR image demonstrates T2 hyperintensity that involves the right basal ganglia, insula, and intervening subinsular region with subtle expansion when compared with the opposite side.



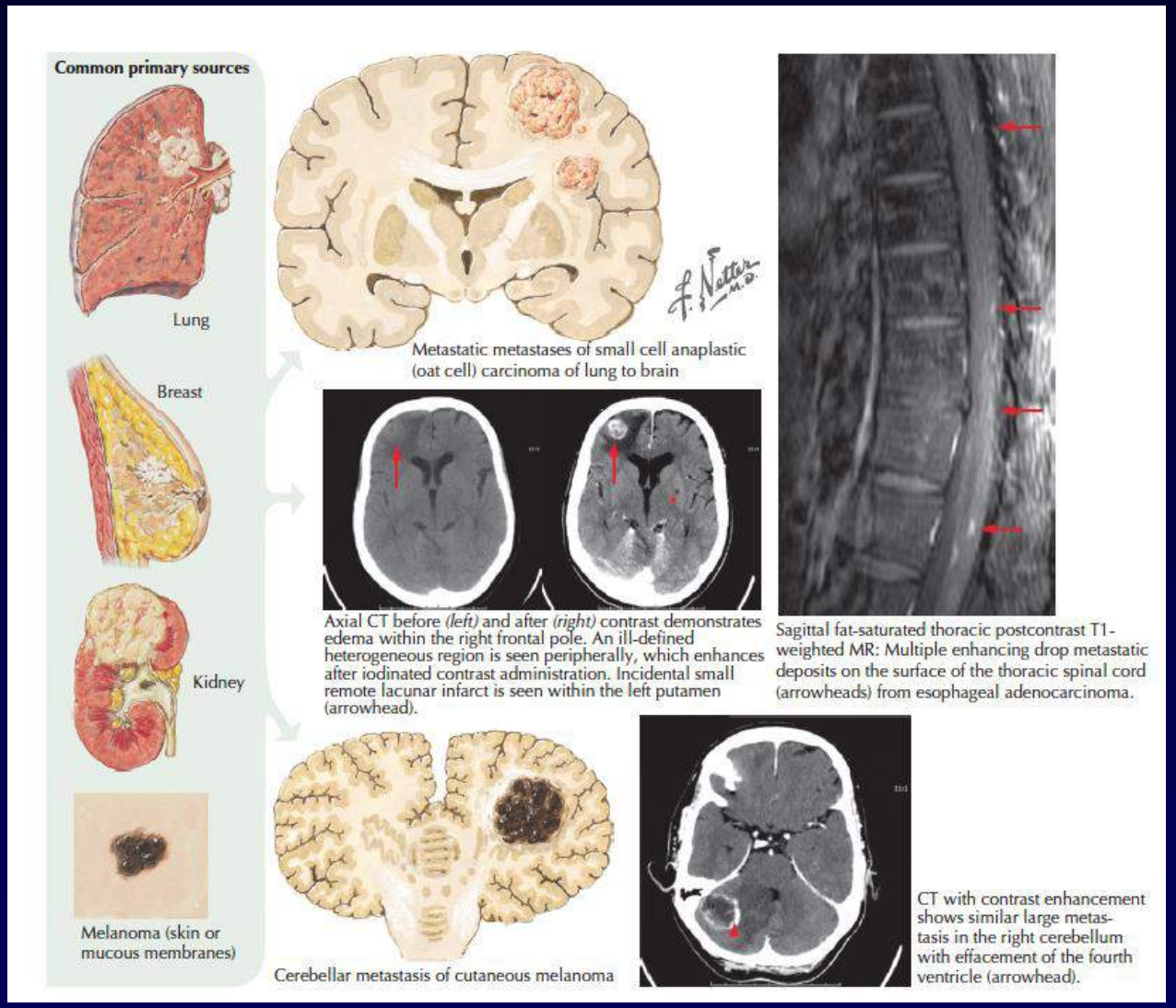
B. Coronal T1-weighted fast spin-echo MR image following gadolinium enhancement shows ill-defined T1 hypointensity within the insula, subinsular region, and adjacent basal ganglia with uncinate fasciculus extension into the superior medial anterior left temporal lobe (arrows). Note absence of enhancement.



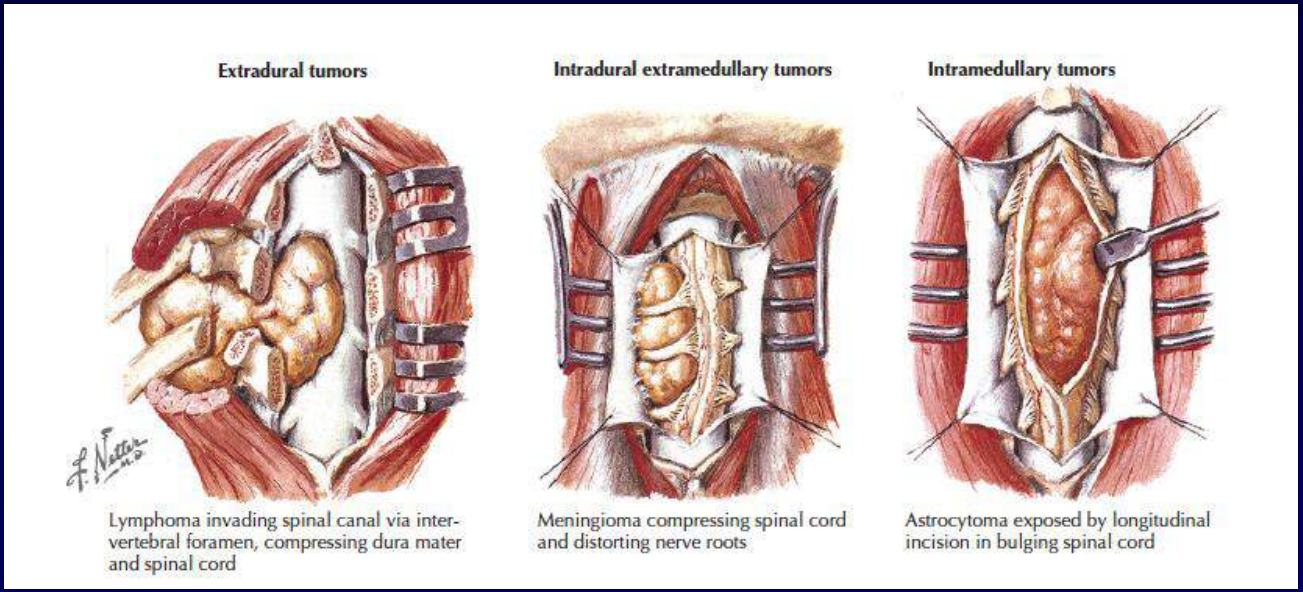
C. Oligodendroglioma. Uniform population of round cells, many with clear cytoplasm—so-called "fried egg" appearance.

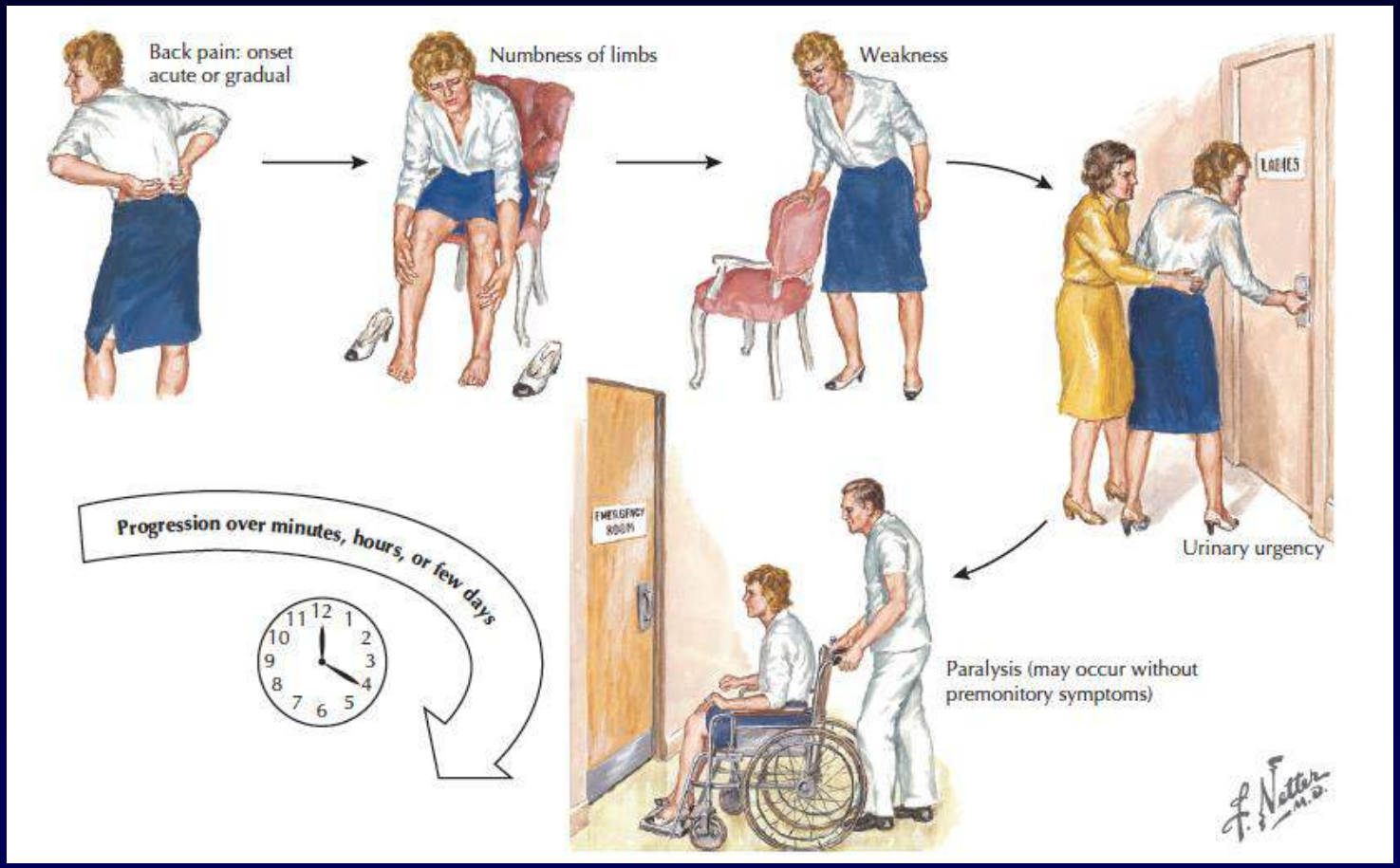
Figure 52-4 Oligodendroglioma.

