Ospedali Riuniti di Ancona-Università Politecnica delle Marche
Dipartimento di Medicina Sperimentale e Clinica
Clinica di Neurologia

PATTERN FENOTIPICO INUSUALE IN UNA FAMIGLIA CON DEMENZA FRONTO-TEMPORALE

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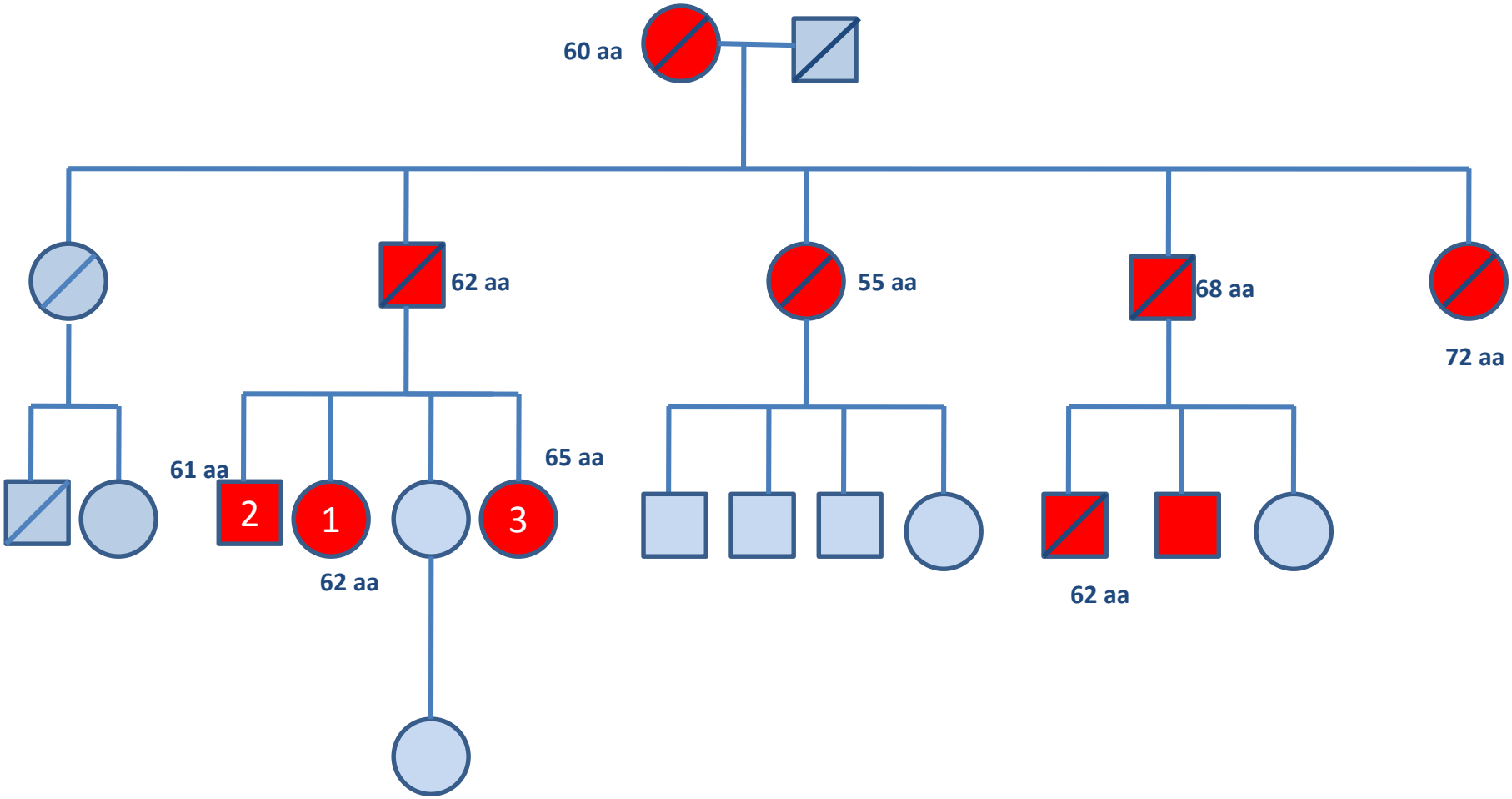
Riunione annuale SIN Umbro-Marchigiana
Perugia, 7 Dicembre 2016

FAMIGLIA ORIGINARIA DI ANCONA



FAMIGLIA ORIGINARIA DI ANCONA

1

62 aa

CASO 1

PAZIENTE

-Donna
-62 anni
-Destrimane
-Scolarità 8 anni

APR

-Ipertensione arteriosa
-Stenosi carotidea lieve
-Ipercolesterolemia

ESORDIO CLINICO

- 2 anni prima
- DISTURBO DEL LINGUAGGIO: difficoltà nel reperimento di vocaboli, parafasie semantiche e fonemiche

CASO 1

EVOLUZIONE CLINICA

-DEFICIT DI COMPRENSIONE del significato delle parole
-ALTERAZIONI COMPORTAMENTALI: impulsività, aggressività verbale

