QUARTA SESSIONE:
Disturbi del Movimento

Caso clinico

Università degli studi di Bari «Aldo Moro»

Prof. ssa I. L. Simone

Dott. Sergio Altomare

2010

Paziente di 49 anni, M

-da un anno tremore a riposo arto superiore sinistro, impaccio motorio arto inferiore sinistro

-Familiarità: padre con diagnosi di m. Parkinson all'età di 76 anni

Segni non motori:

-iposmia (da un anno)

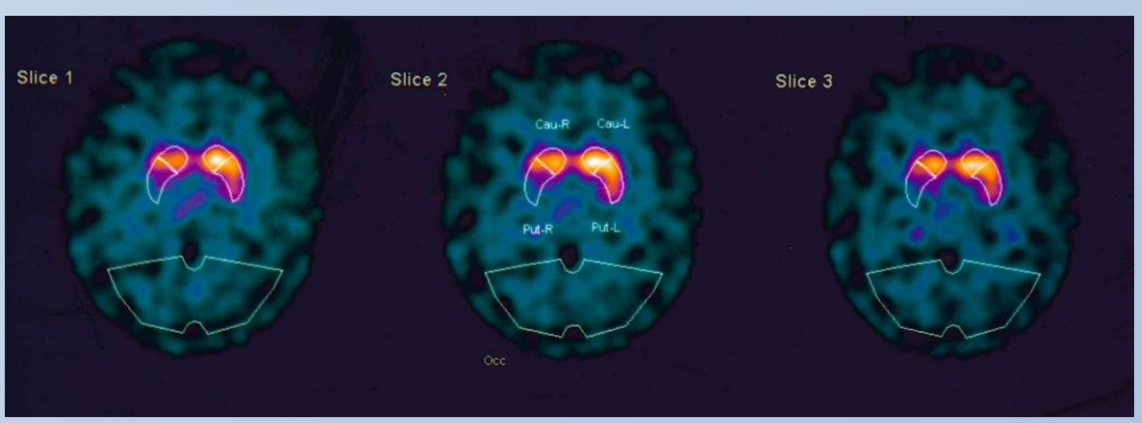
-Depressione all'età di 22 anni trattata con terapia psichiatrica imprecisata

-Ricovero in reparto psichiatrico (2004), diagnosi di "Depressione monopolare, depressione maggiore ricorrente"

EON:

- lieve ipomimia faciale, voce monotona
- Deambulazione con passo accorciato a sinistra, riduzione delle sincinesie pendolari a sinistra
- Tremore a riposo e posturale AS sx
- Bradicinesia moderata al finger e foot-tapping sx>dx
- Ipertono moderato ASsx

- **RM encefalo**: nella norma



- **Dat Scan**: "alterata fissazione del radiofarmaco nei nuclei della base con spiccata riduzione dell'uptake nel putamen di destra"

Ratios			
Striatum Total / Occ :			3.51
Caud-L / Occ :	4.19	\ > /	3.91
Caud-R / Occ :	3.64		
Put-L / Occ :	3.59	\ > /	3.11
Put-R / Occ :	2.62		
Putamen / Nucleus Caudatus :			0.79

- **Genetica**: PARKINA, LRRK2, PINK1, DJ-1: negativi

Diagnosi: malattia di Parkinson

TERAPIA?

1. IMAO-B
2. Dopaminoagonisti
3. L-DOPA
4. Altro?

-Rasagilina, 1 m/die

-Rotigotina, 8 mg/24h

UPRDS III: 29

Gioca a pallone e va in bicicletta

2012

L-DOPA:

-Sinemet 100/25 mg x3/die

-Miglioramento soggettivo

↓

-UPDRS III: 25

2014 ↑ incremento tremore: Rotigotina 12mg

2015

- ipersessualità
-Allucinazioni visive o sensazione di “presenze”
-Delirio di gelosia
-Insonnia

Cosa fareste?

1. Terapia antipsicotica
2. Ridurre DA
3. Terapia invariata
4. Sospendere DA

Riduzione sino a sospensione rotigotina

Regressione sintomatologia

↑ Incremento L-DOPA a 400 mg/die

2015

Episodio depressivo

Escitalopram 20 mg/die

2016

Ricovero in Neurologia “Severo quadro acinetico-rigido da peggioramento della malattia di Parkinson in pz con embolia polmonare, vasto ematoma in fase di risoluzione regione posteriore coscia destra, disturbo depressivo.”
L-DOPA: 500 mg/die+ Sinemet RM 100/25mg

↑

RM encefalo: negativa

Ricovero per episodio depressivo con peggioramento quadro parkinsoniano, mutacismo e idee deliranti

Datscan

↑

Tp: *Clozapina* 25 mg/die

L-DOPA: 750 mg/die

↓

UPDRS III: 18

2017 Sospensione autonoma L-DOPA

↓

Ricovero in Psichiatria: “Sindrome delirante acuta”
Sospensione autonoma L-DOPA

Tp Sinemet 450 mg/die

↑ *Clozapina* 50 mg/die

Comparsa Anterocollo

Distonia da neurolettici?