Tumori Secondari

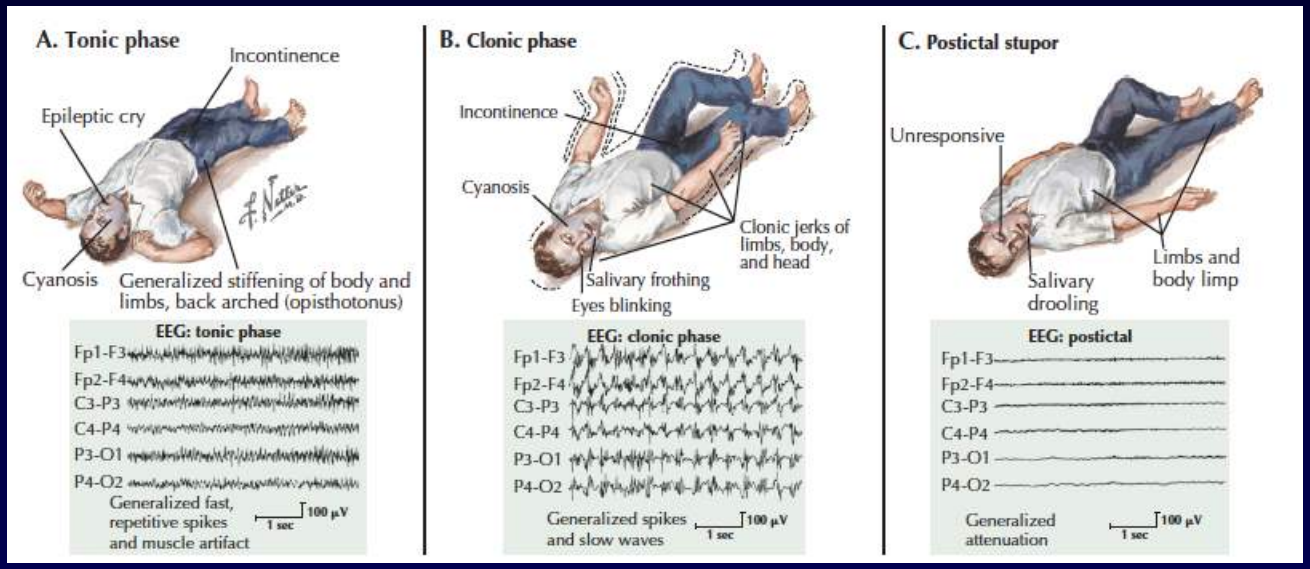


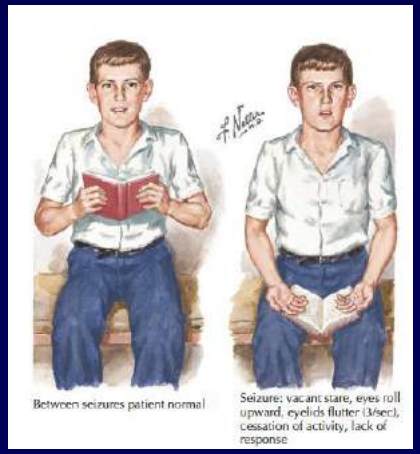
Tumori Midollari



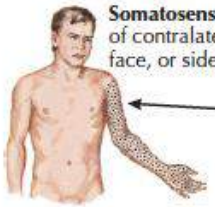

Back pain: onset
acute or gradual
Numbness of limbs
Weakness
LADIES
Urinary urgency
EMERGENCY
ROOM
Paralysis (may occur without
premonitory symptoms)
Progression over minutes, hours, or few days

Epilessia

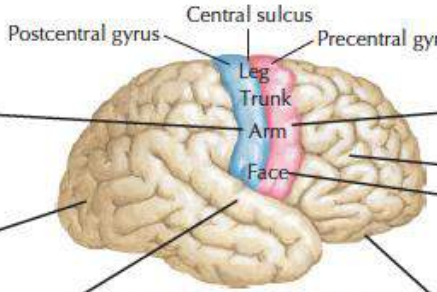

A. Tonic phase
Incontinence
Epileptic cry
Cyanosis
Generalized stiffening of body and limbs, back arched (opisthotonus)
EEG: tonic phase
Fp1-F3
Fp2-F4
C3-P3
C4-P4
P3-O1
P4-O2
Generalized fast, repetitive spikes and muscle artifact
1 sec
100 μV
B. Clonic phase
Incontinence
Cyanosis
Clonic jerks of limbs, body, and head
Salivary frothing
Eyes blinking
EEG: clonic phase
Fp1-F3
Fp2-F4
C3-P3
C4-P4
P3-O1
P4-O2
Generalized spikes and slow waves
1 sec
100 μV
C. Postictal stupor
Unresponsive
Limbs and body limp
Salivary drooling
EEG: postictal
Fp1-F3
Fp2-F4
C3-P3
C4-P4
P3-O1
P4-O2
Generalized attenuation
1 sec
100 μV


Between seizures patient normal
Seizure: vacant stare, eyes roll upward, eyelids flutter (3/sec), cessation of activity, lack of response

Simple Partial Seizures



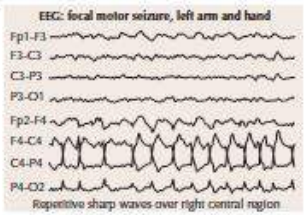
Somatosensory. Tingling of contralateral limb, face, or side of body

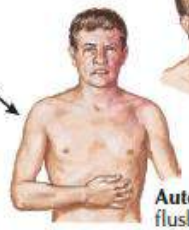


Focal motor. Tonic-clonic movements of upper (or lower) limb

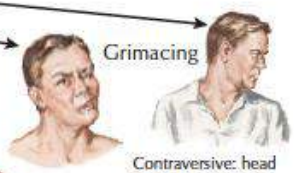
Visual. Sees flashes of light, scotomas, unilateral or bilateral blurring

Auditory. Hears ringing, hissing, or noises





Autonomic. Sweating flushing or pallor, and/or epigastric sensations

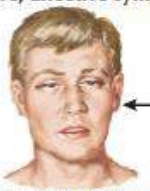


Grimacing

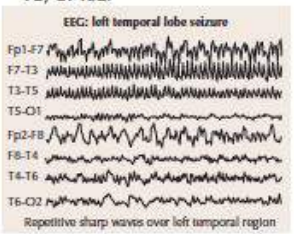
Contraversive: head and eyes turned to opposite side

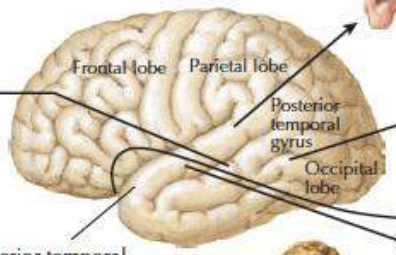
Complex Partial Seizures

Impairment of consciousness: cognitive, affective symptoms



Dreamy state; blank, vacant expression; déjà vu; jamais vu; or fear





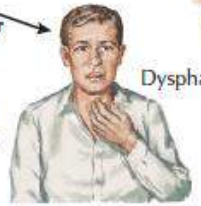
Formed auditory hallucinations
Hears music, etc.

Formed visual hallucinations
Sees house, trees that are not there

Bad or unusual smell

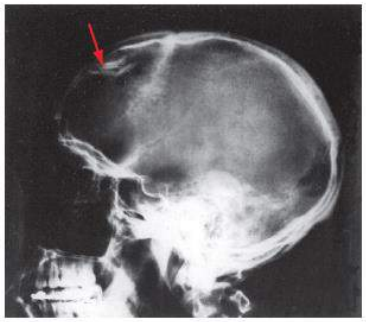
Olfactory hallucinations

Psychomotor phenomena
Chewing movements, wetting lips, automatisms (picking at clothing)

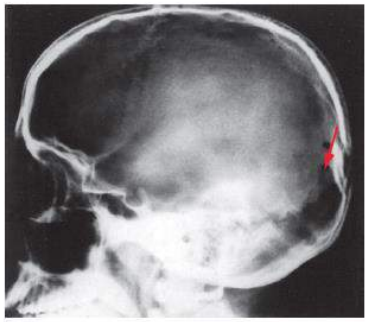


Dysphasia

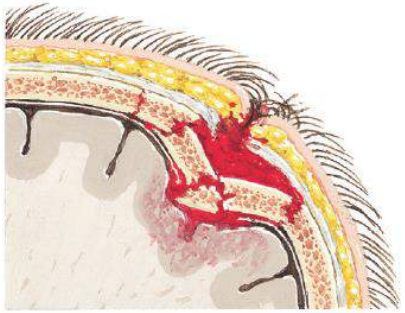
Traumi



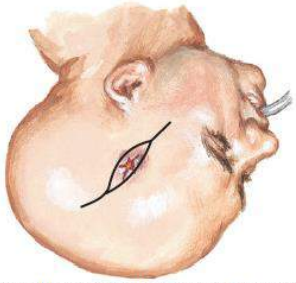
Left lateral skull film showing left frontal depressed skull fracture



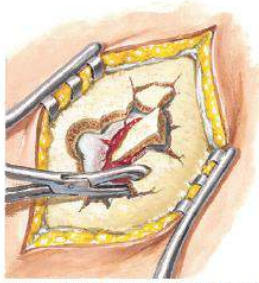
Left lateral skull film revealing occipital depressed skull fracture



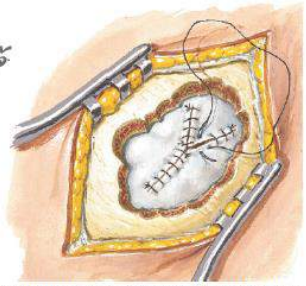
Compound depressed skull fracture. Note hair impacted into wound



Elliptical incision with extensions to remove devitalized skin and pericranium

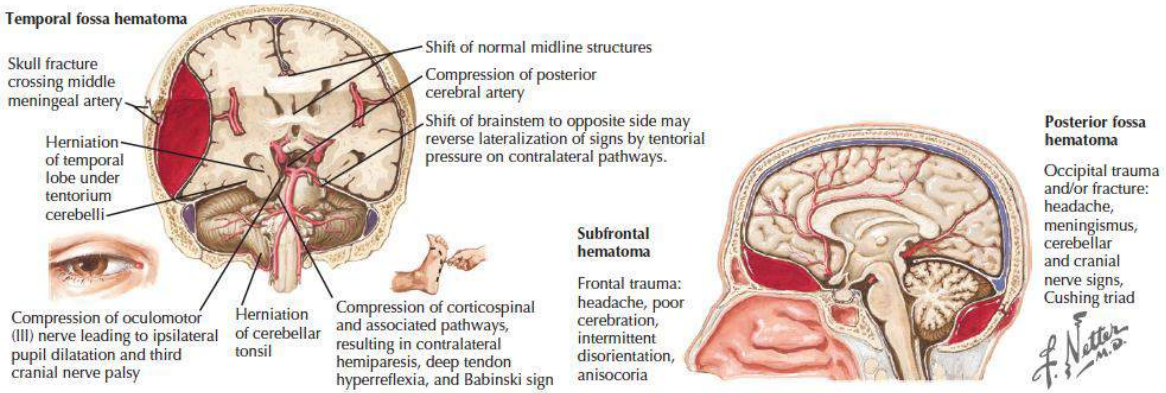


Burr hole placed at margin of fracture to facilitate elevation of depressed bone fragments. Bone edges, dura, and brain then debrided



Watertight dural closure. Optionally, bone fragments may be cleaned and wired in place Skin is closed in one layer

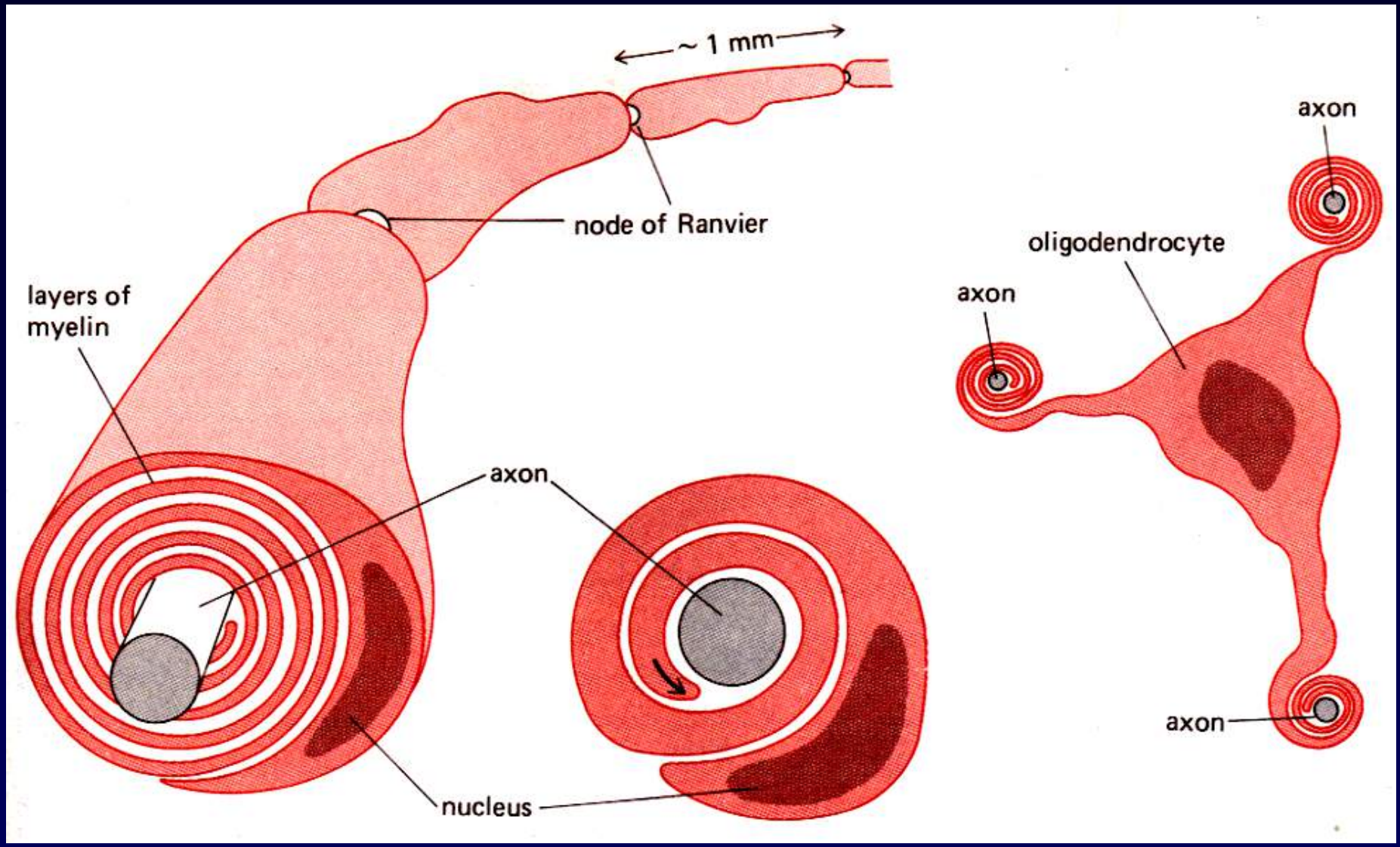
Figure 59-4 Compound Depressed Skull Fractures.