ESAME OBIETTIVO NEUROLOGICO

Normale

CASO 1

ESAME NEUROPSICOLOGICO

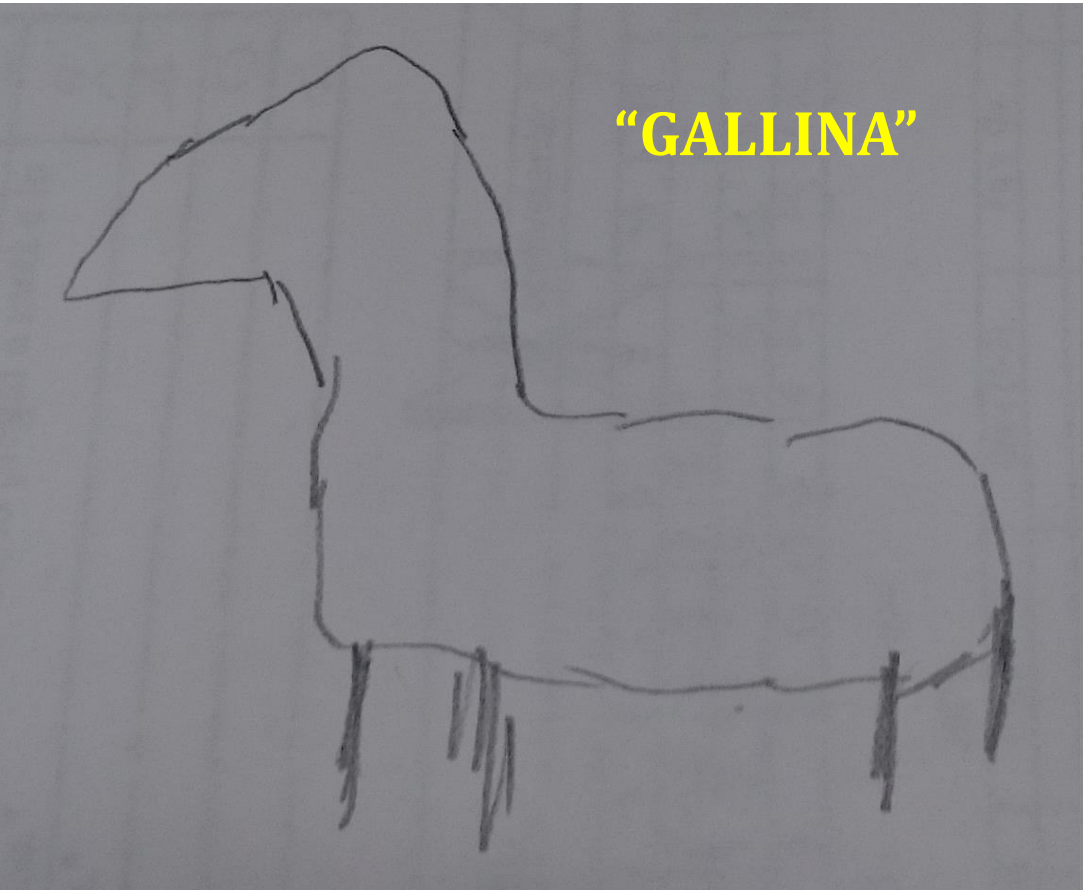
- **DISTURBO DI LINGUAGGIO:**

-prevalente compromissione del sistema SEMANTICO-LESSICALE;
-anomie, utilizzo di parole pass-partout;
- errori di tipo fonologico e sintattico.

- **Compromissione del sistema semantico anche nelle sue componenti NON VERBALI (prosopagnosia associativa)**

- **DEFICIT DELLE FUNZIONI ESECUTIVE**

CASO 1



"GALLINA"

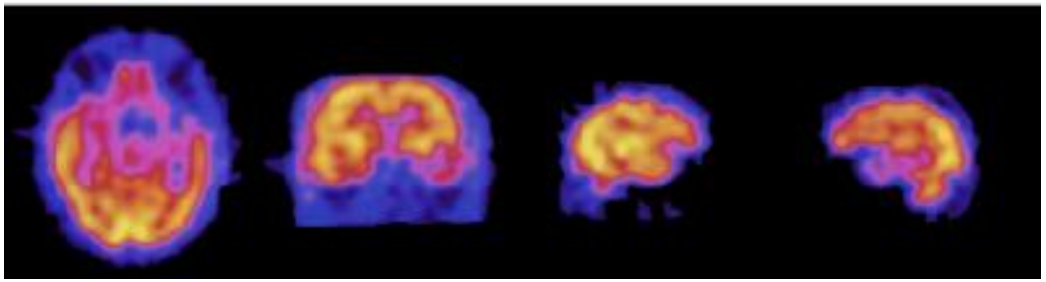
"ANNAFFIATOIO"

CASO 1

QUADRO NEURORADIOLOGICO

RMN encefalo:
atrofia temporale sinistra

PET -FDG:
ipometabolismo nelle regioni frontali e temporali di sinistra



CASO 1

DIAGNOSI:

DEMENZA SEMANTICA “ATIPICA”

AFASIA PROGRESSIVA PRIMARIA-VARIANTE SEMANTICA

CLINICAL diagnosis of svPPA

Both of the following core features must be present:

1. Impaired confrontation naming
2. Impaired single-word comprehension

At least three of the following other diagnostic features must be present:

1. Impaired object knowledge, particularly for low frequency or low familiarity items
2. Surface dyslexia and/or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

IMAGING-supported svPPA diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of semantic variant PPA

2. Imaging must show one or more of the following results:
A. predominant anterior temporal lobe atrophy
B. predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

svPPA with definite pathology

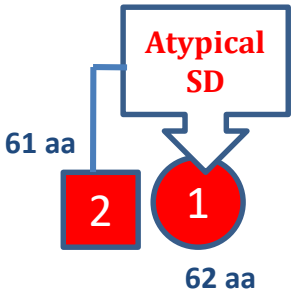
Clinical diagnosis (Criteria 1 below) and either Criterion 2 or 3 must be present

1. Clinical diagnosis of semantic variant PPA

2. Histopathological evidence of a specific neurodegenerative pathology (eg, FTLD-tau, FTLD-TDP, AD, other)

C. Presence of a known pathogenic mutation

Gorno-Tempini ML et al. Classification of primary progressive aphasia and its variants. Neurology 2011


Atypical
SD
61 aa
2
1
62 aa

CASO 2

PAZIENTE

-Uomo
- 61 anni
- Destrimane
-Scolarità: 17 anni

APR

-Nessuna patologia degna di nota

ESORDIO CLINICO

- Un anno prima
- Impaccio motorio all'arto superiore sinistro
(tendenza a usare meno l'arto, difficoltà a indossare vestiti e nell'utilizzo di oggetti)

CASO 2

EVOLUZIONE CLINICA

•ALTERAZIONI COMPORTAMENTALI:
- disinibizione verbale e comportamentale;
- irritabilità e aggressività verbale;
-aumento dell'assunzione di alcolici

•PEGGIORAMENTO del disturbo motorio all'arto superiore sinistro con impatto sull'autonomia funzionale

•Impaccio motorio all'arto inferiore omolaterale con progressiva compromissione della deambulazione