2018

UPDRS III: 31

Quadro acinetico-rigido, meno simmetrico, non sente effetto singola dose L-DOPA

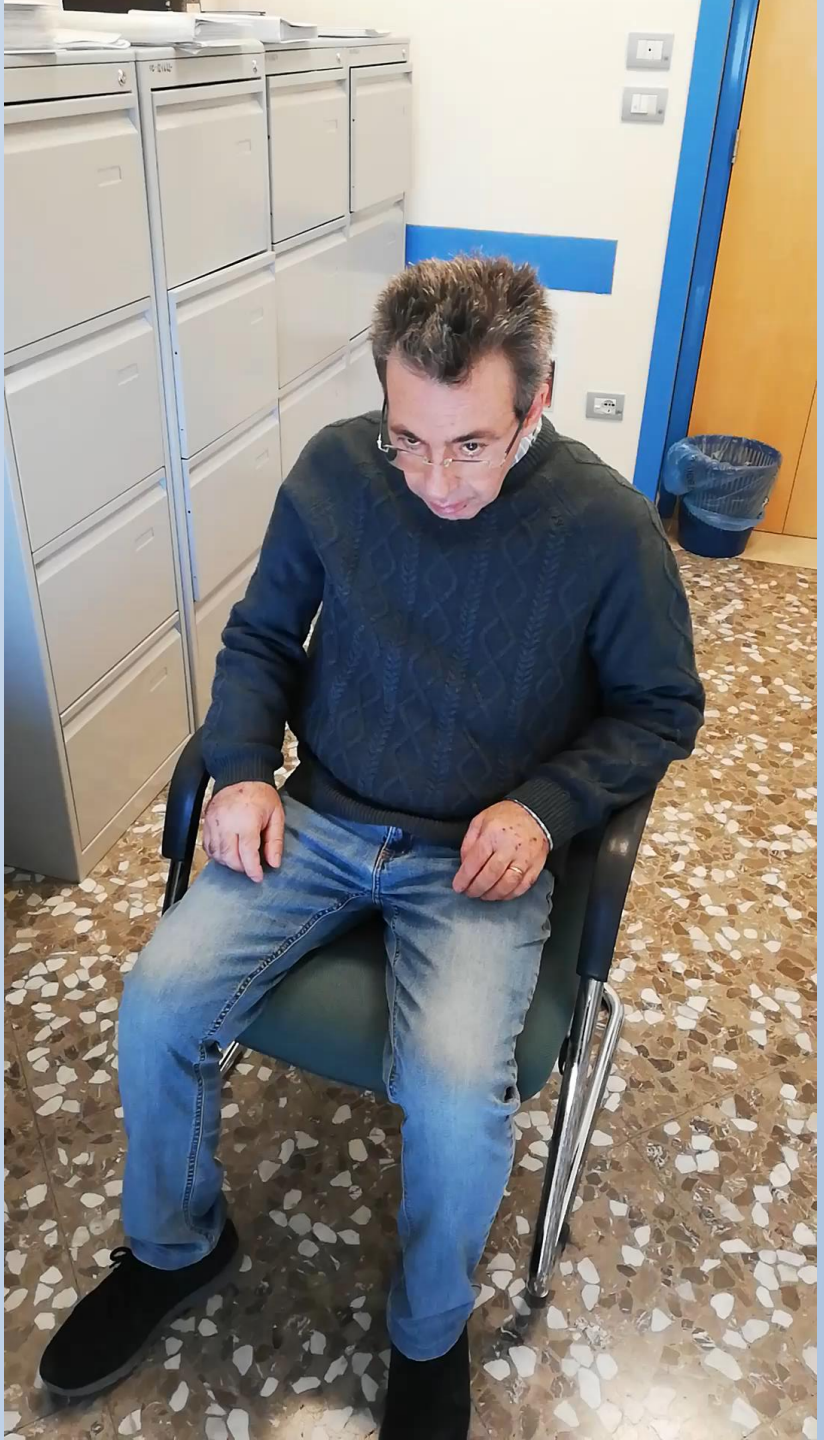
Severo anterocollo

Lieve urgenza minzionale

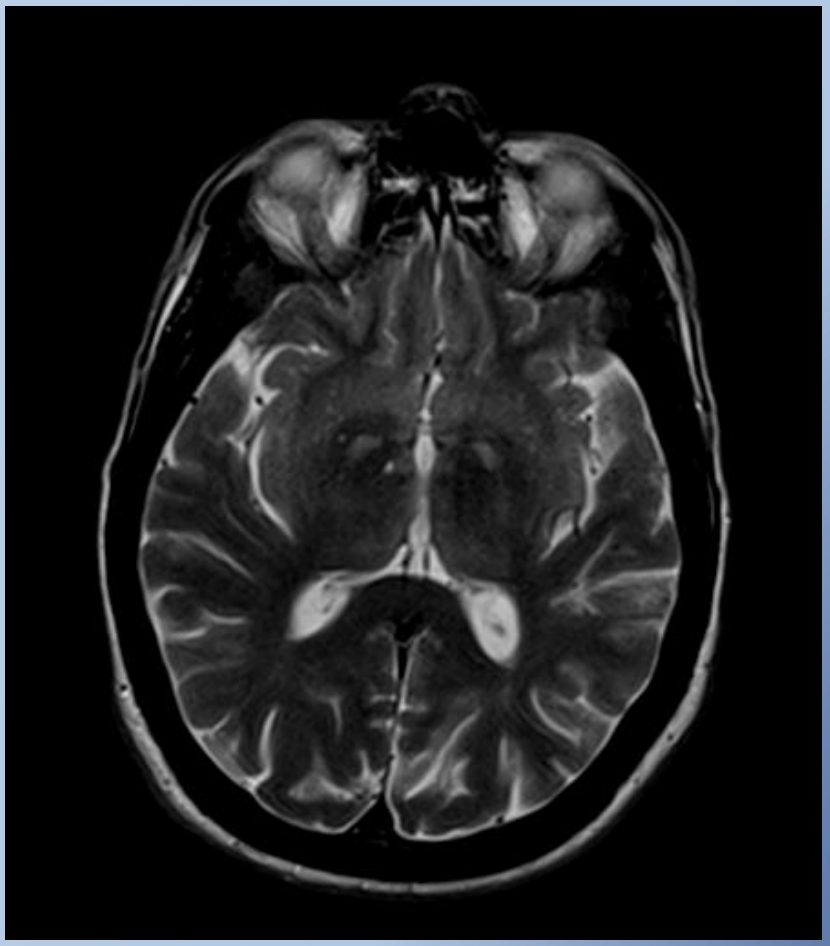
Clozapina 100 mg

Cosa fareste?

1. Ridurre clozapina
2. Ripetere RM encefalo
3. Aumentare L-dopa
4. Sospendere clozapina
5. Terapia invariata

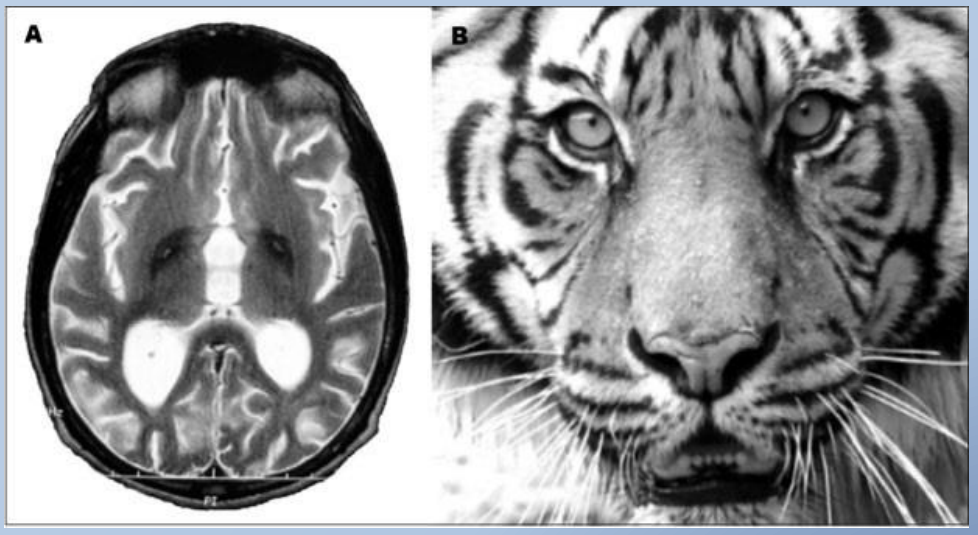


RM encefalo: “depositi verosimilmente ferrosi a carattere neurodegenerativo in corrispondenza dei nuclei della base d’ambo i lati”