SCLEROSI MULTIPLA e MALATTIE DEMIELINIZZANTI

- Malattia infiammatoria, demielinizzante
- Specifica del sistema nervoso centrale
- La più frequente causa di disabilità cronica da patologia neurologica nei giovani adulti
- Esordio generalmente tra i 20 e i 40 anni
- Nelle fasi iniziali il decorso è di tipo recidivante-remittente (relapsing-remitting)
- Disabilità progressiva con il passare del tempo

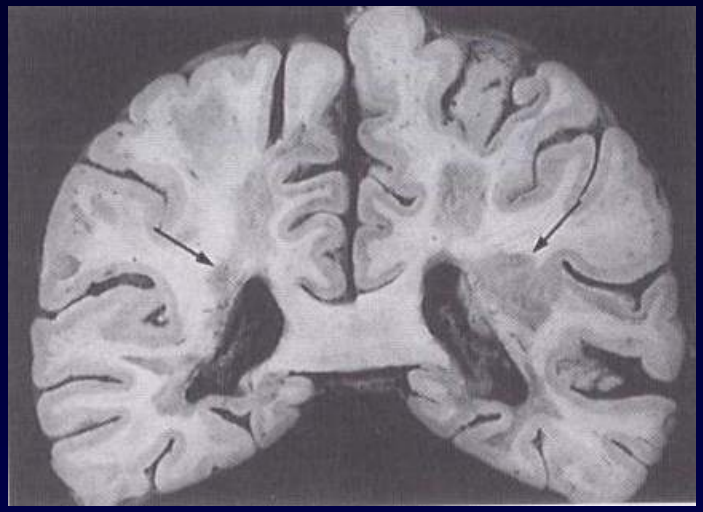
Caratteristiche fondamentali della SM

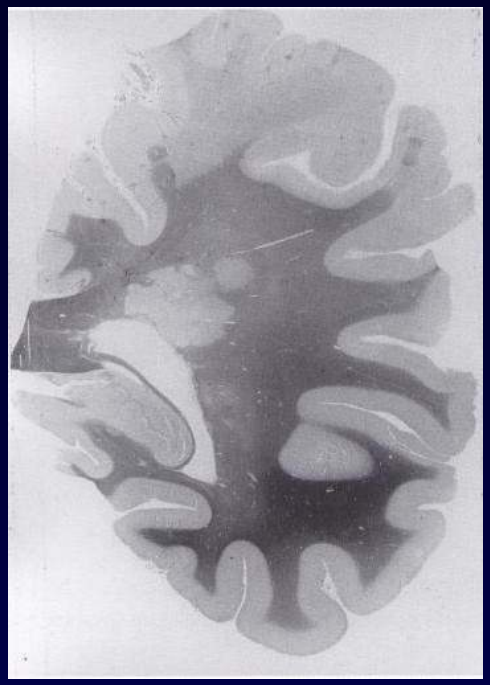


La fibra nervosa e la mielina

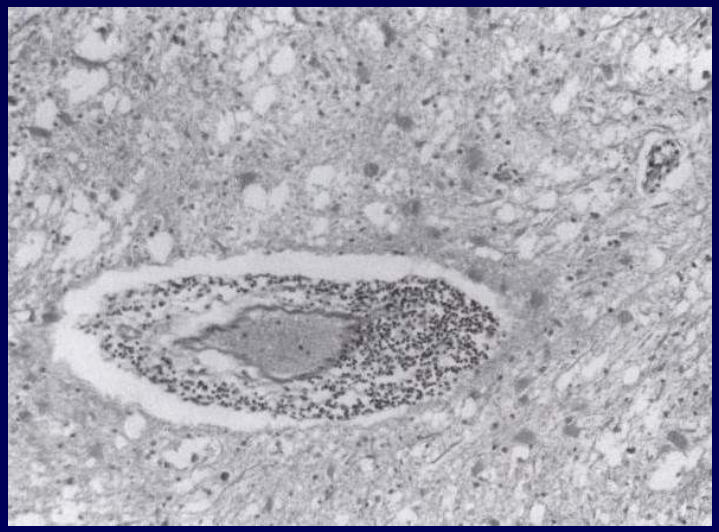
NEUROPATOLOGIA

PLACCA: aspetto macroscopico

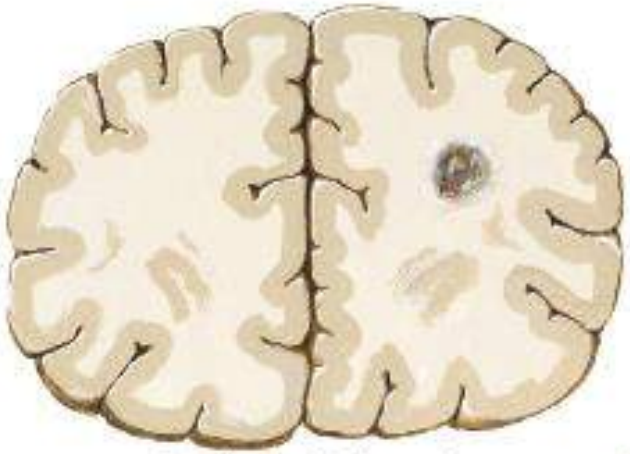




PLACCA: aspetto microscopico



Multiple Sclerosis: Central Nervous System Plaques



Demyelination of white matter in frontal lobe of cerebral hemisphere

Sclerotic areas in cerebral peduncle

In cervical spinal cord

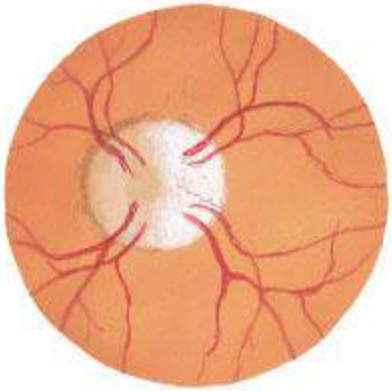
In medulla

In thoracic spinal cord

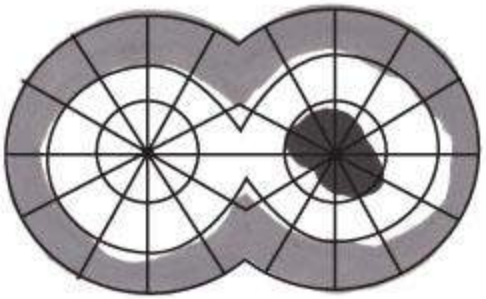
SINTOMATOLOGIA

Optic neuritis

Sudden unilateral blindness, self-limited (usually 2 to 3 weeks). Patient covering one eye, suddenly realizes other eye is partially or totally blind.



Temporal pallor in optic disc, caused by delayed recovery of temporal side of optic (II) nerve

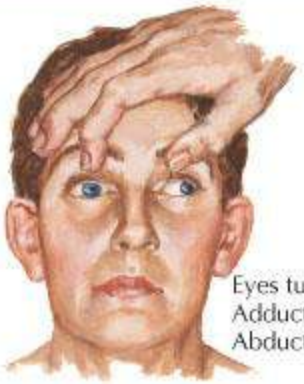


Visual fields reveal central scotoma due to acute retrobulbar neuritis

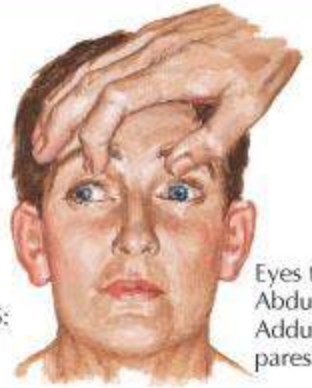
F. Netter M.D.

Internuclear ophthalmoplegia

(OD = right, OS = left)

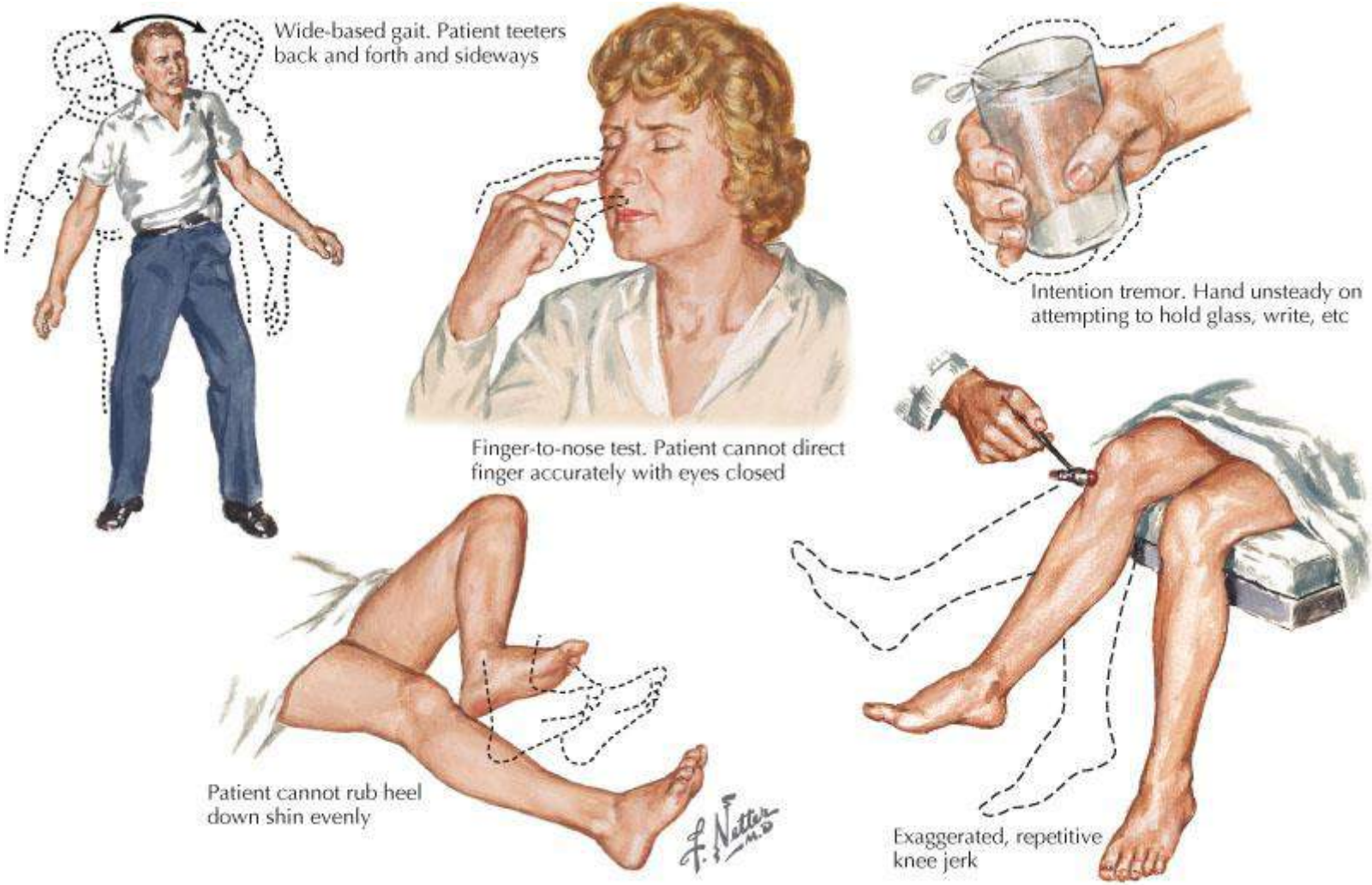


Eyes turned to left. OD: Adduction paralysis; OS: Abduction nystagmus

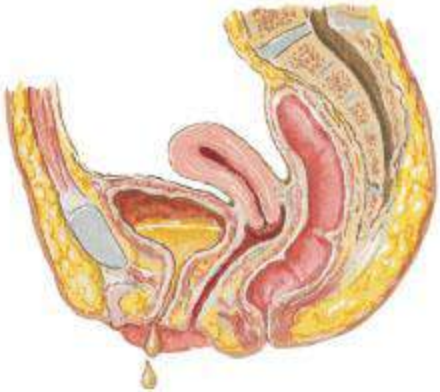


Eyes turned to right. OD: Abduction nystagmus; OS: Adduction lesser mild paresis

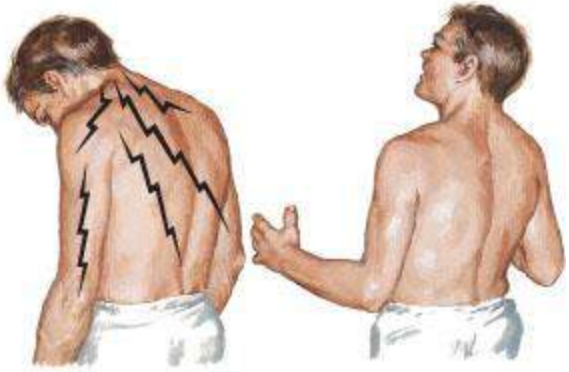
Convergence. Fully preserved adduction; both eyes have full medial movement