CASO 2

ESAME OBIETTIVO NEUROLOGICO

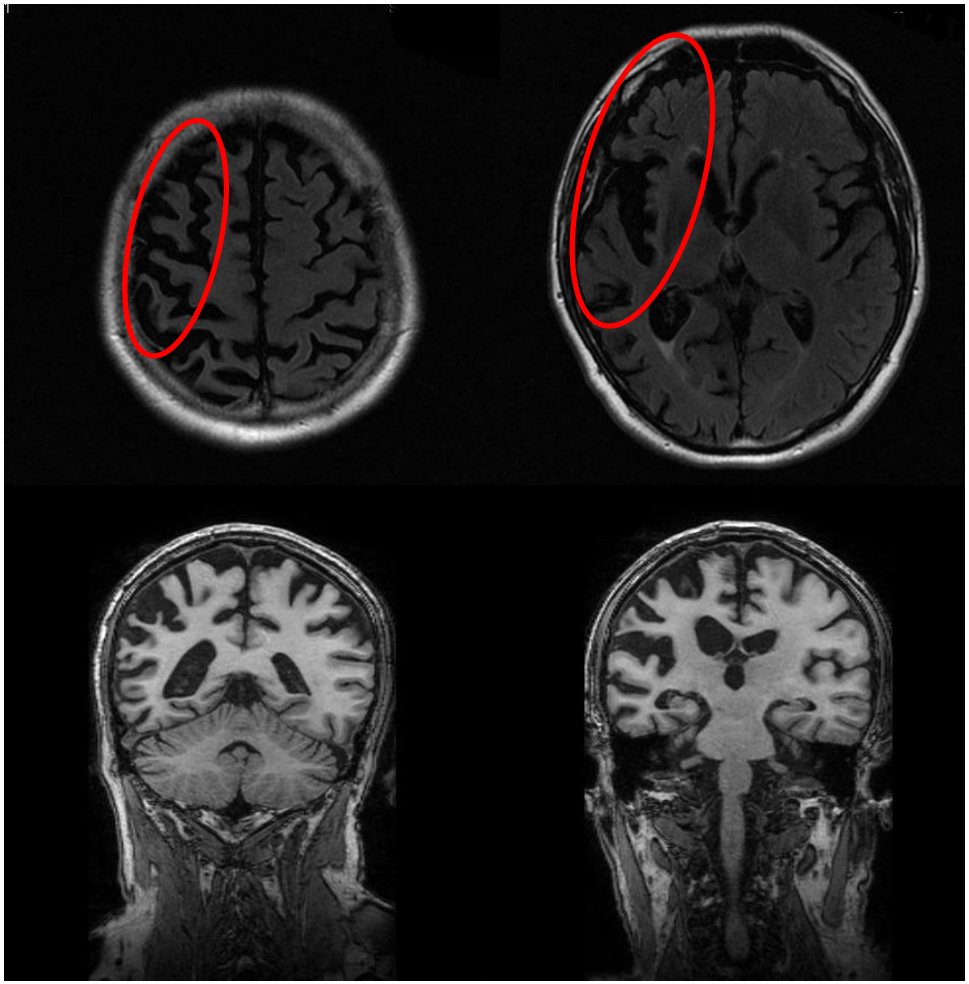
-sindrome extrapiramidale rigido-acinetica asimmetrica (assente pendolarismo arto superiore sinistro, segno della troclea al gomito e al polso sinistro)
-estinzione al doppio stimolo tattile

QUADRO NEUROPSICOLOGICO

-APRASSIA IDEOMOTORIA e ASTEREOGNOSIA arto superiore sinistro
-SINDROME DISESECUTIVA
-Rari errori fonologici in scrittura