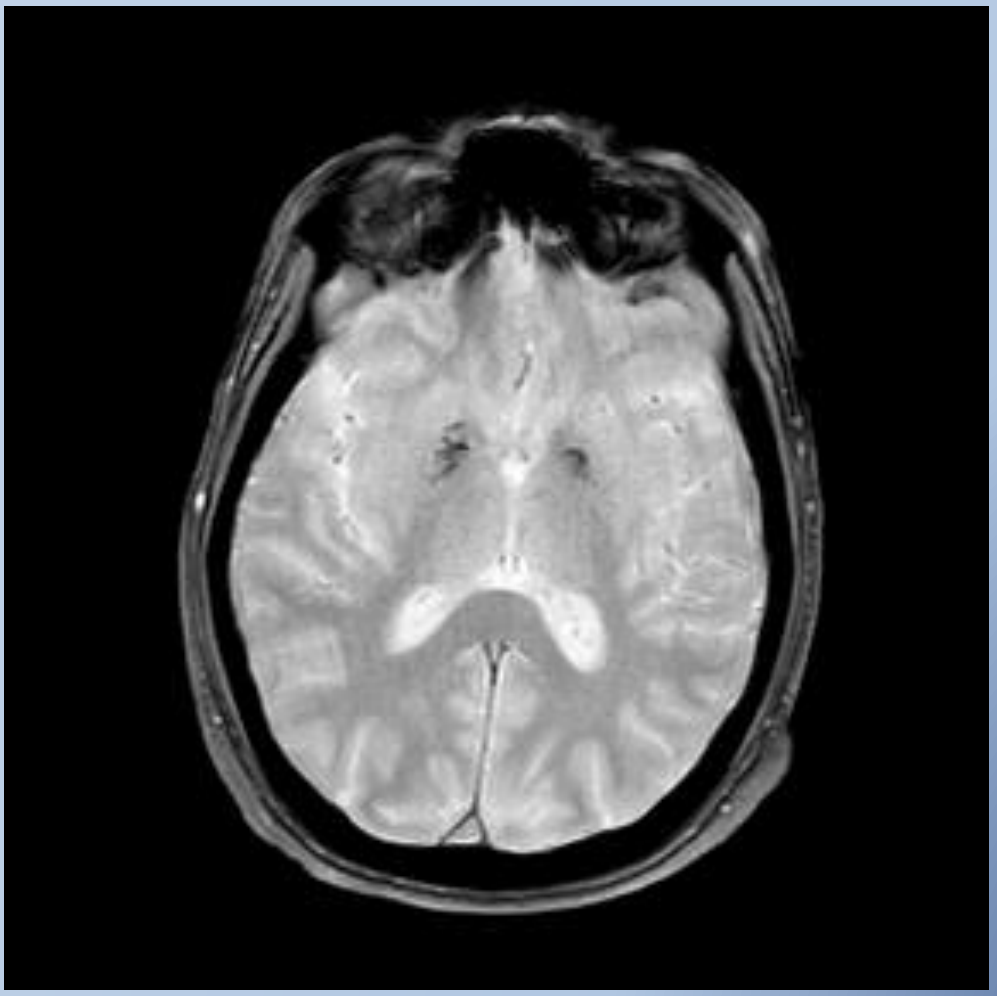
Eye tyger sign

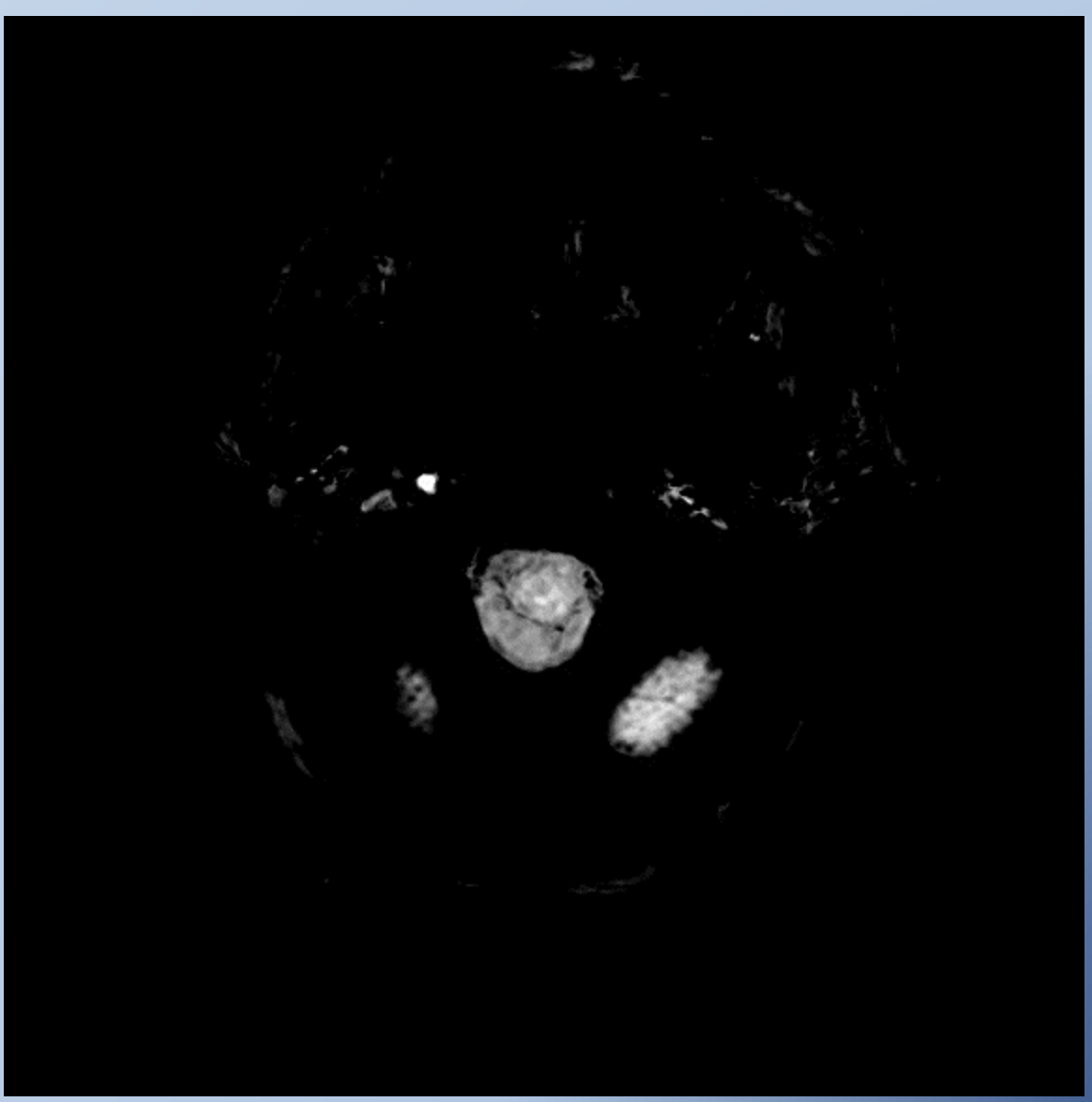
A cosa pensate?