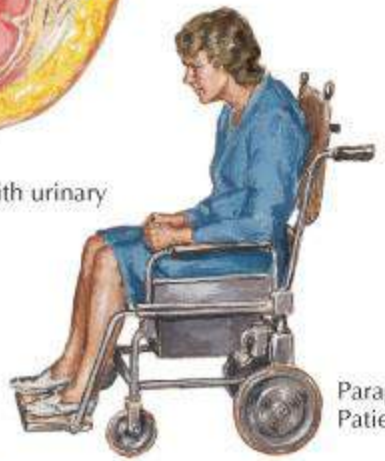
Spastic gait. Patient needs help walking



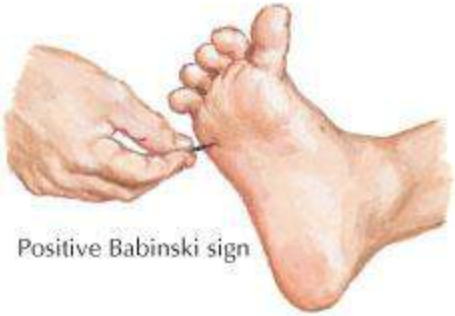
Neurogenic bladder, with urinary urgency and dribbling



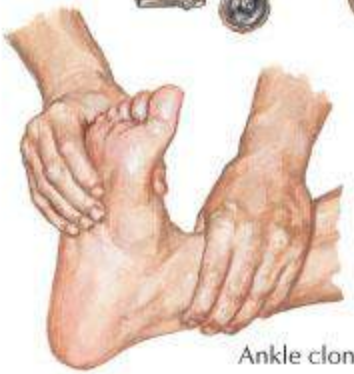
Lhermitte's sign: sudden sensation of electric shock down spine and along arms when patient flexes neck



Paraplegia, partial or complete. Patient in wheelchair

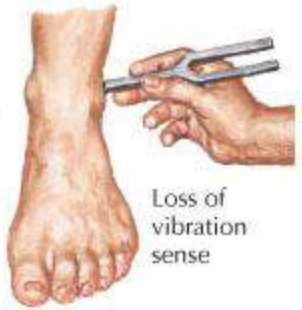


Positive Babinski sign



Ankle clonus

Loss of position sense



Loss of vibration sense

Incidenza di sintomi iniziali nella SM.

SINTOMI	INCIDENZA in %
Ipostenia in uno o più arti	40
Neurite Ottica	22
Parastesie	21
Diplopia	12
Vertigine	5
Disturbi della minzione	5
Altro	< 5

Lesioni in 300 pazienti con SM.

REGIONE	SINTOMI	%
MIDOLLO SPINALE	Ipostenia, disturbi sensibilità (spinotalamico o pallestesica/statochinestesica) in un arto, signo di Babinski, assenza dei riflessi addominali, iperreflessia, clono	74
VIE OTTICHE	Alterata acuità visiva o visione dei colori, defetti del campo visivo, pallore della papilla	92
TRONCOENCEFALO e CERVELLETTO	NIstagmo, disturbi dei movimenti oculari, iposteniua faciale, disfagia, disartria, atassia	55
CORTECCIA	Disturbi dell' umore, deficit intellettuali, epilessia	40

Sintomatologia I

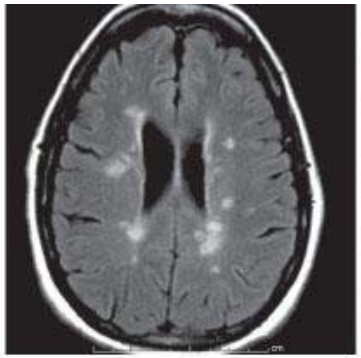
sede	sintomi	segni
Emisfero	Deficit cognitivo	Deficit attenzione, programmazione, funzioni esecutive (fase iniziale). Demenza (fase tardiva)
	Emisindrome sensitivo-motoria	Segni di interessamento del motoneurone superiore
	Affettivi	Depressione
	Epilessia (raro)	
	Deficit focali corticali (rari)	

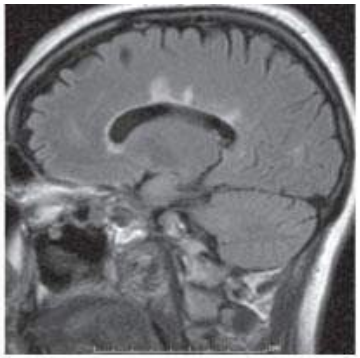
Sintomatologia II

sede	sintomi	segni
Nervo ottico	Calo del visus unilaterale doloroso	Scotoma, riduzione dell'acuità visiva, della visione dei colori e deficit delle relative afferenze pupillari
Cervelletto	Tremore Deficit d'equilibrio	Tremore d'azione e posturale, disartria Incoordizione degli arti e atassia della marcia
Tronco encefalo	Diplopia, oscillopsia	Nistagmo, oftalmoplegia internucleare ed altre oftalmoparesi
	Vertigini	
	Difficoltà nel linguaggio e disfagia	Disartria e paralisi pseudobulbare
	Sintomi parossistici	

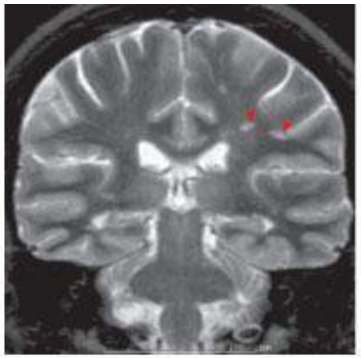
Sintomatologia III

sede	sintomi	segni
Midollo spinale	Debolezza	Segni di interessamento del I motoneurone
	Rigidità e spasmi dolorosi	Spasticità
	Disfunzioni urinarie	
	Impotenza	
	Stipsi	
Altre	Dolore	
	"Fatigue"	
	Sensibilità alla temperatura e intolleranza all'esercizio	

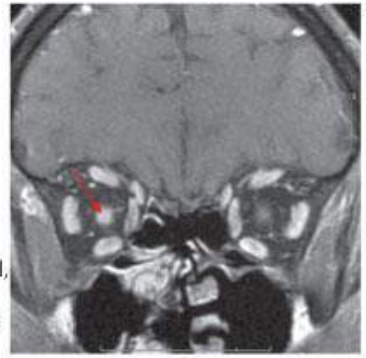




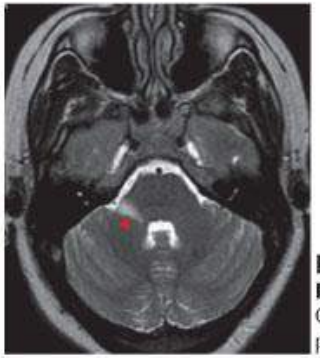
A. and **B.** Axial and sagittal FLAIR images with increased T2 signal within the corpus callosum and paraventricular white matter with extension into central white matter along vascular pathways.



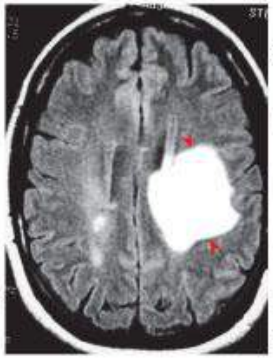
C. Coronal T2, where the typical oval lesions are oriented along vascular pathways, typical of "Dawson fingers" (*arrowheads*).

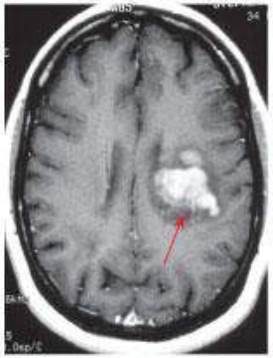


D. Coronal T1-weighted, fat-saturated, post–gadolinium-enhanced image shows enhancement and enlargement of the right optic nerve (*arrow*).



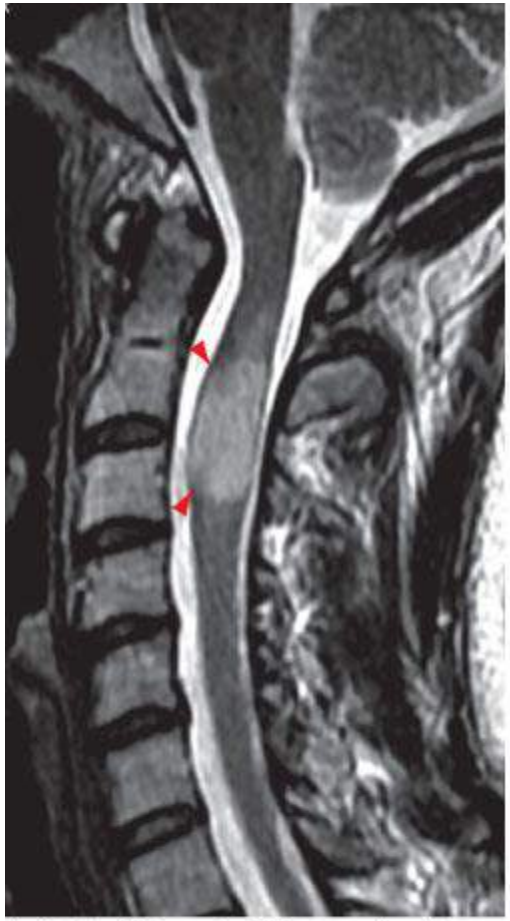
E. Cerebellar Peduncle: Axial T2 Brain MR: Multiple Sclerosis: Cleft-like right brachium pontis plaque (arrowhead).



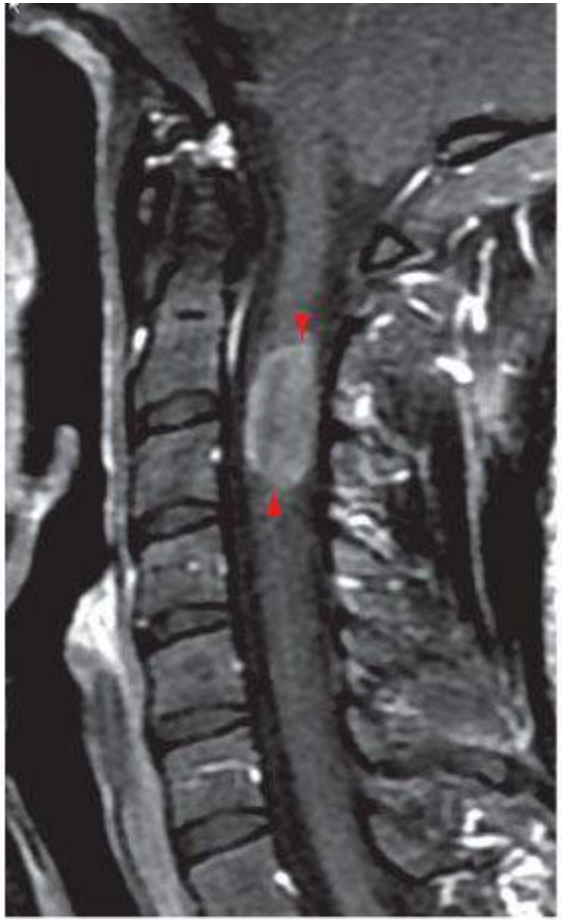


F. Fulminate MS 1: Tumefactive Multiple Sclerosis: Axial FLAIR Brain MR: Large demyelinating mass left frontoparietal periventricular white matter (arrowheads).