CASO 2

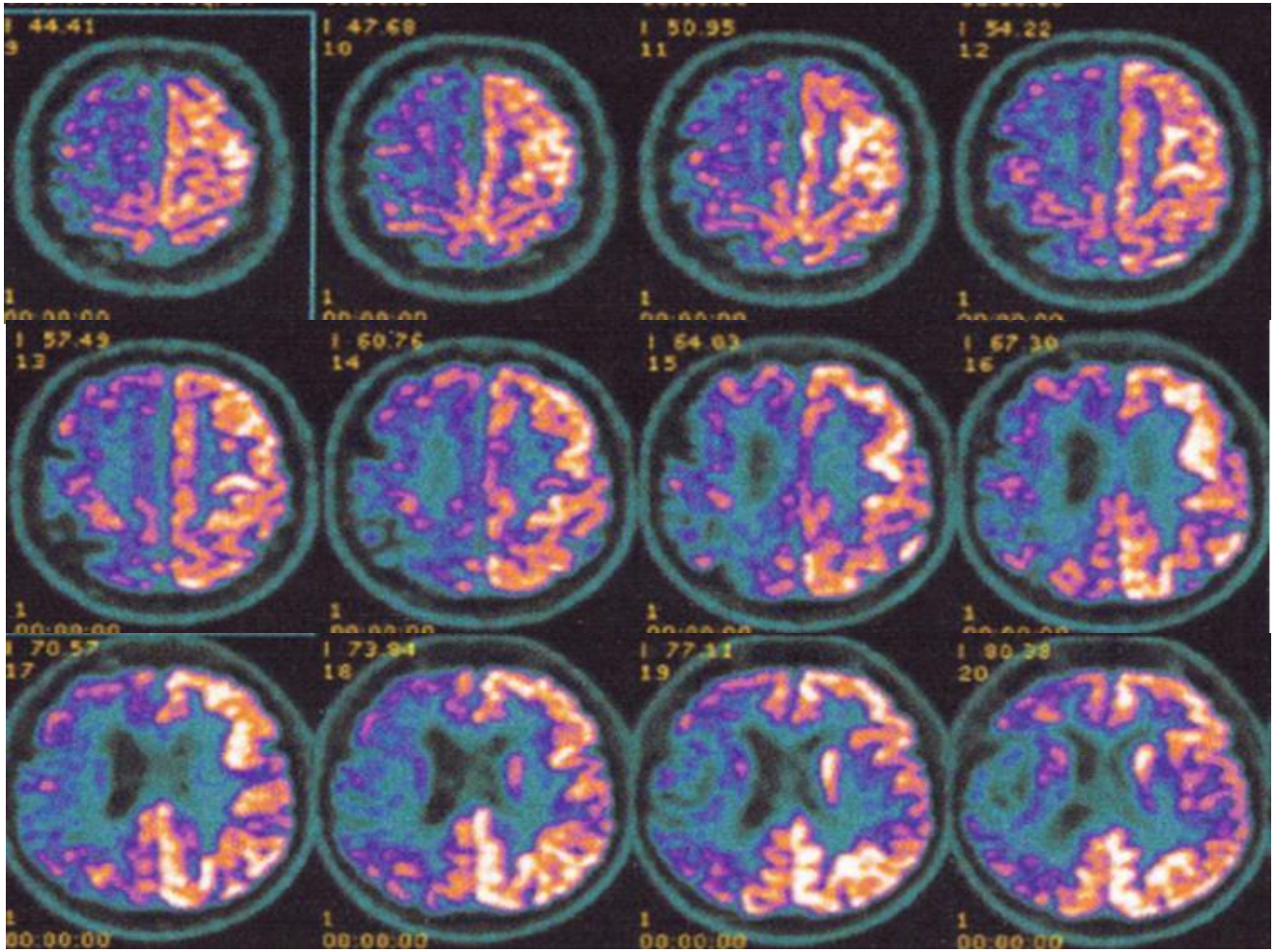
QUADRO NEURORADIOLOGICO



RMN CEREBRALE: atrofia fronto-parieto-temporale destra

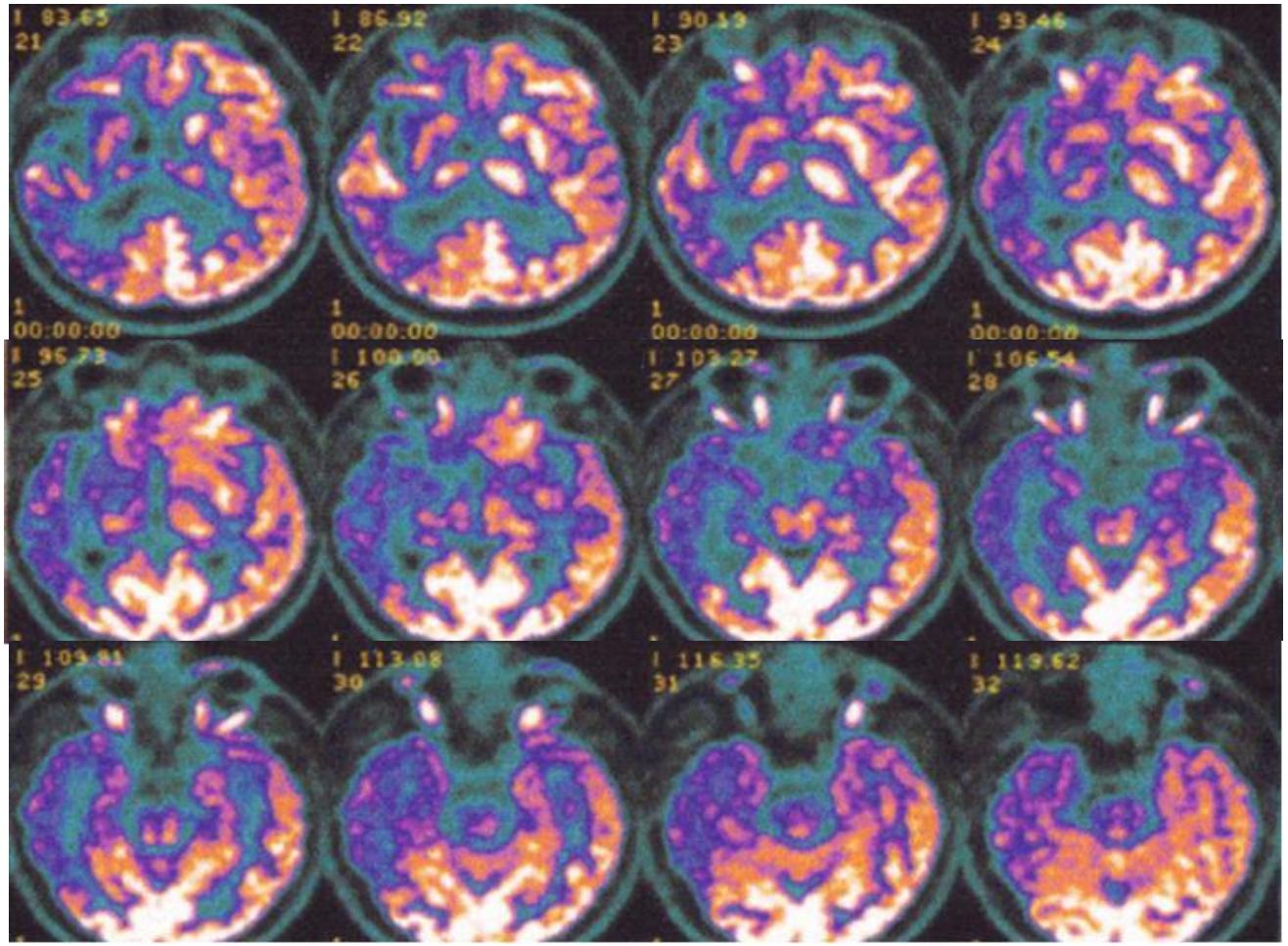
CASO 2

PET-FDG: ipometabolismo nelle regioni fronto-parietali di destra



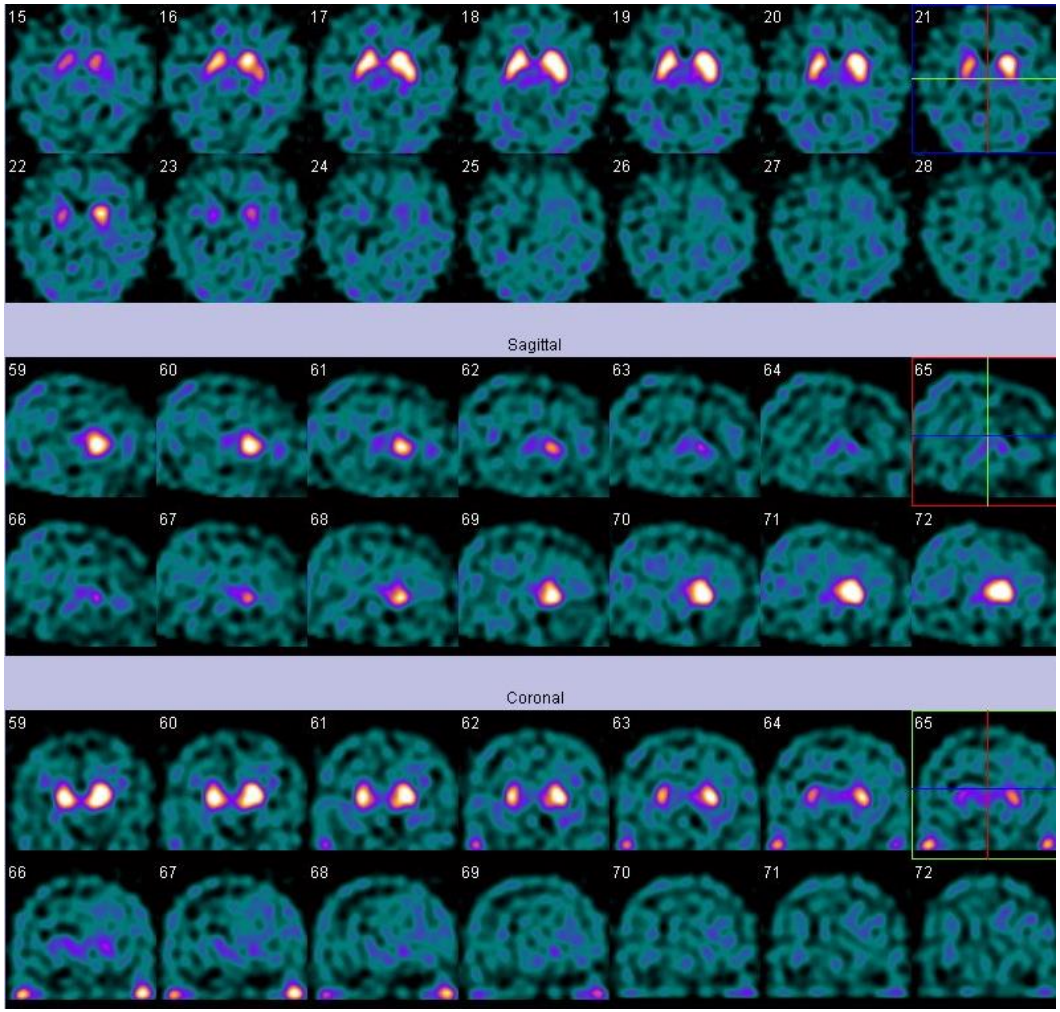
CASO 2

PET-FDG: ipometabolismo nelle regioni fronto-parietali di destra



CASO 2

DAT-SCAN: ridotta concentrazione del radiofarmaco nel putamen e caudato di destra



CASO 2

DIAGNOSI:

SINDROME CORTICO-BASALE

SINDROME CORTICO-BASALE

Table 4 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration[a]

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

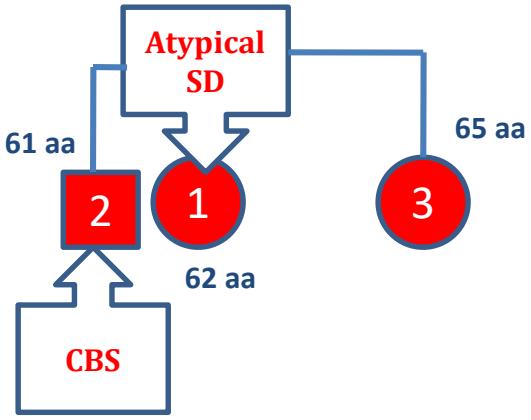
Armstrong M.J., 2013

SINDROME CORTICO-BASALE

Table 2 **Diagnoses reported in patients with corticobasal syndrome (pathologically proven or diagnosed based on laboratory or genetic testing)**

Corticobasal degeneration[1,2]
Alzheimer disease[16,17]
Pick disease[12,17]
Progressive supranuclear palsy[17]
Dementia with Lewy bodies (Gross et al., personal communication, 2013)
Nonspecific degenerative changes[12,17]
Neurofilament inclusion body disease[18]