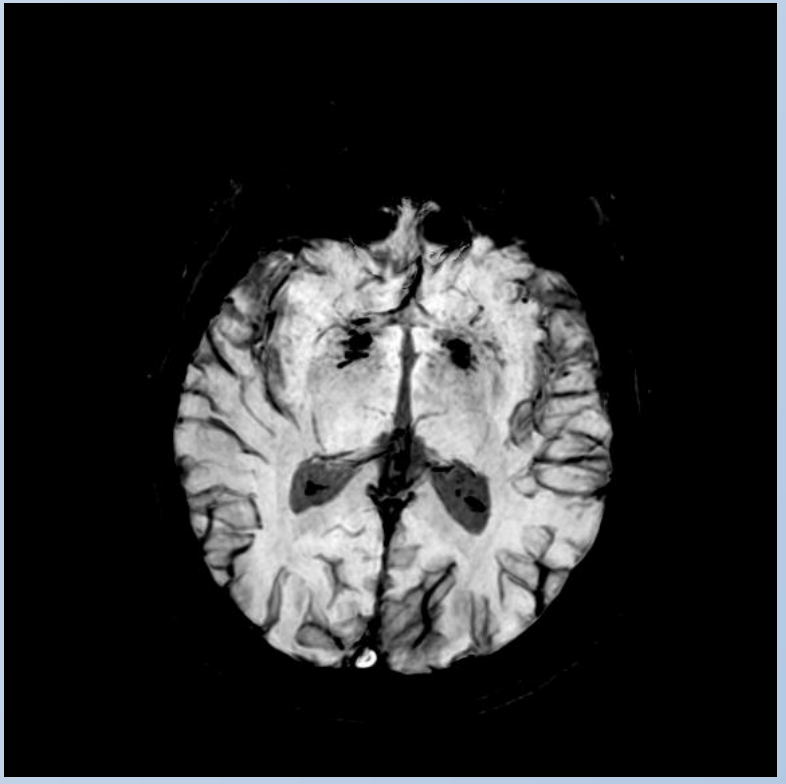


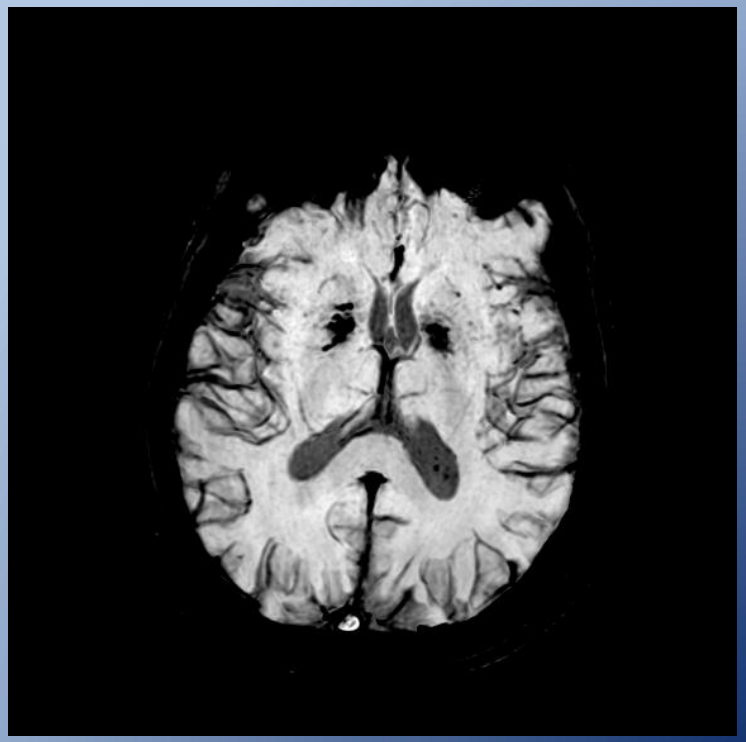
Hallervorden-Spatz disease

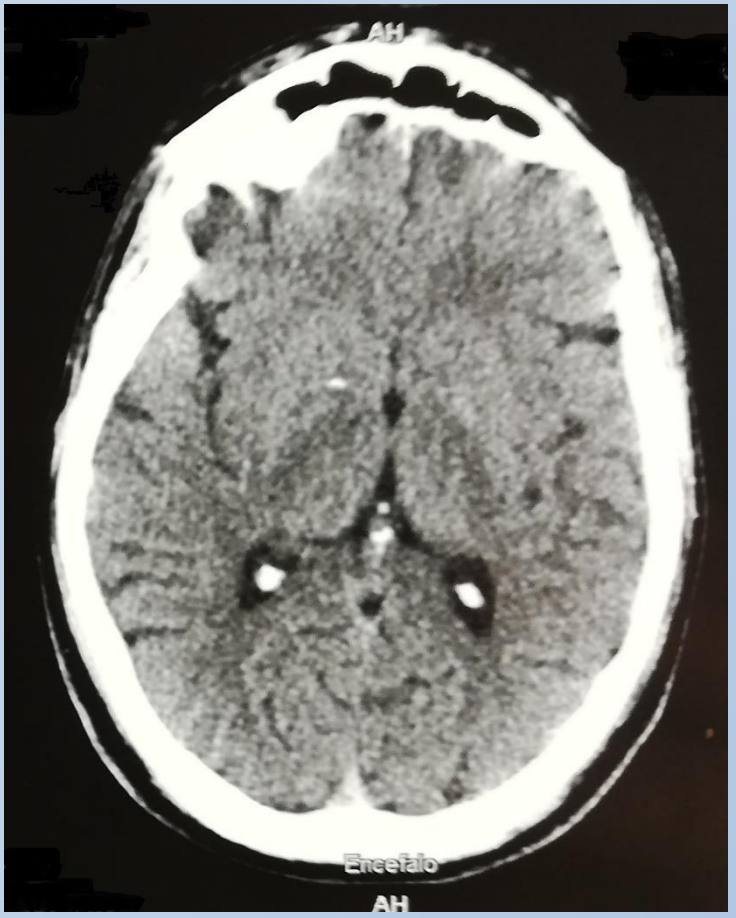
NBIA: neurodegeneration with brain iron accumulation

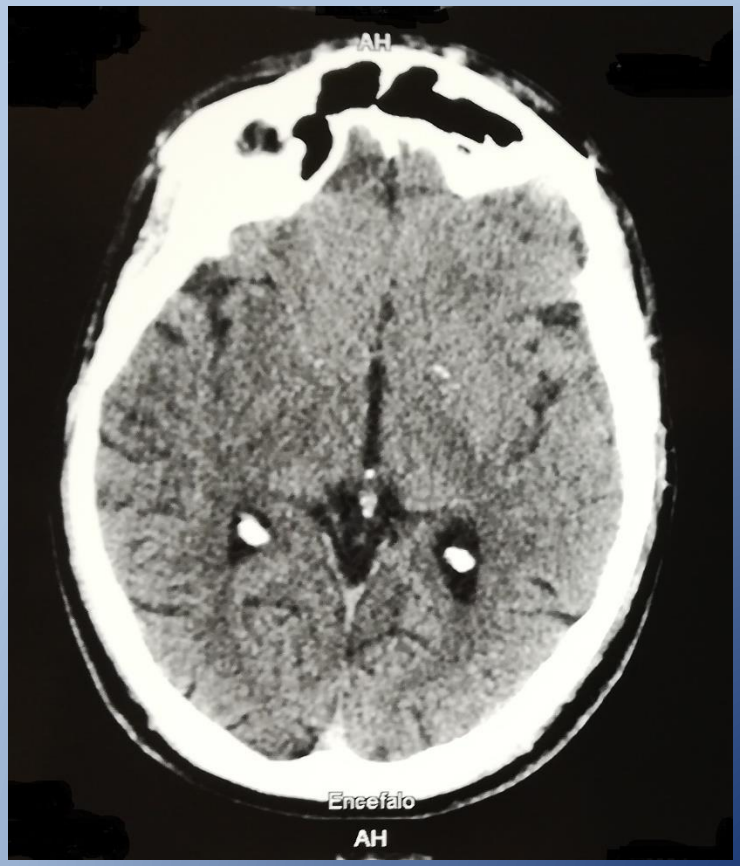


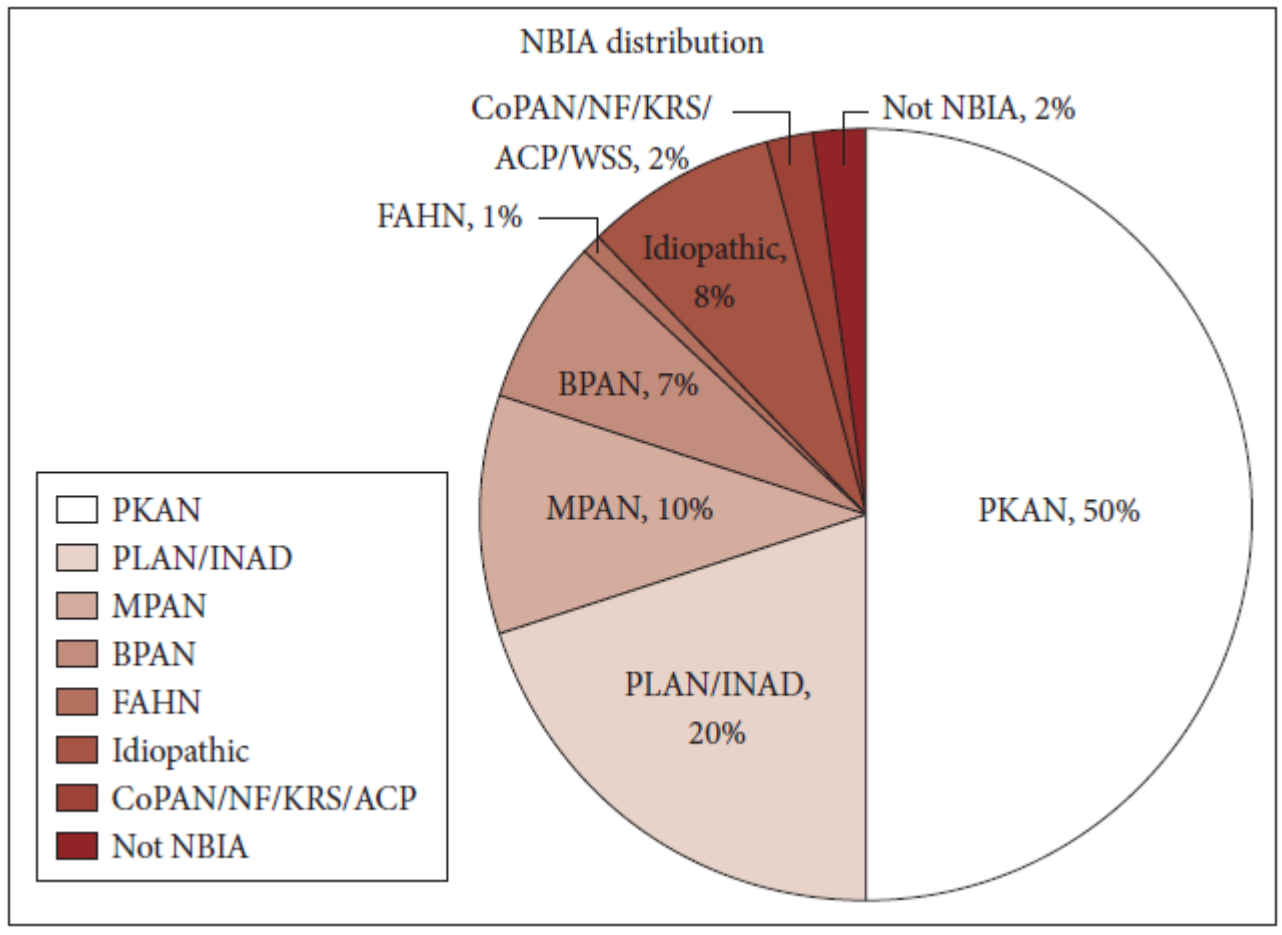







AH
Encefalo
AH


AH
Encefalo
AH


NBIA distribution
CoPAN/NF/KRS/
ACP/WSS, 2%
Not NBIA, 2%
FAHN, 1%
Idiopathic,
8%
BPAN, 7%
MPAN, 10%
PKAN, 50%
PLAN/INAD,
20%
PKAN
PLAN/INAD
MPAN
BPAN
FAHN
Idiopathic
CoPAN/NF/KRS/ACP
Not NBIA

Eye tyger sign not pathognomonic!