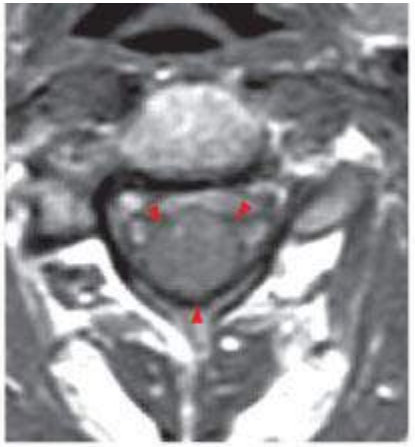
G. Fulminate MS Contrast: Tumefactive Multiple Sclerosis: Axial Postcontrast T2 Brain MR: Markedly enhancing large left frontoparietal periventricular white matter demyelinating mass (arrow).



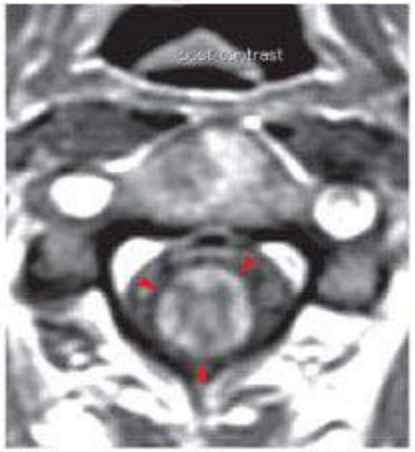
A. Sagittal T2 cervical MR (arrowheads).



B. Sagittal T1 post-gadolinium cervical MR: Large expansile hyperintense upper cervical cord plaque (arrowheads).

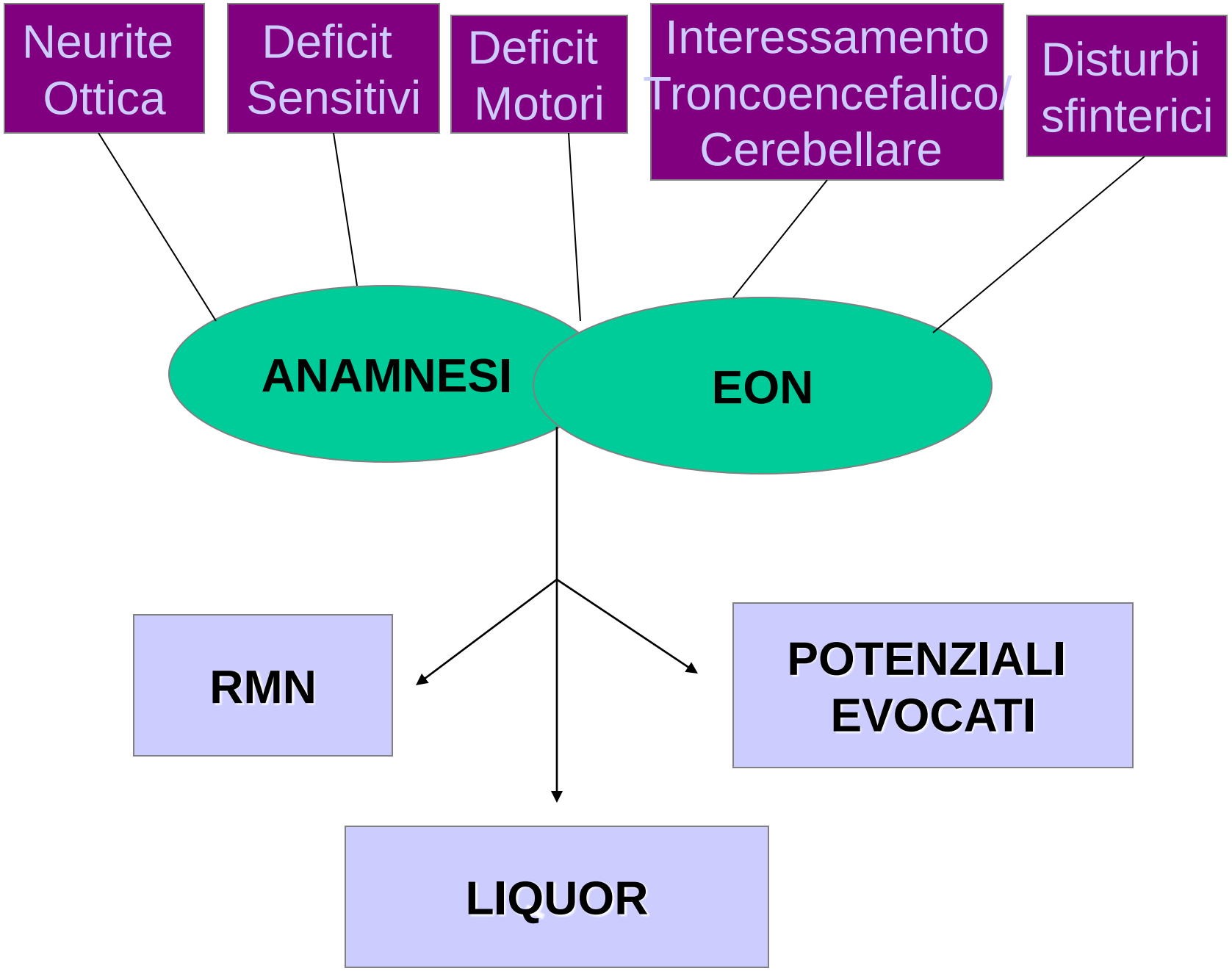


C. Axial precontrast T1 cervical MR: Markedly expanded cervical spinal cord (arrowheads).

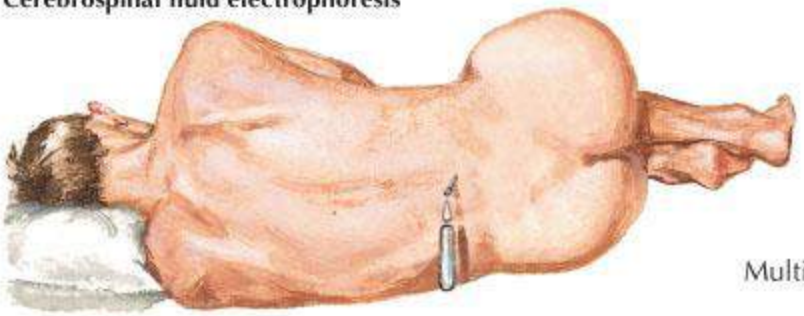


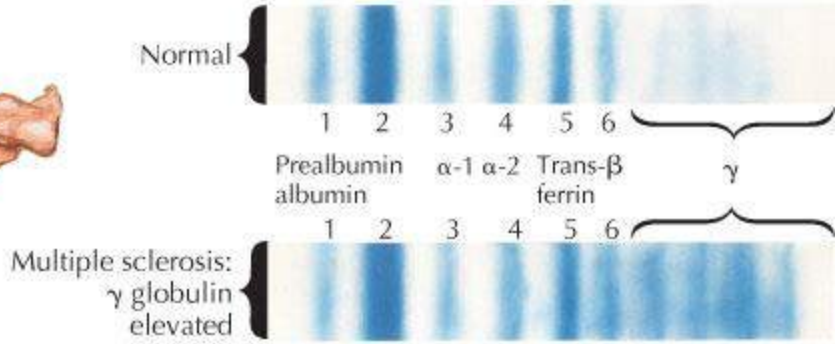
D. Axial postcontrast T1 cervical MR: Expansile peripherally enhancing plaque (arrowheads).

FORME CLINICHE


Neurite Ottica
Deficit Sensitivi
Deficit Motori
Interessamento Troncoencefalico/ Cerebellare
Disturbi sfinterici
ANAMNESI
EON
RMN
POTENZIALI EVOCATI
LIQUOR

Cerebrospinal fluid electrophoresis

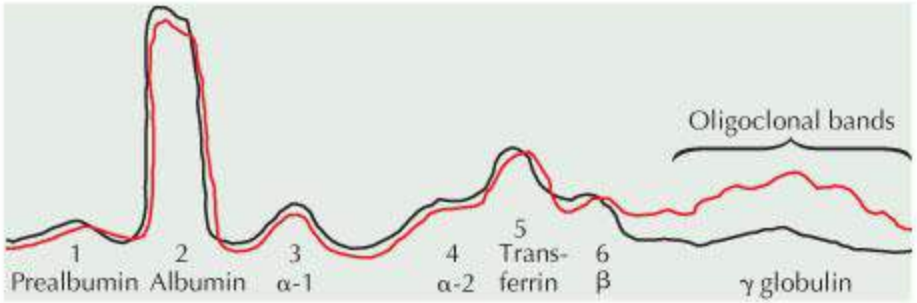




F. Netter M.D.

JOHN A. CRAIG M.D.