MAPT gene mutation (frontotemporal dementia and parkinsonism linked to chromosome 17)
Frontotemporal lobar degeneration–TDP43 with motor neuron disease[7,8]
Progranulin gene mutation (frontotemporal dementia linked with ubiquitin inclusions on pathology)[19,20]
Progressive multifocal leukoencephalopathy[e1]
Cerebrovascular disease[16]
Creutzfeldt-Jakob disease[17]
Fahr disease[e2]
Neurosyphilis[e3]
Spinocerebellar ataxia type 8[e4]
Central pontine myelinolysis[e5]
Microtubule-associated protein tau (*MAPT*) gene mutation[e6]
Leucine-rich repeat kinase 2 (*LRRK2*) gene mutation[e7]
Cerebrotendinous xanthomatosis[e8]
Carotid artery stenosis/occlusion[e9,e10]
C9orf72 hexanucleotide expansion[e11]

Chanine L.M. et al., 2014


Atypical
SD
61 aa
65 aa
2
1
3
62 aa
CBS

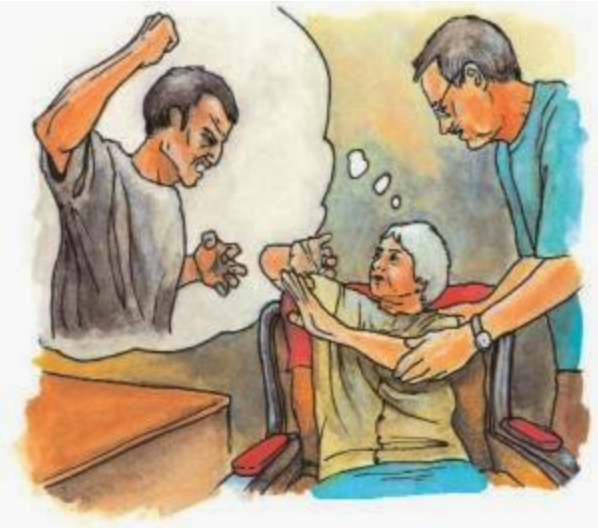
CASO 3

PAZIENTE

- Donna
- 65 anni
- Destrimane
- Scolarità 5 anni

APR

-Aritmia cardiaca
-Connettivite mista
-Ipercolesterolemia



ESORDIO CLINICO

-Un anno prima
-Ideazione delirante

CASO 3

EVOLUZIONE CLINICA

•**Disturbi comportamentali:**
-disinibizione
-voracità e preferenza per cibi dolci
-comportamenti bizzarri
-aggressività verbale
-shopping compulsivo