1. Atrofia mutisistemica
2. Paralisi sopranucleare progressiva
3. Sindrome corticobasale
4. M. Wilson
5. Corea Huntington

Table 1 Criteria for the diagnosis of probable MSA

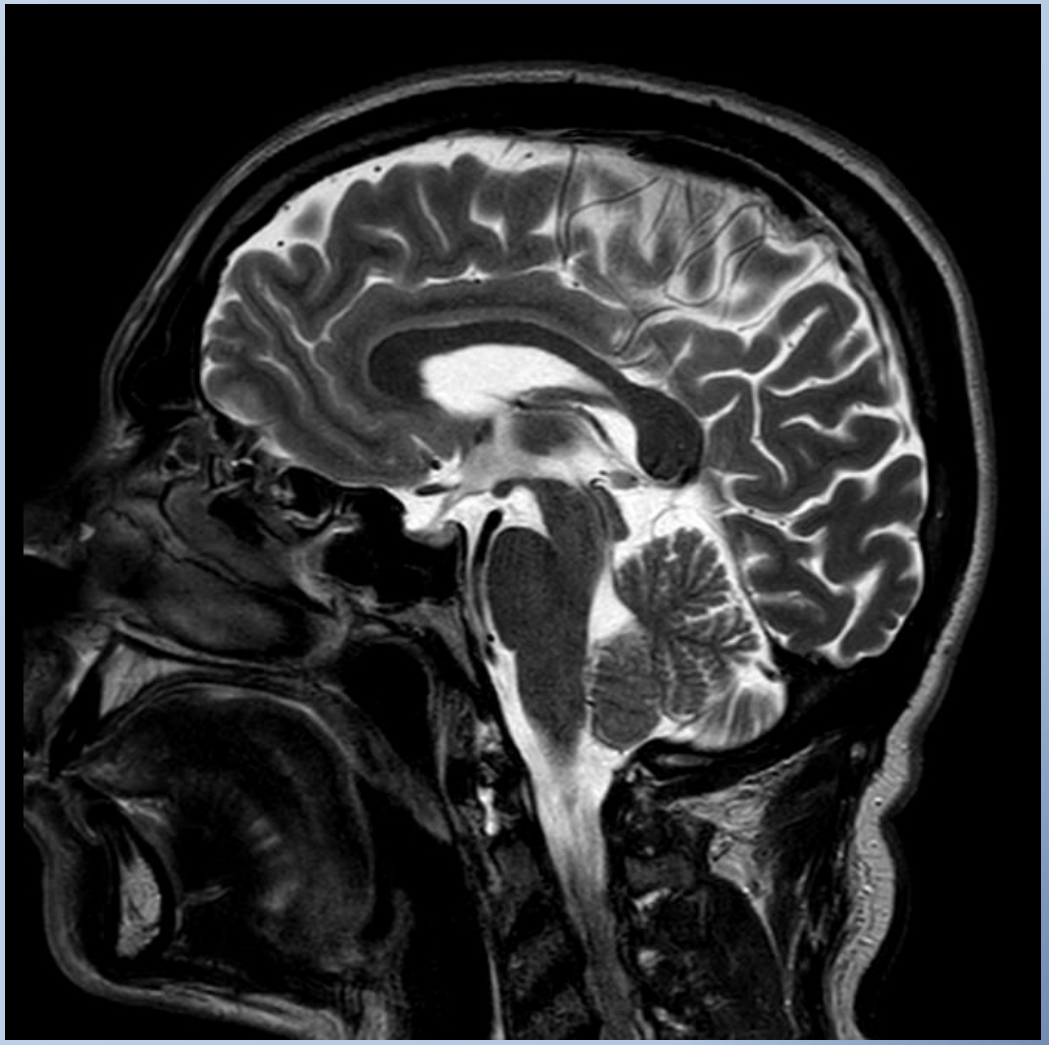
A sporadic, progressive, adult (>30 y)- onset disease characterized by
• Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic *and*
• Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Table 2 Criteria for possible MSA

A sporadic, progressive, adult (>30 y)- onset disease characterized by
• Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) *and*
• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) *and*
• At least one of the additional features shown in table 3

Table 3 **Additional features of possible MSA**

Possible MSA-P or MSA-C
• Babinski sign with hyperreflexia
• Stridor
Possible MSA-P
• Rapidly progressive parkinsonism
• Poor response to levodopa
• Postural instability within 3 y of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
• Dysphagia within 5 y of motor onset
• Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
• Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C
• Parkinsonism (bradykinesia and rigidity)
• Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET



M. Di Wilson

↓ ceruloplasmina

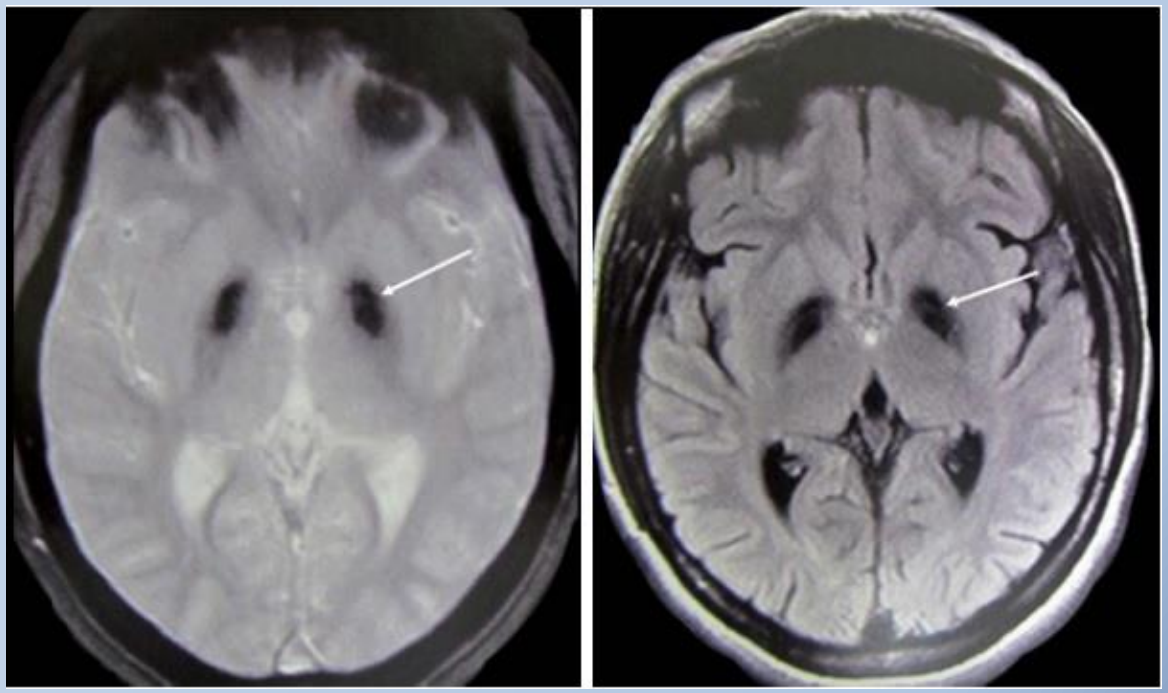
↑ cupremia

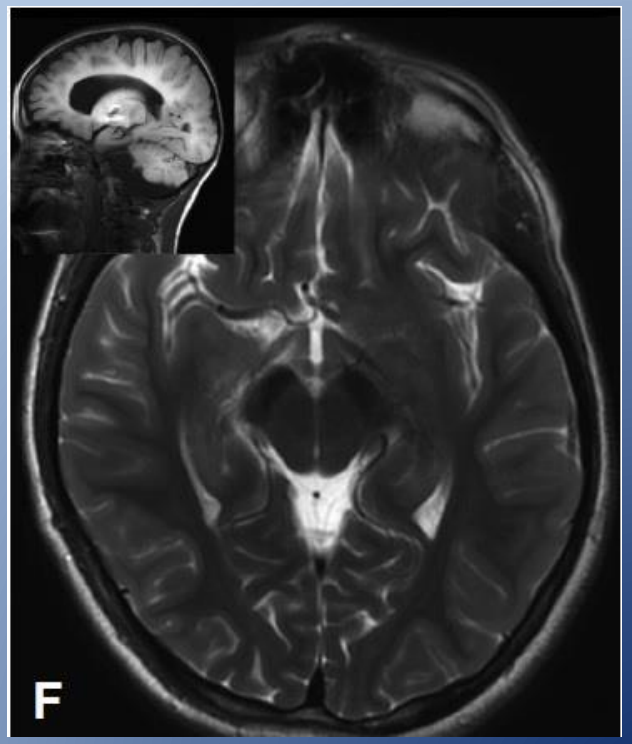
↑ cupruria

Table 1. The ten forms of NBIA described to date, with name, acronym, mutated gene, and mode of inheritance