D. Mascaro



Computed recordings

Normal

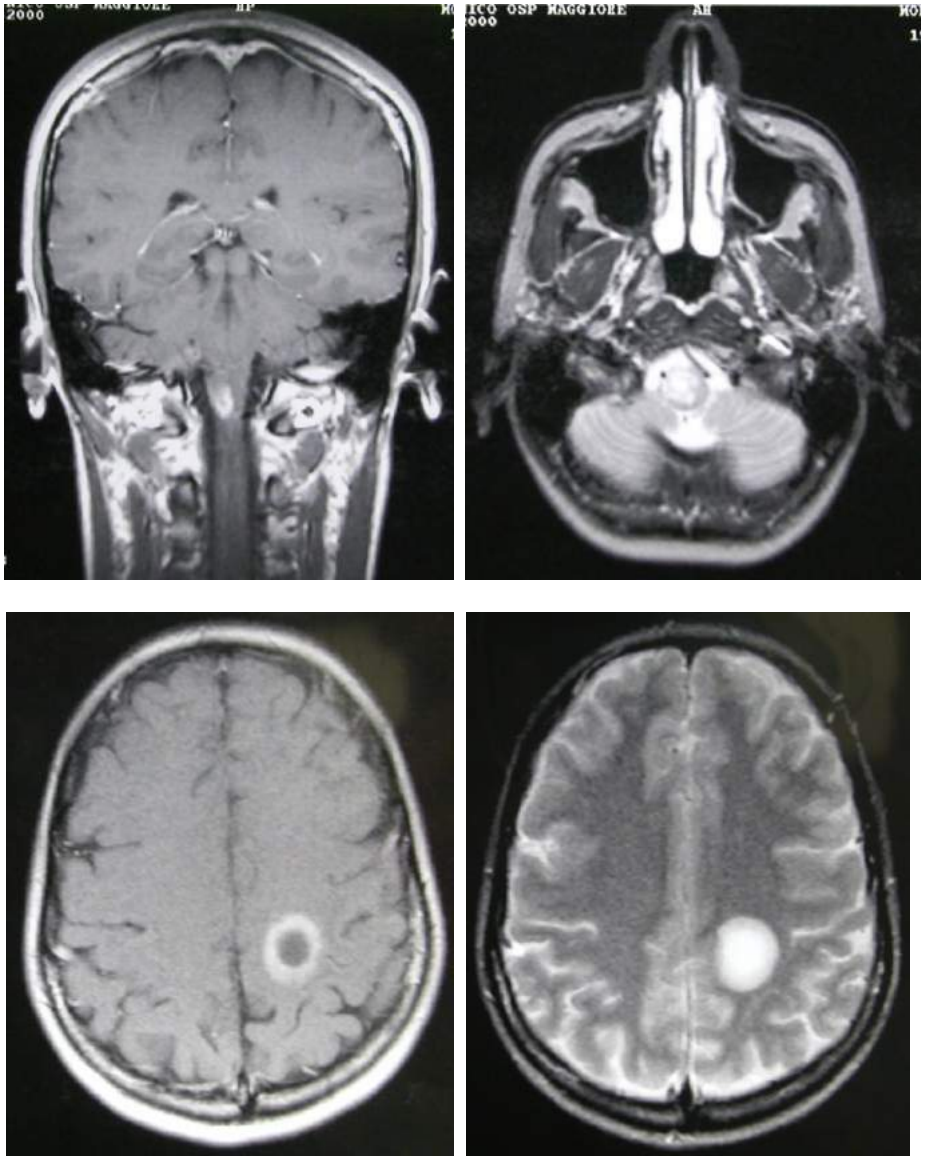
Multiple sclerosis

Criteri diagnostici

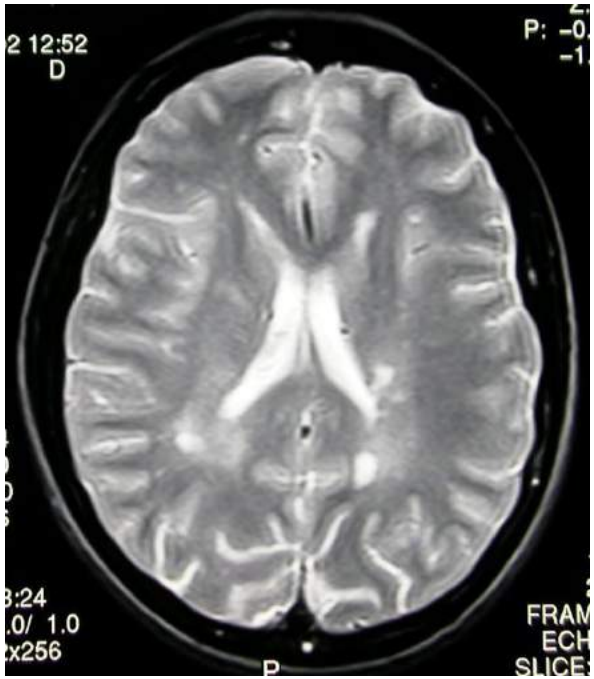
- ✓ Concetto di disseminazione spaziale
- ✓ Concetto di disseminazione temporale