•**Deliri e allucinazioni visive**

•**Deficit attentivi**

ESAME OBIETTIVO NEUROLOGICO

Nella norma
(NON segni extrapiramidali nè di coinvolgimento di I o II motoneurone)

CASO 3

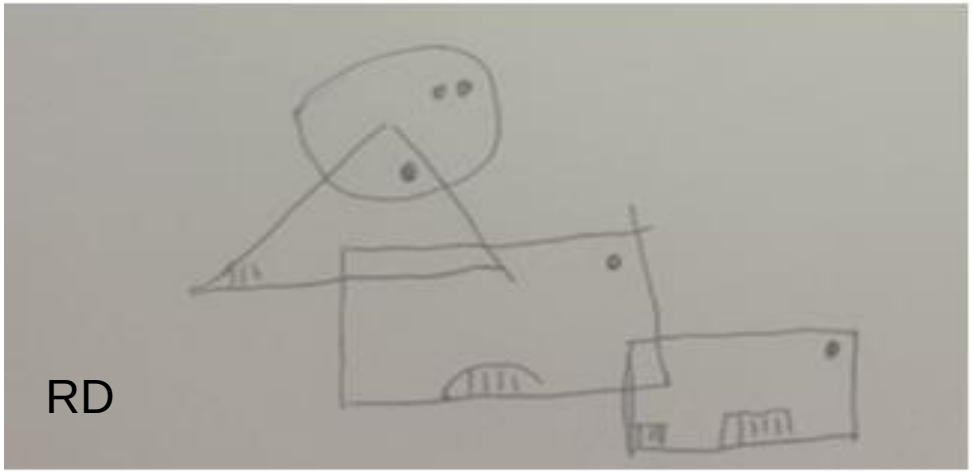
QUADRO NEUROPSICOLOGICO

-Severa SINDROME FRONTALE COMPORTAMENTALE

-Deficit delle FUNZIONI ESECUTIVE di controllo (attenzione selettiva e divisa, difficoltà nella comprensione di metafore ed espressioni astratte, perseverazioni)

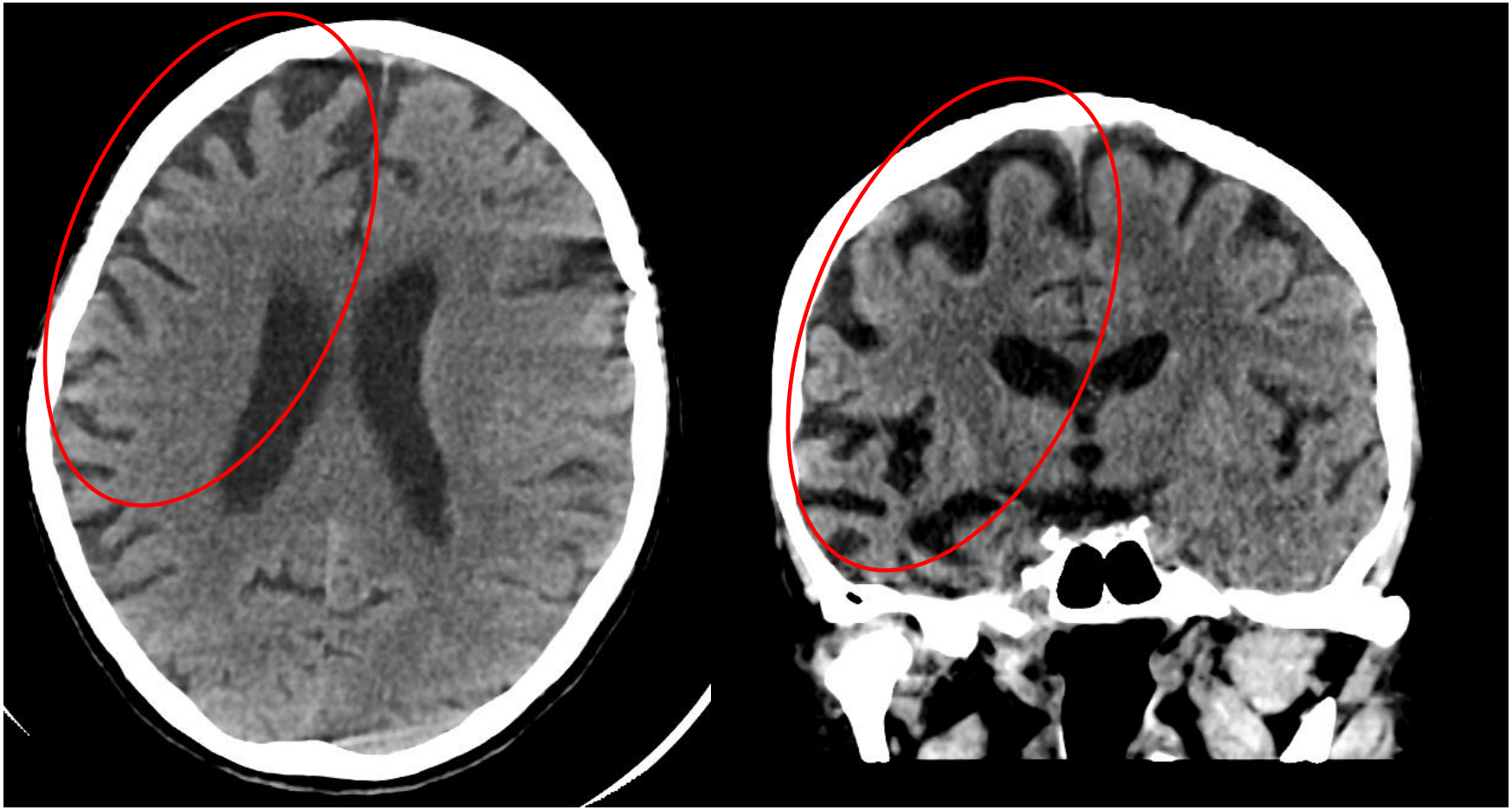
-Memoria a breve e lungo termine conservata

CASO 3



CASO 3

QUADRO NEURORADIOLOGICO



TC CEREBRALE: atrofia fronto-temporale destra

CASO 3

DIAGNOSI:

DEMENZA FRONTO-TEMPORALE VARIANTE COMPORTAMENTALE

* Nei primi tre anni

FTD-VARIANTE COMPORTAMENTALE (Criteri riformulati nel 2011 da Rascovsky K et al.)