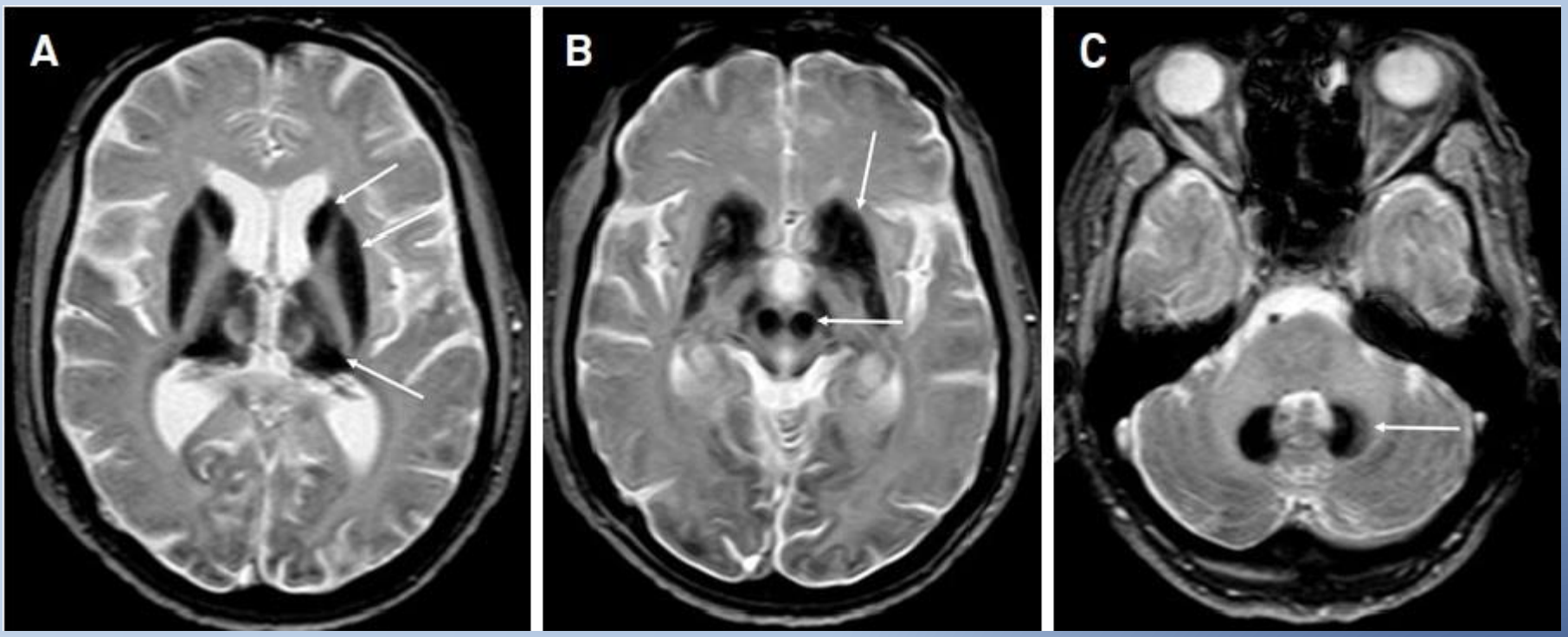
NBIA subtype	Gene	Mode of inheritance
Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*	Autosomal recessive
Phospholipase A2-associated neurodegeneration (PLAN)	*PLA2G6*	Autosomal recessive
Mitochondrial membrane protein-associated neurodegeneration (MPAN)	*C19orf12*	Autosomal recessive
Beta-propeller protein-associated neurodegeneration (BPAN)	*WDR45*	X-linked dominant
Fatty acid hydroxylase-associated neurodegeneration (FAHN)	*FA2H*	Autosomal recessive
Coenzyme A synthase protein-associated neurodegeneration (CoPAN)	*COASY*	Autosomal recessive
Kufor-Rakeb syndrome	*ATP13A2*	Autosomal recessive
Woodhouse-Sakati syndrome	*DCAF17*	Autosomal recessive
Neuroferritinopathy	*FTL*	Autosomal dominant
Aceruloplasminemia	*CP*	Autosomal recessive

Phospholipase A2 associated neurodegeneration (PLAN)





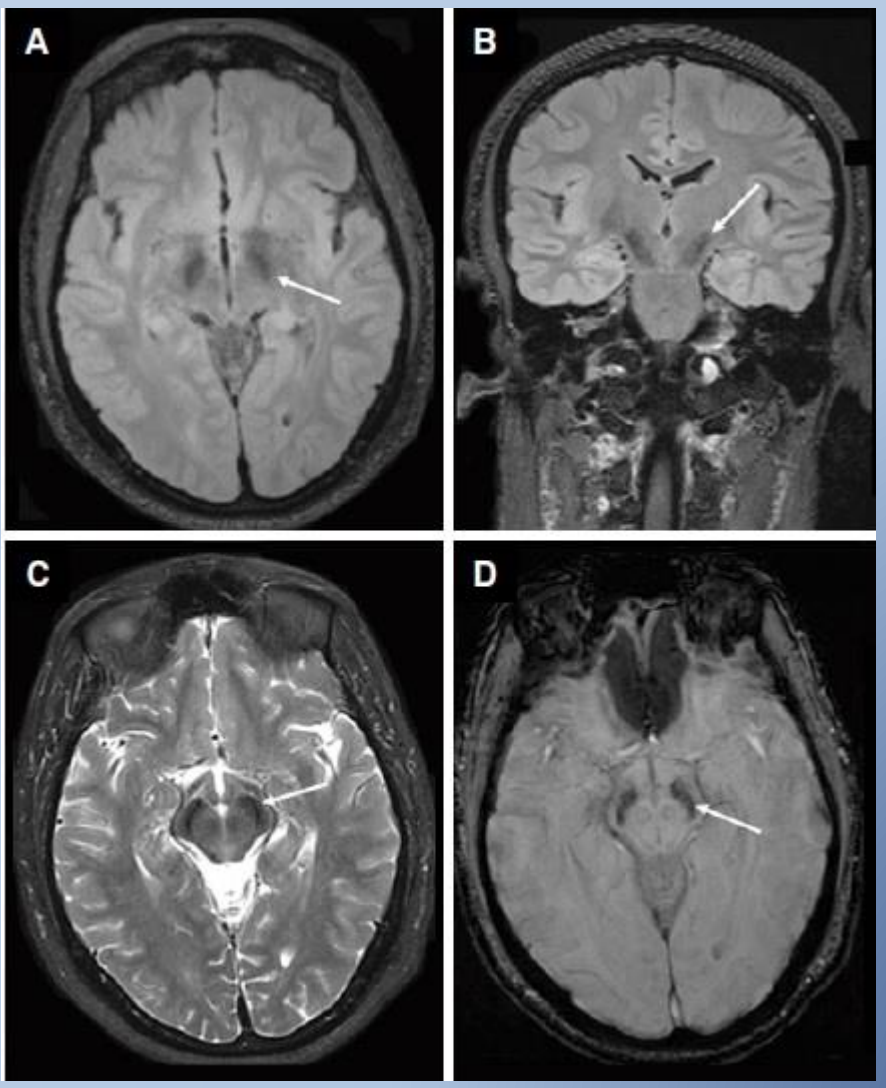
Aceruloplasminemia



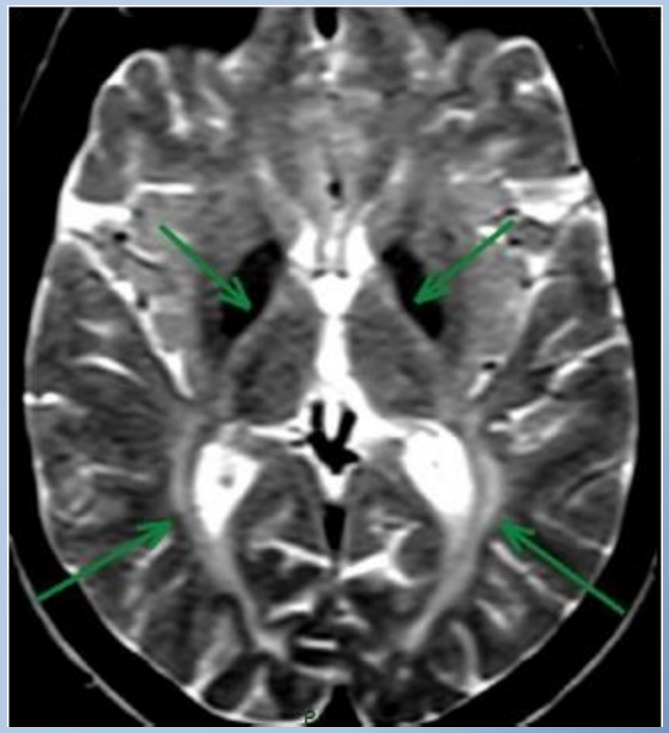
Anemia microcitica, diabete, retinopatia