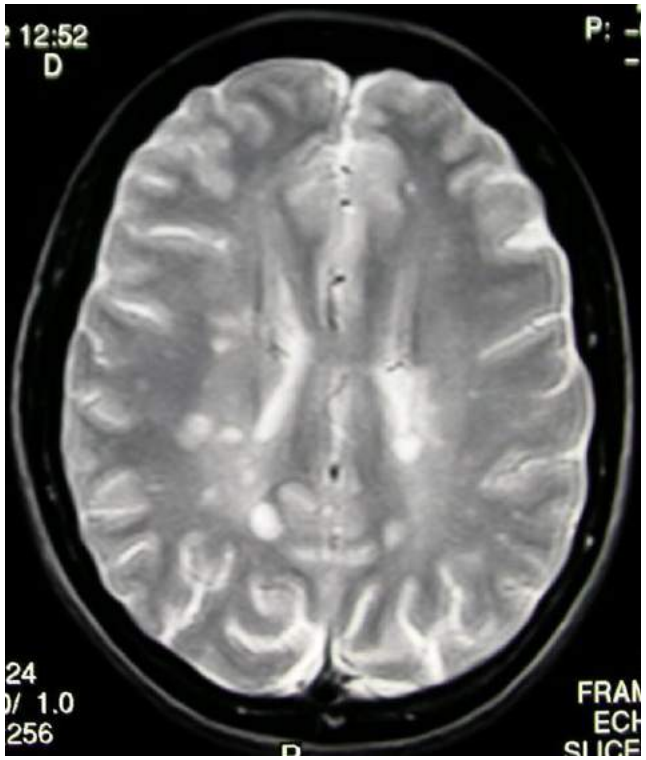
McDonald et al., 2001

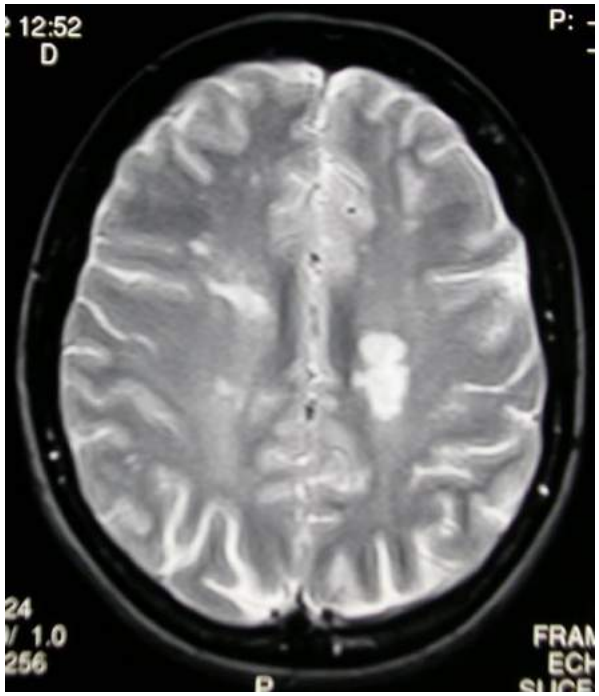
1 lesione captante gd



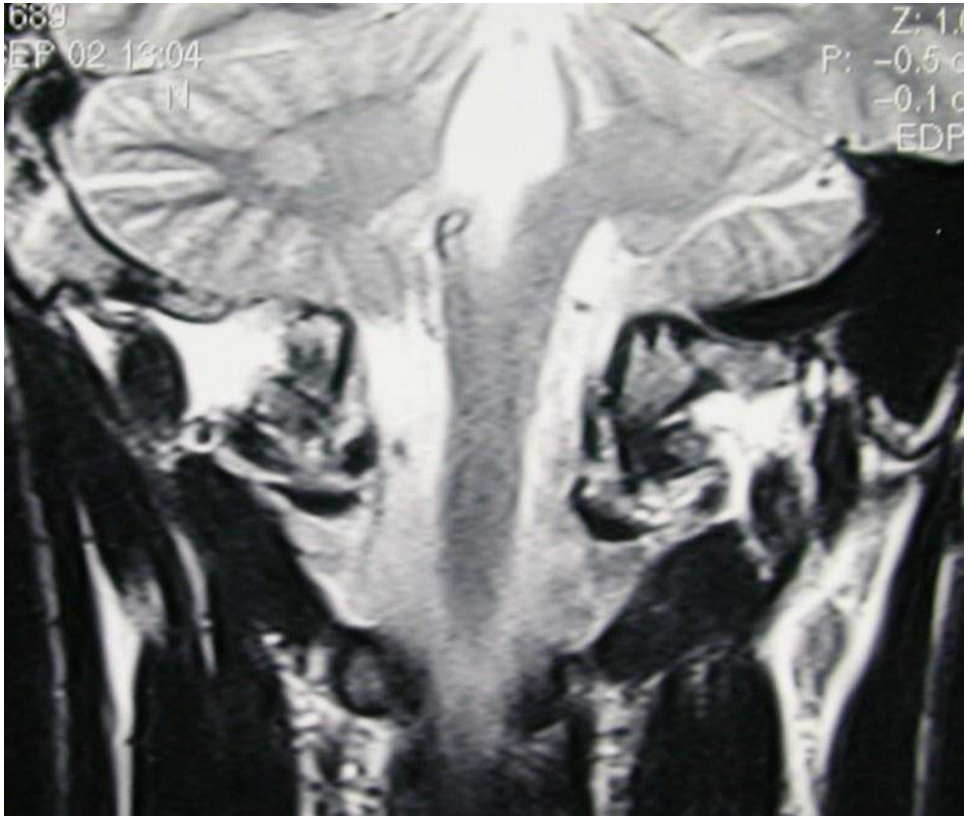
9 lesioni iperintense in T2

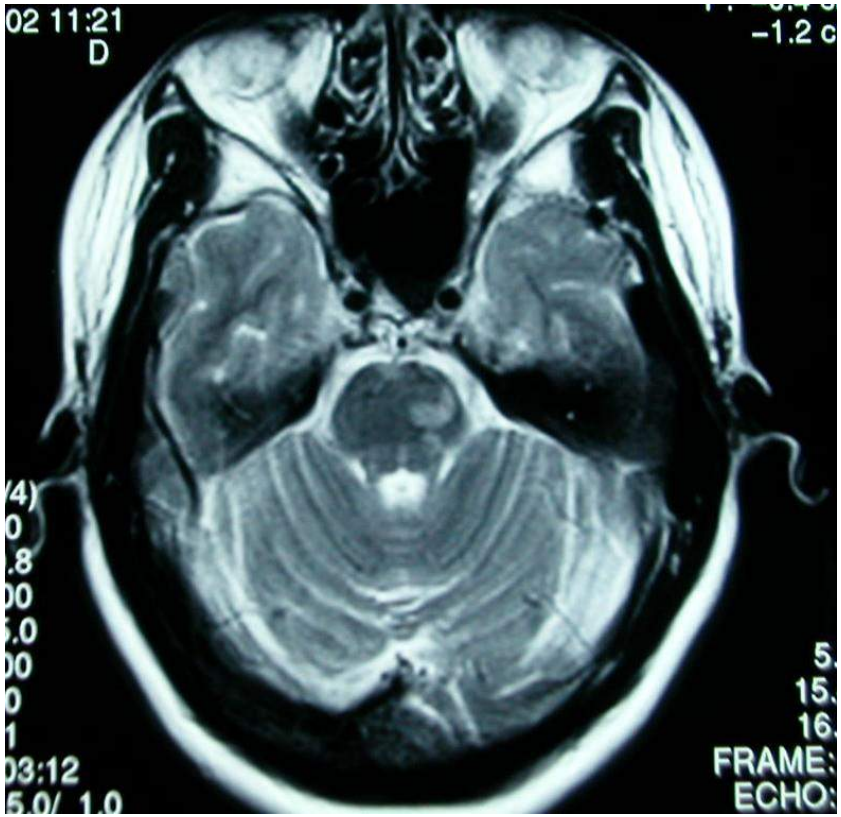




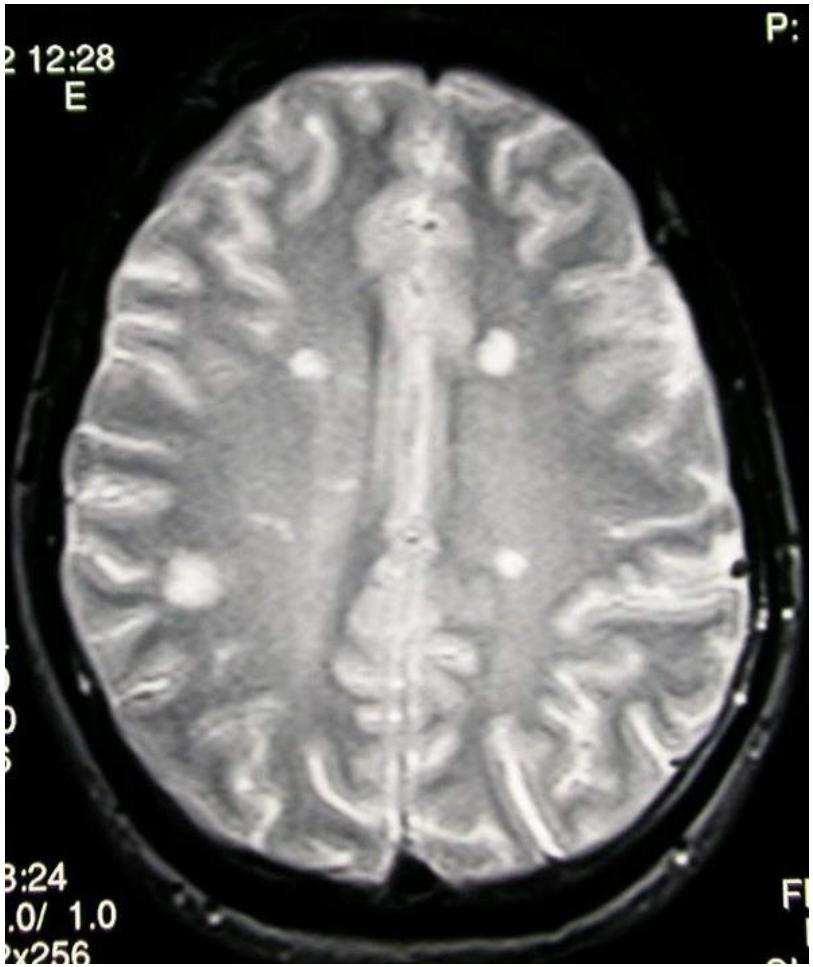


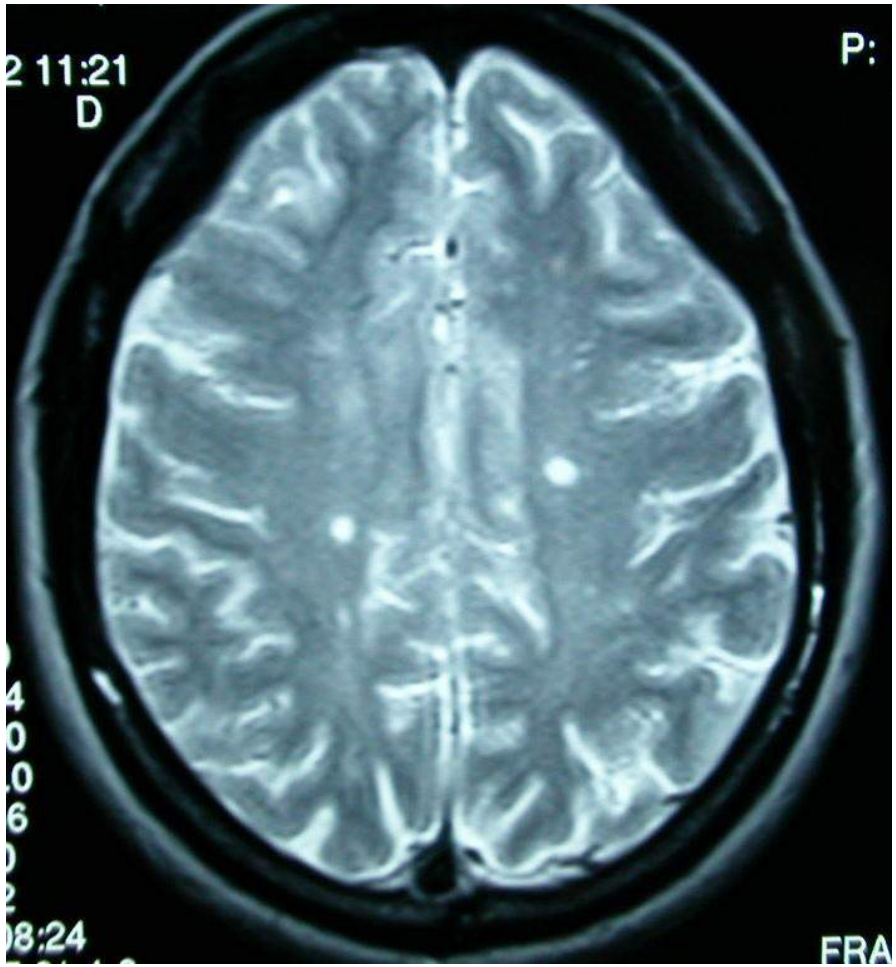
1 o più lesioni sottotentoriali



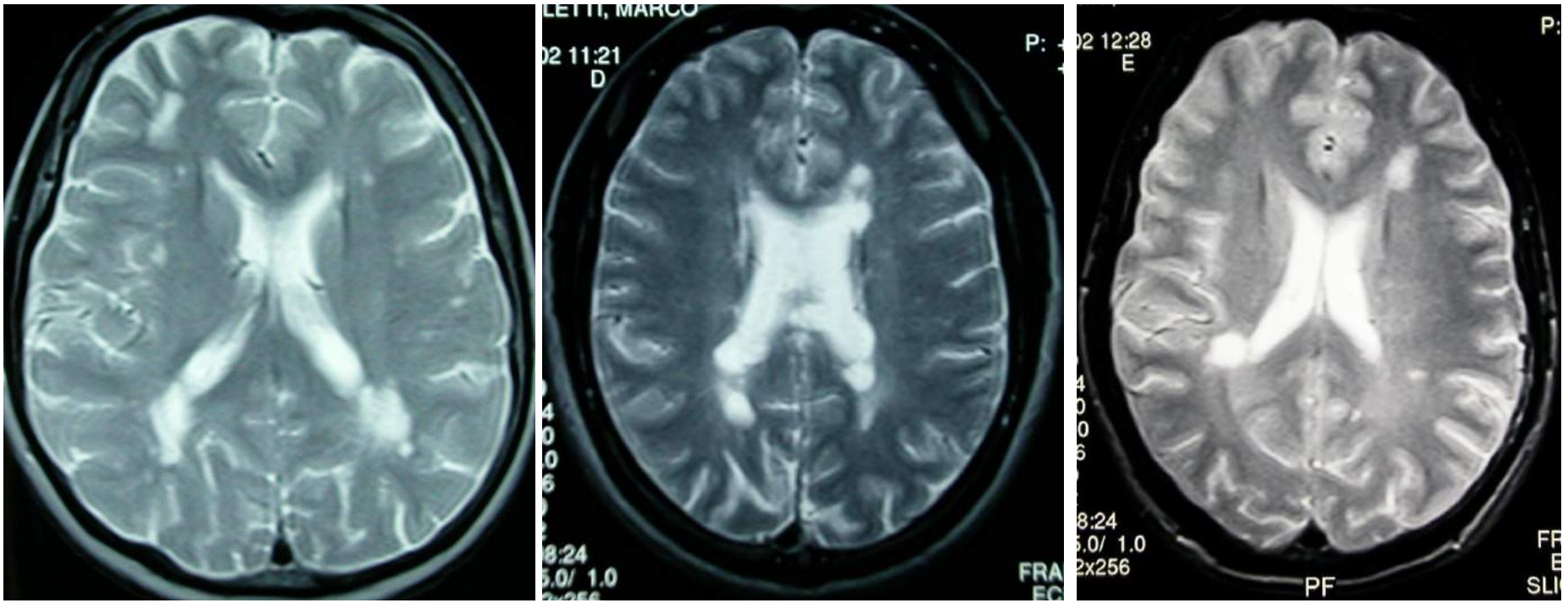


1 o più lesioni iuxtacorticali

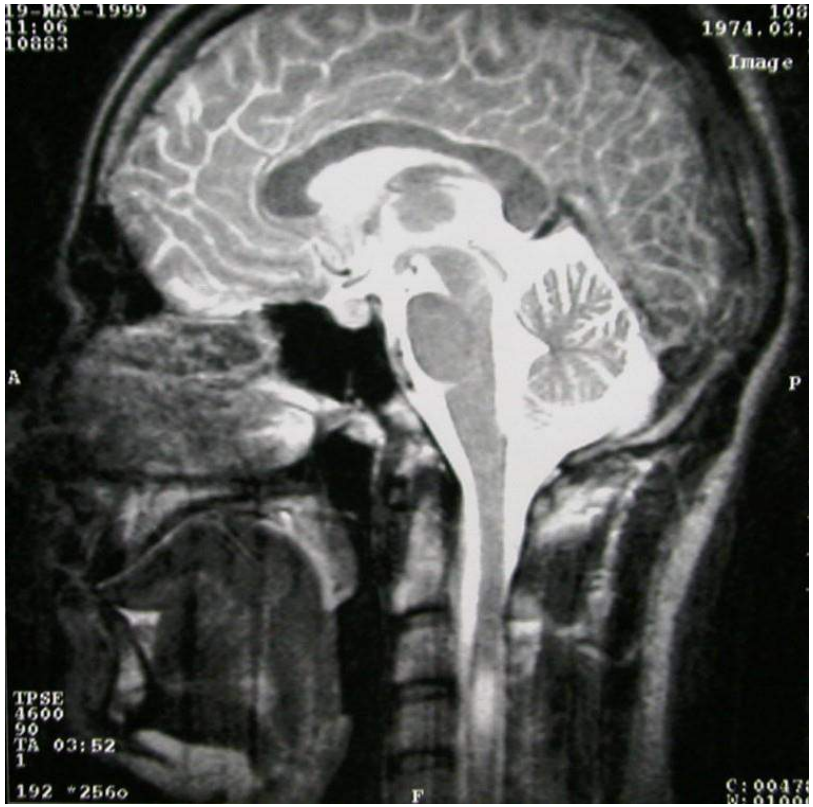


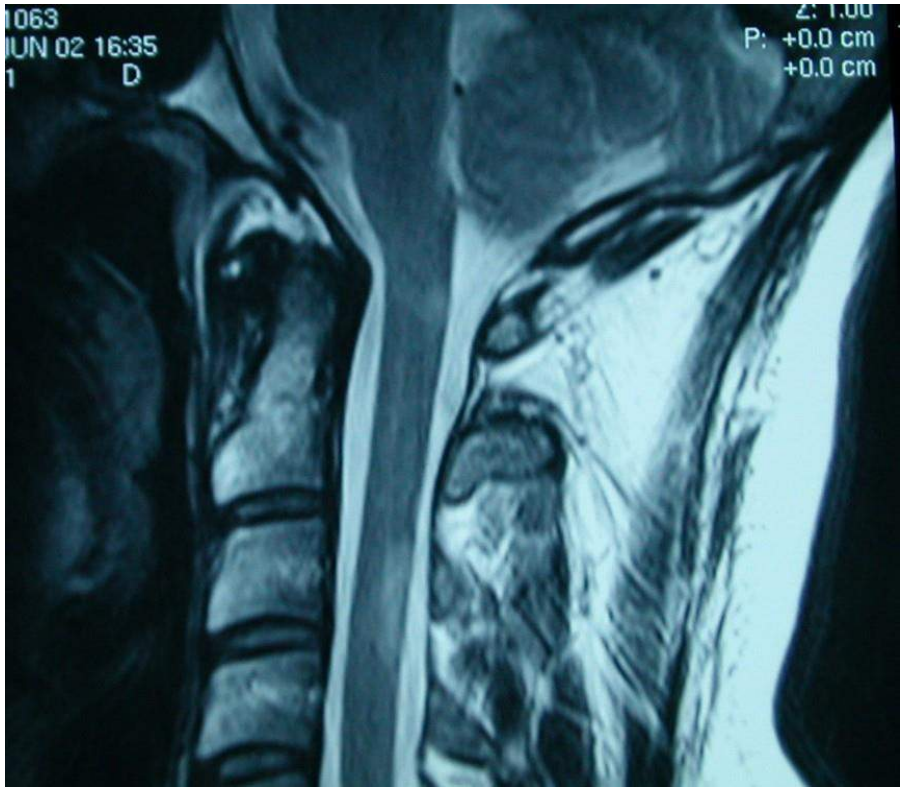


3 o più periventricolari



Lesione midollare





DIAGNOSI DIFFERENZIALE

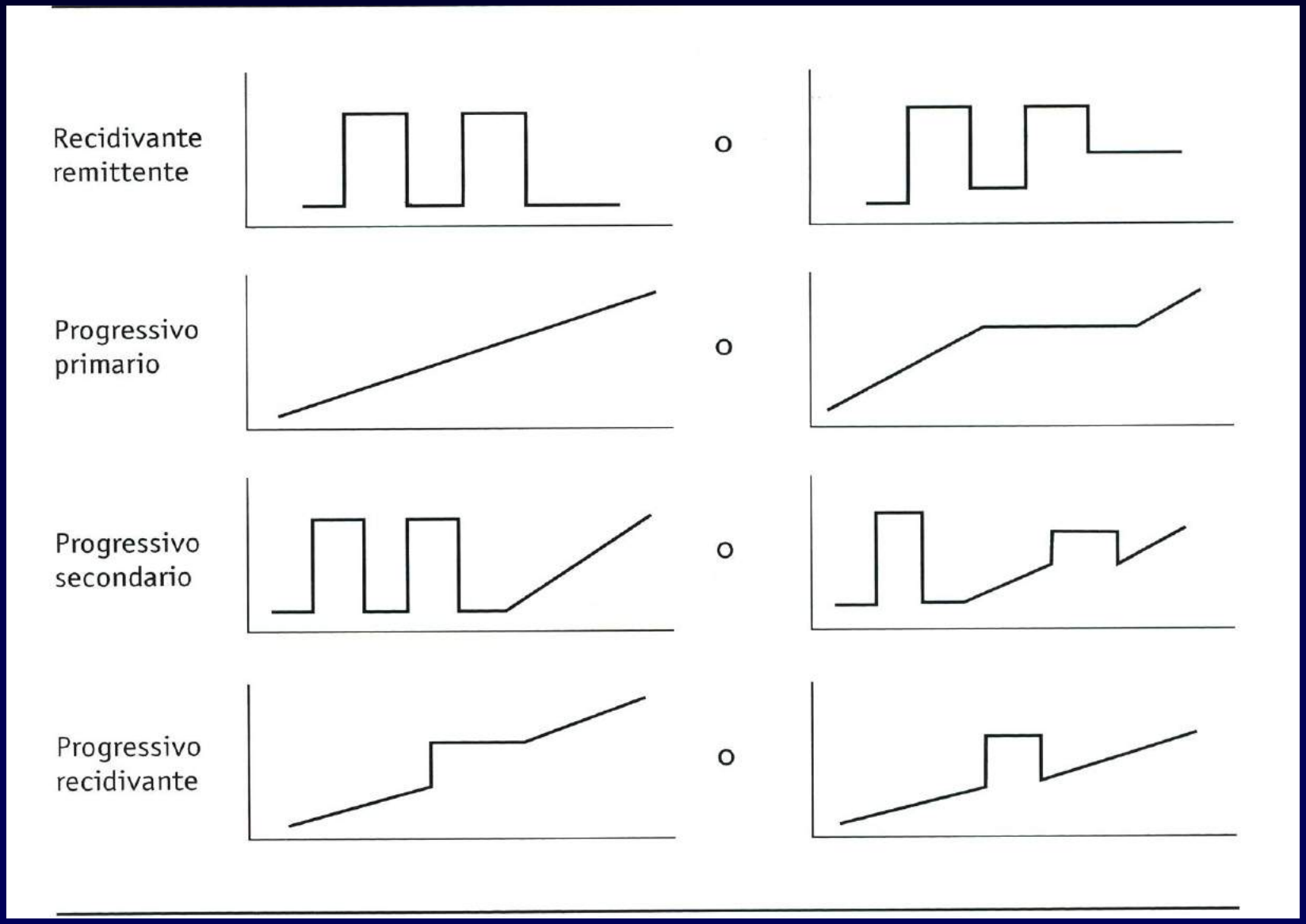
- Non deficit neurologici obiettivabili
- Nessun evidenza obiettivabile di disseminazione delle lesioni nel tempo e nello spazio
- Anamnesi familiare fortemente positiva
- Malattia ad andamento progressivo fin dall'esordio in pazienti giovani
- Nessun interessamento oculare
- Malattia localizzata
- Assenza di anomalie liquorali
- Dolore come sintomo predominante

Caratteristiche che indicano la necessità di rivedere criticamente la diagnosi di SM

- Malattie autoimmuni
  - Lupus eritematoso sistemico
  - Sindrome di Sjoegren primitiva
  - Malattia di Behçet
  - Poliarterite nodosa
  - Encefalomielite acuta disseminata
- Malattie infettive
  - Malattia di Lyme
  - Sifilide
  - AIDS
- Adrenomieloneuropatia
- Encefalopatia mitocondriale
- Malformazione di Arnold-Chiari
- Atrofia olivopontocerebellare
- Emboli cardiaci

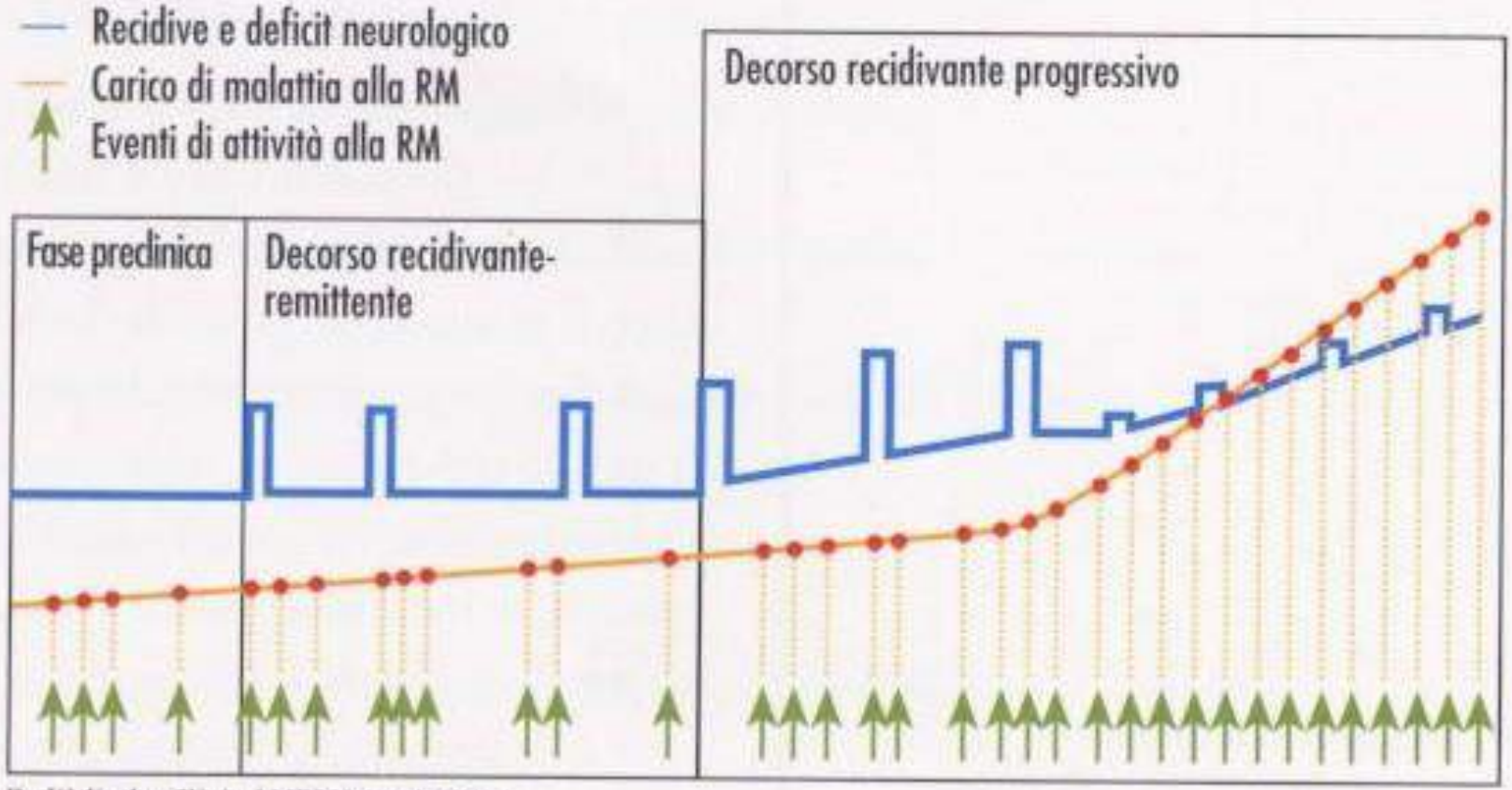
Malattie spesso erroneamente diagnosticate come SM

Forme cliniche di SM



Lublin and Reingold, 1996