POSSIBLE bvFTD

Three of the following behavioral/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* **behavioral disinhibition** [one of the following symptoms (A.1–A.3) must be present]:
A.1. Socially inappropriate behavior
A.2. Loss of manners or decorum
A.3. Impulsive, rash or careless actions

B. Early **apathy or inertia** [one of the following symptoms (B.1–B.2) must be present]:
B.1. Apathy
B.2. Inertia

C. Early **loss of sympathy or empathy** [one of the following symptoms (C.1–C.2) must be present]:
C.1. Diminished response to other people's needs and feelings
C.2. Diminished social interest, interrelatedness or personal warmth

D. Early **perseverative, stereotyped or compulsive/ritualistic behavior** [one of the following symptoms (D.1–D.3) must be present]:
D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviors
D.3. Stereotypy of speech

E. **Hyperorality and dietary changes** [one of the following symptoms (E.1–E.3) must be present]:
E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits **with relative sparing of memory and visuospatial functions** [all of the following symptoms (F.1–F.3) must be present]:
F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills

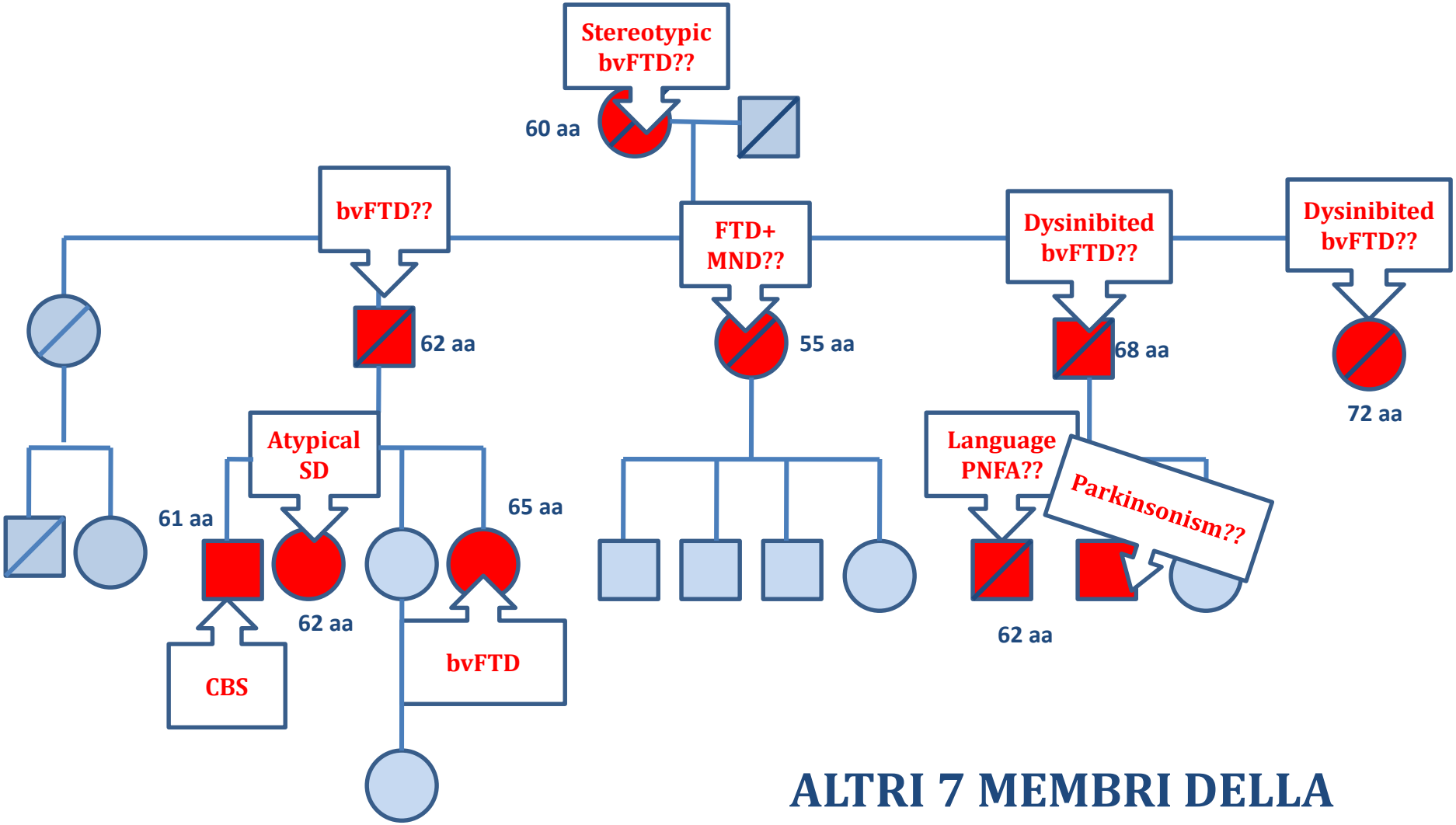
FTD-VARIANTE COMPORTAMENTALE

- 70 % delle FTD
- Più elevata incidenza di familiarità (45% dei casi)
- Forma più frequentemente associata a malattia del motoneurone
- Iniziali lievi cambiamenti nel comportamento e nella personalità, che peggiorano nel tempo
- Le abilità cognitive del paziente possono rimanere intatte per un certo periodo

Johnson JK, Diehl J, Mendez MF, Neuhaus J, Shapira JS, Forman M, Chute DJ, Roberson ED, Pace-Savitsky C, Neumann M. Frontotemporal lobar degeneration: demographic characteristics of 353 patients. Arch Neurol. 2005;62:925–930. doi: 10.1001/archneur.62.6.925

Pan XD, Chen Xc. Clinic, neuropathology and molecular genetics of frontotemporal dementia: a mini-review. Transl Neurodegener. 2013 Apr 19;2(1):8. doi: 10.1186/2047-9158-2-8.