- Ceruloplasmina sierica ridotta o assente
- ferritina elevata, ferro basso
- rame sierico basso e rame urinario normale

Beta-propeller protein-associated neurodegeneration (BPAN) or SENDA

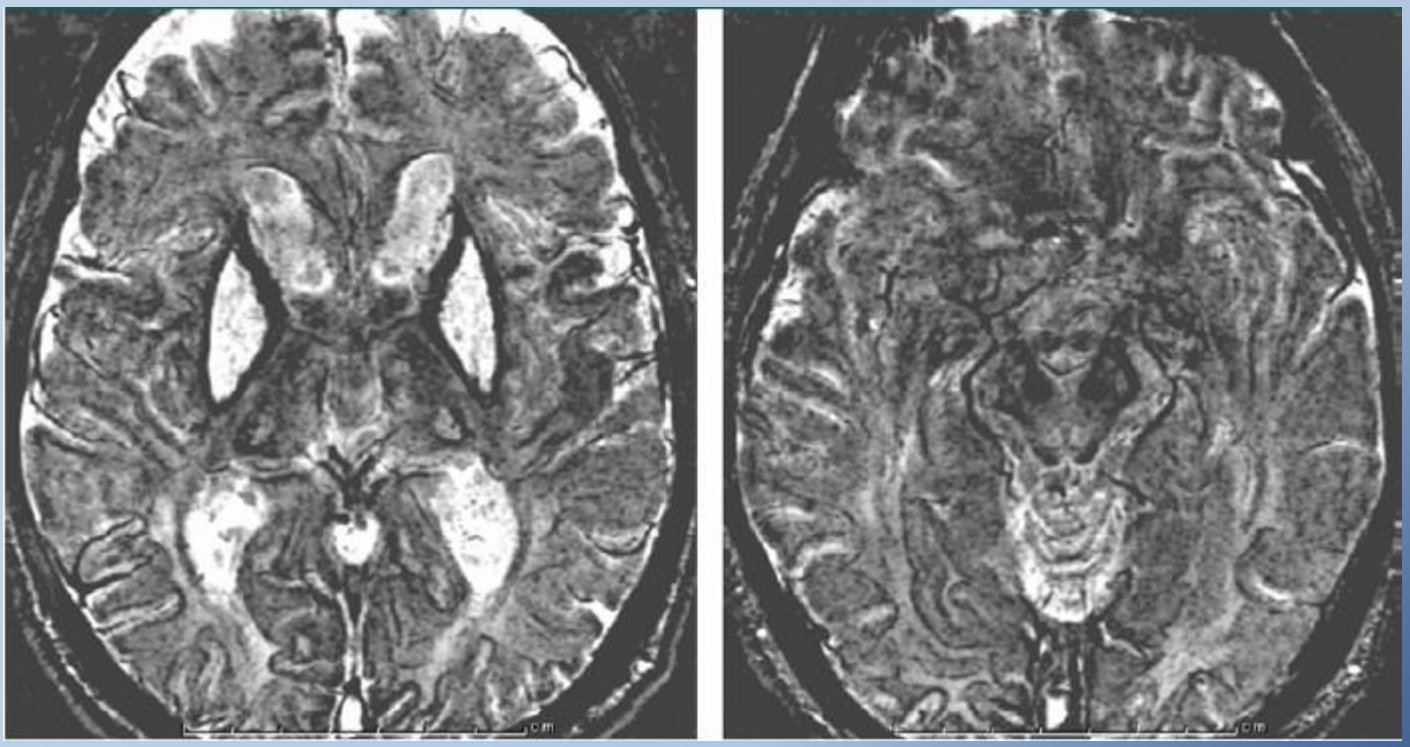


Fatty acid hydroxylase-associated neurodegeneration (FAHN)