Storia clinica di malattia



Da Wolinsky, Clinical MRI Natural History

PROGNOSI

Fattori che indicano un decorso clinico sfavorevole

- Esordio coinvolgente più sistemi funzionali
- Esordio con disturbi piramidali o cerebellari
- Sesso maschile
- Esordio dopo 40 anni
- Frequenza di ricadute elevata nei primi anni
- Breve intervallo tra le prime due ricadute
- Disabilità elevata già nei primi anni
- Decorso primariamente progressivo

TERAPIA

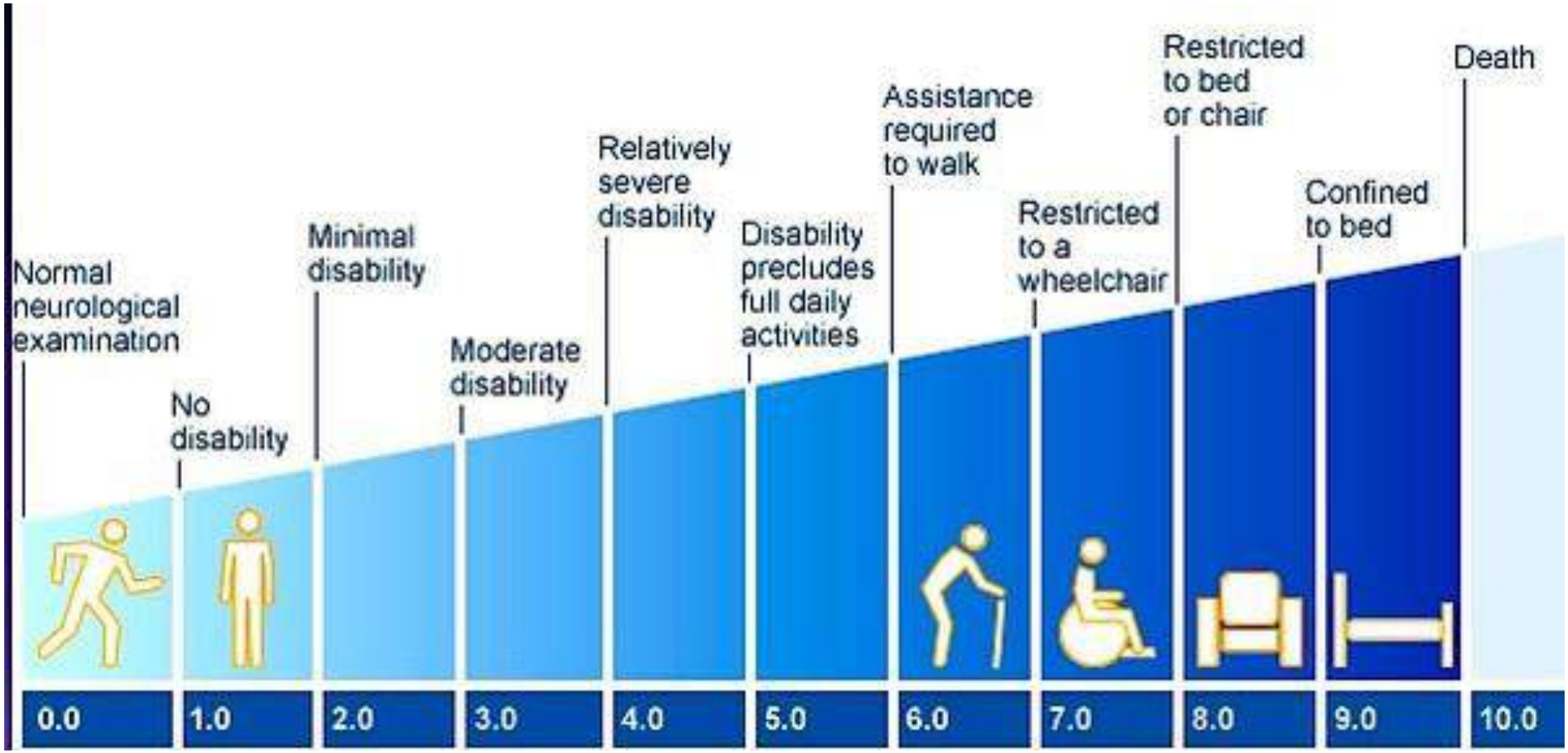
TERAPIA IMMUNOSOPPRESSIVA

- Steroidi
- IFN-b
- Copolimero
- IgG ev
- Azatioprina
- Metotrexate
- Ciclosporina
- Ciclofosfamide

TERAPIA SINTOMATICA

- FKT
- Antispastici
- Antiepilettici
- Antidepressivi
- Amantadina
- Beta bloccanti

Scala EDSS


Normal neurological examination
No disability
Minimal disability
Moderate disability
Relatively severe disability
Disability precludes full daily activities
Assistance required to walk
Restricted to a wheelchair
Restricted to bed or chair
Confined to bed
Death
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0

Scala EDSS


0.0
Normal neurologic exam
1.0
No disability
2.0
Minimal disability
3.0
Moderate disability
4.0
Relatively severe disability; able to walk without assistance for 500 meters
5.0
Disability affects daily routine; able to walk without assistance for 200 meters
6.0
Assistance required to walk
7.0
Restricted to wheelchair
8.0
Restricted to bed or wheelchair
9.0
Confined to bed
Minimal-to-Moderate Disability
Fully Ambulatory Despite Relatively Severe Disability
Loss of Ambulation, Full Daily Activities Impaired

Herpes Zoster
diagnosi precoce e terapia