ALBERO GENEALOGICO



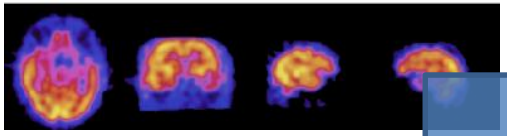
ALTRI 7 MEMBRI DELLA FAMIGLIA SINTOMATICI

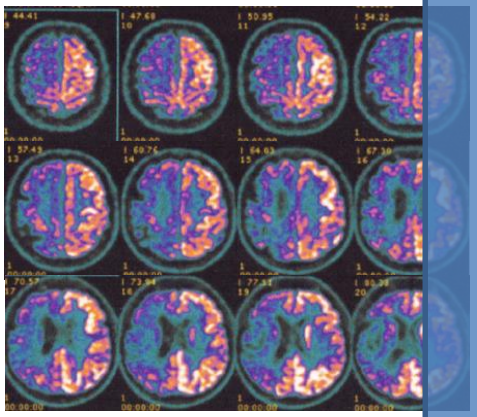
CLINICA	NEUROIMAGING	PATOLOGIA

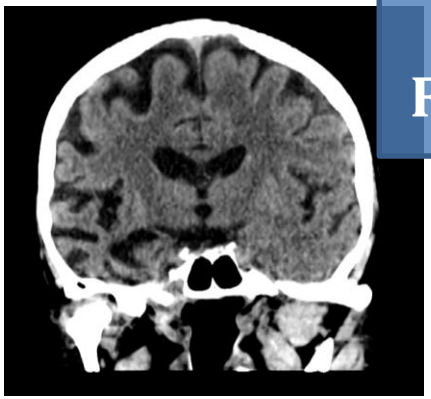
svFTD
atipica

CBS

bvFTD







FTLD

FAMILIARE

FTLD-FAMILIARITÀ

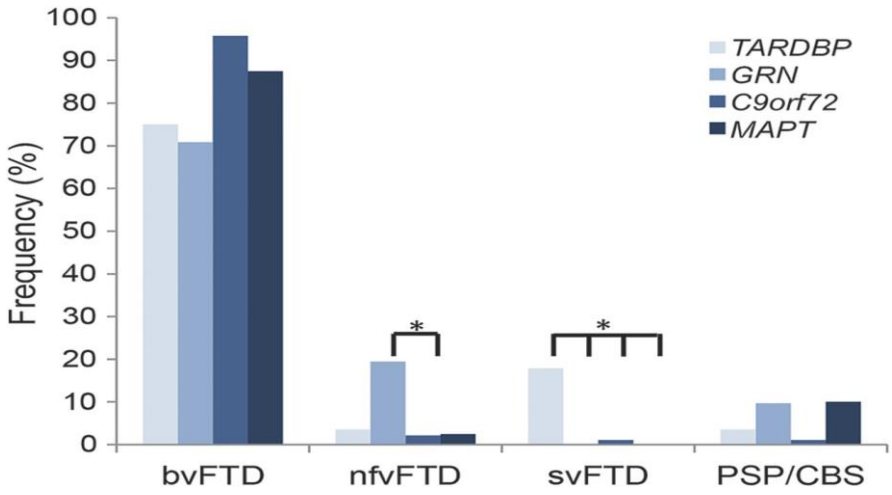
•Storia familiare di demenza nel 25-50% dei casi; il 10% circa ha un'ereditarietà autosomica dominante (Seelaar et al., 2008; Rohrer et al., 2009).

•I nuovi criteri diagnostici per la bvFTD (Rascovsky et al, 2011) includono la presenza di una mutazione nota come biomarcatore di tale malattia.

•I geni principali ad oggi identificati sono: C9ORF72, MAPT, GRN, CHMP2B, VCP, TARDPB, FUS.

Gene symbol	Chromosomal location	Gene name	Mutation frequency
C9orf72	9p21.2	Chromosome 9 open reading frame 21	14%–48%
GRN	17q21.32	Progranulin	3%–26%
MAPT	17q21.1	Microtubule-associated protein tau	0%–50%
CHMP2B	3p11.2	Charged multivesicular body protein 2B	<1%
VCP	9p13.3	Valosin-containing protein	<1%

Note: Data from Sieben et al.[57]
Abbreviation: FTLD, frontotemporal lobar degeneration.

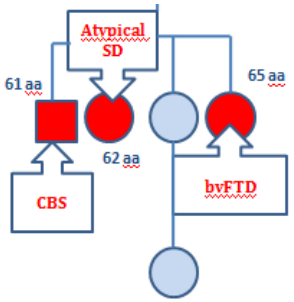


Paola Caroppo et al., Neurol Genet 2016

PAZIENTE 1, 2 E 3: TEST GENETICI

ANALISI GENETICA

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

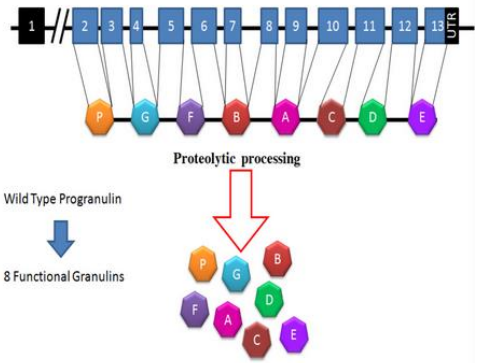


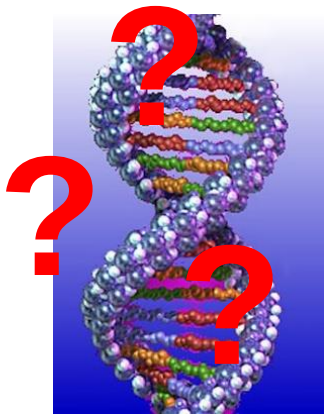
-NON riscontrate mutazioni note a carico dei geni MAPT, GRN, C9ORF72

-LIVELLI PLASMATICI DI PROGRANULINA RIDOTTI!

(circa 40 ng/ml) ***Cut off 61.55 ng/ml*** *(Ghidoni et al. 2012)*

PROBABILE MUTAZIONE NEL GENE GRN





MUTAZIONE NON ANCORA NOTA


GRAZIE !