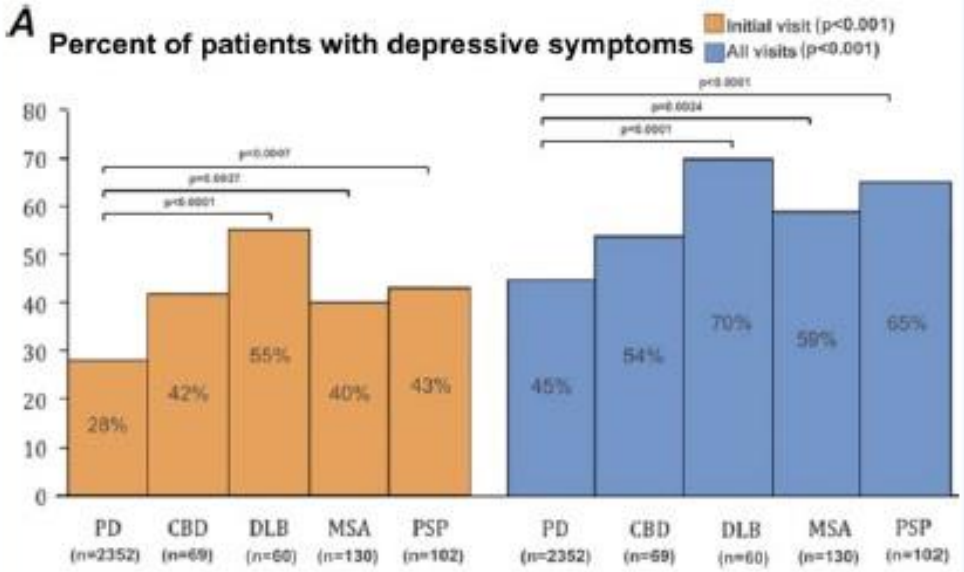


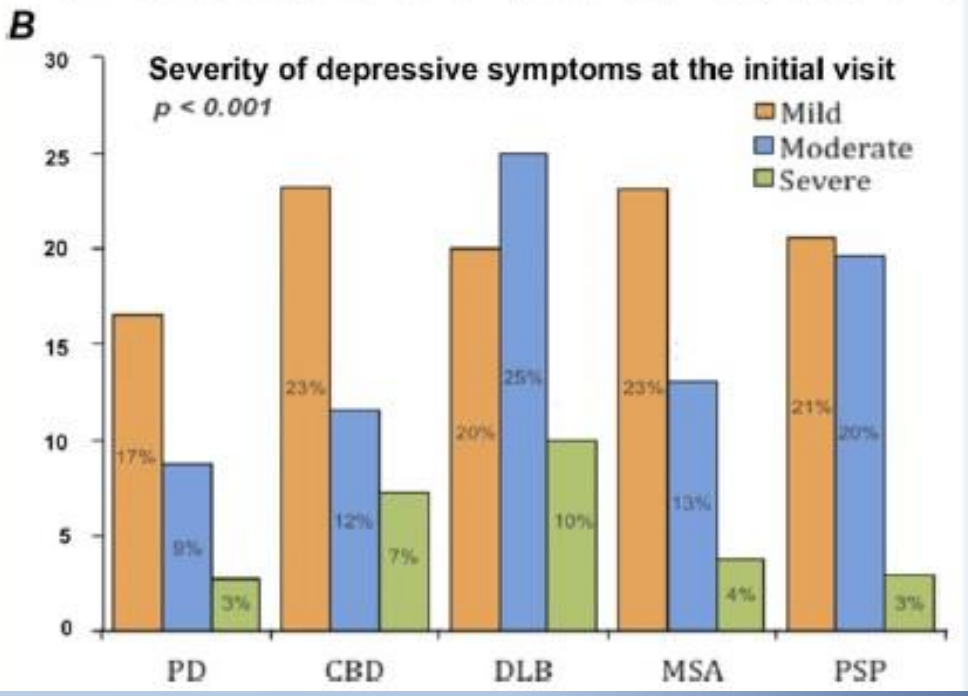
Neuroferritinopathy

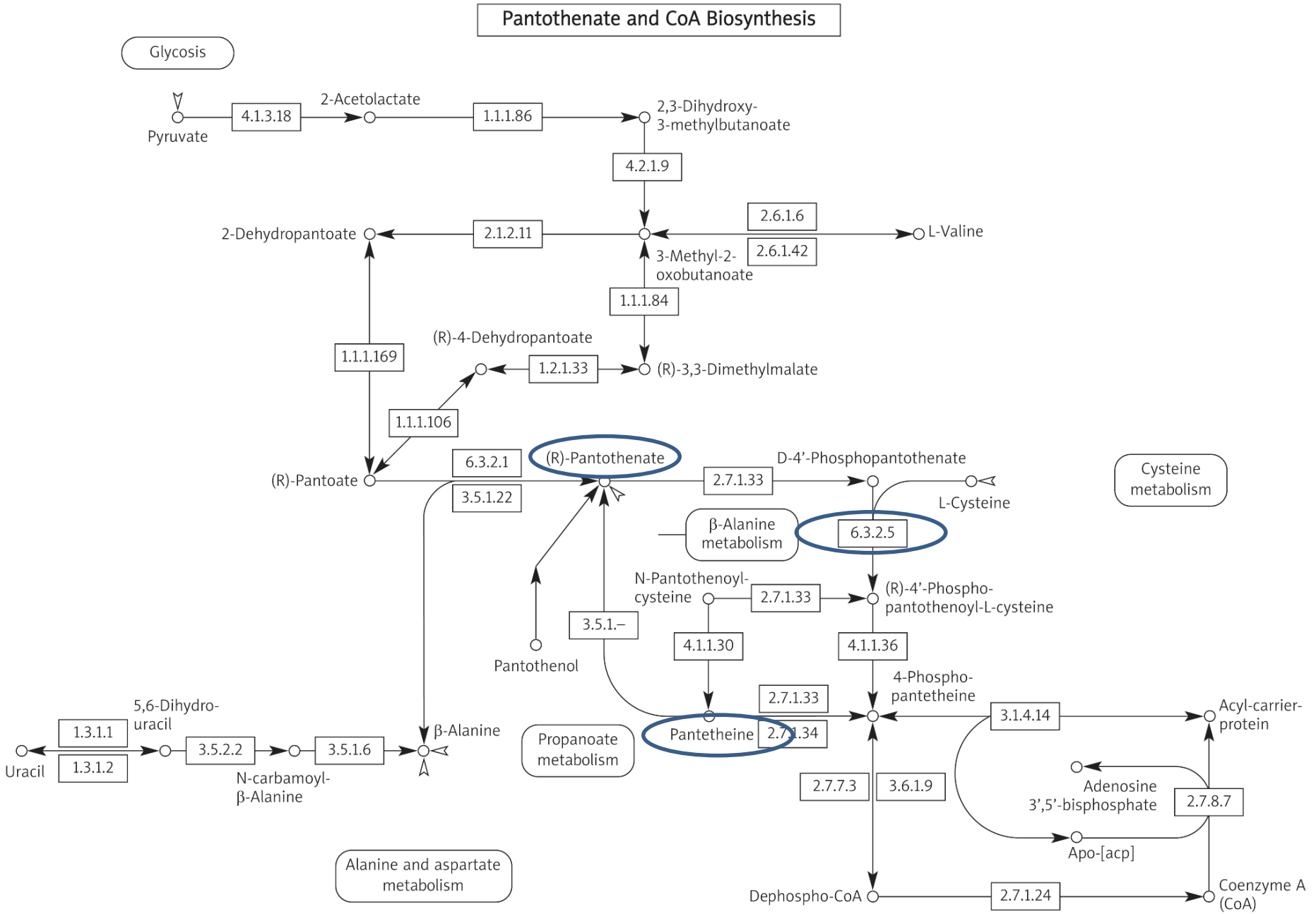
Cystic degeneration!



Ferritina ematica ridotta


A
Percent of patients with depressive symptoms
Initial visit (p<0.001)
All visits (p<0.001)
80
70
60
50
40
30
20
10
0
28%
42%
55%
40%
43%
45%
54%
70%
59%
65%
PD (n=2352)
CBD (n=69)
DLB (n=60)
MSA (n=130)
PSP (n=102)
PD (n=2352)
CBD (n=69)
DLB (n=60)
MSA (n=130)
PSP (n=102)


B
Severity of depressive symptoms at the initial visit
p < 0.001
Mild
Moderate
Severe
30
25
20
15
10
5
0
17%
9%
3%
23%
12%
7%
20%
25%
10%
23%
13%
4%
21%
20%
3%
PD
CBD
DLB
MSA
PSP


Pantothenate and CoA Biosynthesis
Glycosis
Pyruvate
4.1.3.18
2-Acetolactate
1.1.1.86
2,3-Dihydroxy-
3-methylbutanoate
4.2.1.9
2-Dehydropantoate
2.1.2.11
2.6.1.6
2.6.1.42
L-Valine
3-Methyl-2-
oxobutanoate
1.1.1.84
1.1.1.169
(R)-4-Dehydropantoate
1.2.1.33
(R)-3,3-Dimethylmalate
1.1.1.106
(R)-Pantoate
6.3.2.1
3.5.1.22
(R)-Pantothenate
2.7.1.33
D-4'-Phosphopantothenate
L-Cysteine
Cysteine
metabolism
β-Alanine
metabolism
6.3.2.5
N-Pantothenoyl-
cysteine
2.7.1.33
(R)-4'-Phospho-
pantothenoyl-L-cysteine
3.5.1.–
Pantothenol
4.1.1.30
4.1.1.36
4-Phospho-
pantetheine
2.7.1.33
Pantetheine
2.7.1.34
3.1.4.14
Acyl-carrier-
protein
5,6-Dihydro-
uracil
1.3.1.1
1.3.1.2
Uracil
3.5.2.2
N-carbamoyl-
β-Alanine
3.5.1.6
β-Alanine
Propanoate
metabolism
2.7.7.3
3.6.1.9
Adenosine
3',5'-bisphosphate
2.7.8.7
Apo-[acp]
Alanine and aspartate
metabolism
Dephospho-CoA
2.7.1.24
Coenzyme A
(CoA)

Classic PKAN: 75 %

- Onset: before age 6 years (mean age 3.4 years), with some variability (6 months–12 years)

- Early clinical features are commonly gait abnormalities and postural instability

- Dystonia and spasticity

- Opisthotonic posturing

- Visual symptoms may be the presenting feature (pigmentary retinopathy, Adie's pupil)

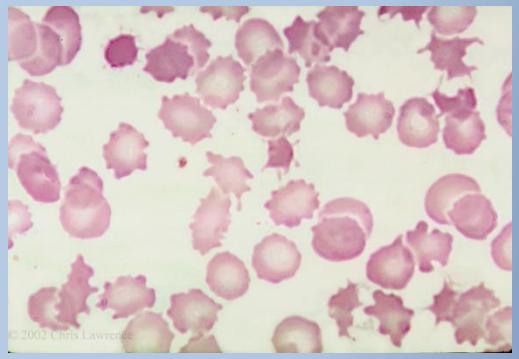
Atypical PKAN:

- Onset: mean age of 14 years (range 1–28 years)

- Parkinsonism, rest tremor less common

- stuttering, a Parkinsonian-type palilalia or hypophonia, spasmodic dysphonia, or dysarthria due to oropharyngeal dystonia.

- Neuropsychiatric: mood lability, impulsivity, non-specific behavioral changes, and obsessive-compulsive features may be early signs



Acanthocytes (8%)

Therapy

Deferiprone, an iron chelator

- crosses the blood-brain barrier

- robust reduction of brain iron on brain MRI in PKAN, but no measurable clinical

A double-blind, placebo-controlled international multicenter clinical trial to more rigorously investigate the drug's benefit
89 pz

Pantothenate

- chemical backbone of coenzyme A, essential for hundreds of biochemical reactions

- enzymatic substrate overload partial PANK2 enzyme function, (atypical PKAN)

- No clinical trial has been performed to evaluate the efficacy of pantothenate.

- high dose pantothenate for at least 3 months for all PKAN, starting at a dose of 250 mg orally and increasing weekly by 500 mg until a daily dose of 2–5 g is reached or side effects become evident

- low toxicity

- Some adults with atypical PKAN perceive benefit from pantothenate to their gait, speech and clarity of thinking.

- classic PKAN, pantothenate seems to offer little or no benefit

Genetica in corso…

… to be continued…

Grazie per l'attenzione