# Encefalopatie Spongiformi

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*Università Magna Graecia di Catanzaro*

*Centro Regionale Epilessie di Reggio Calabria*

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

***Riunione annuale SIN Calabria***

***23 novembre 2019***

# Malattie da prioni umane

- ✓ Malattia di Creutzfeldt-Jakob (sporadica, genetica, iatrogena).
- ✓Sindrome di Gerstmann-Sträussler-Scheinker
- ✓Variante della Malattia di Creutzfeldt-Jakob
- ✓Insonnia Fatale Familiare
- ✓Kuru

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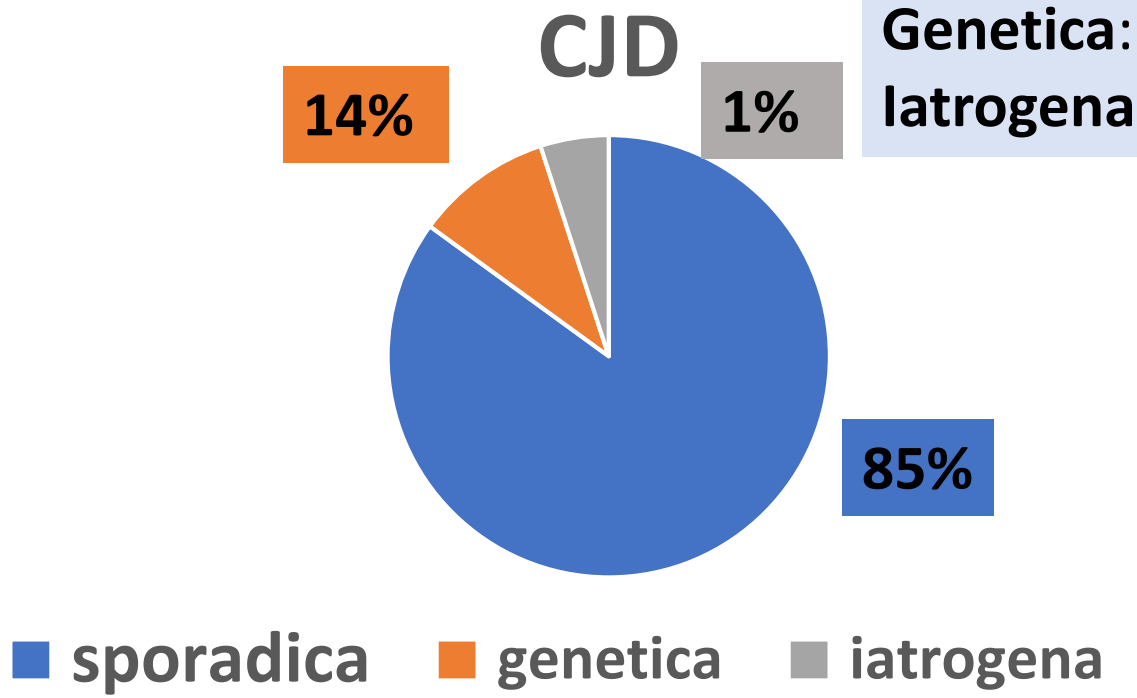
# Malattia di Creutzfeldt-Jakob

- Incidenza 1,5/1.000.000.

**Casi accertati in Italia dal 1993 ad oggi**

**Sporadica**: 2294
**Genetica**: 444
**Iatrogena** (impianto dura madre): 10



# CJD sporadica: clinica

| | Onset (%) | Course (%) |
|---|---|---|
| Dementia | 72 | 91 |
| Ataxia | 72 | 83 |
| Pyramidal signs | 40 | 77 |
| Myoclonus | 40 | 84 |
| Visual/oculomotor | 38 | 58 |
| Extrapyramidal signs | 36 | 75 |
| Akinetic mutism | 9 | 45 |
| Paresthesia | 13 | 16 |
| Epileptic fits | 3 | 12 |

Zerr e Parchi, 2018

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Zerr e Parchi, 2018

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Zerr e Parchi, 2018

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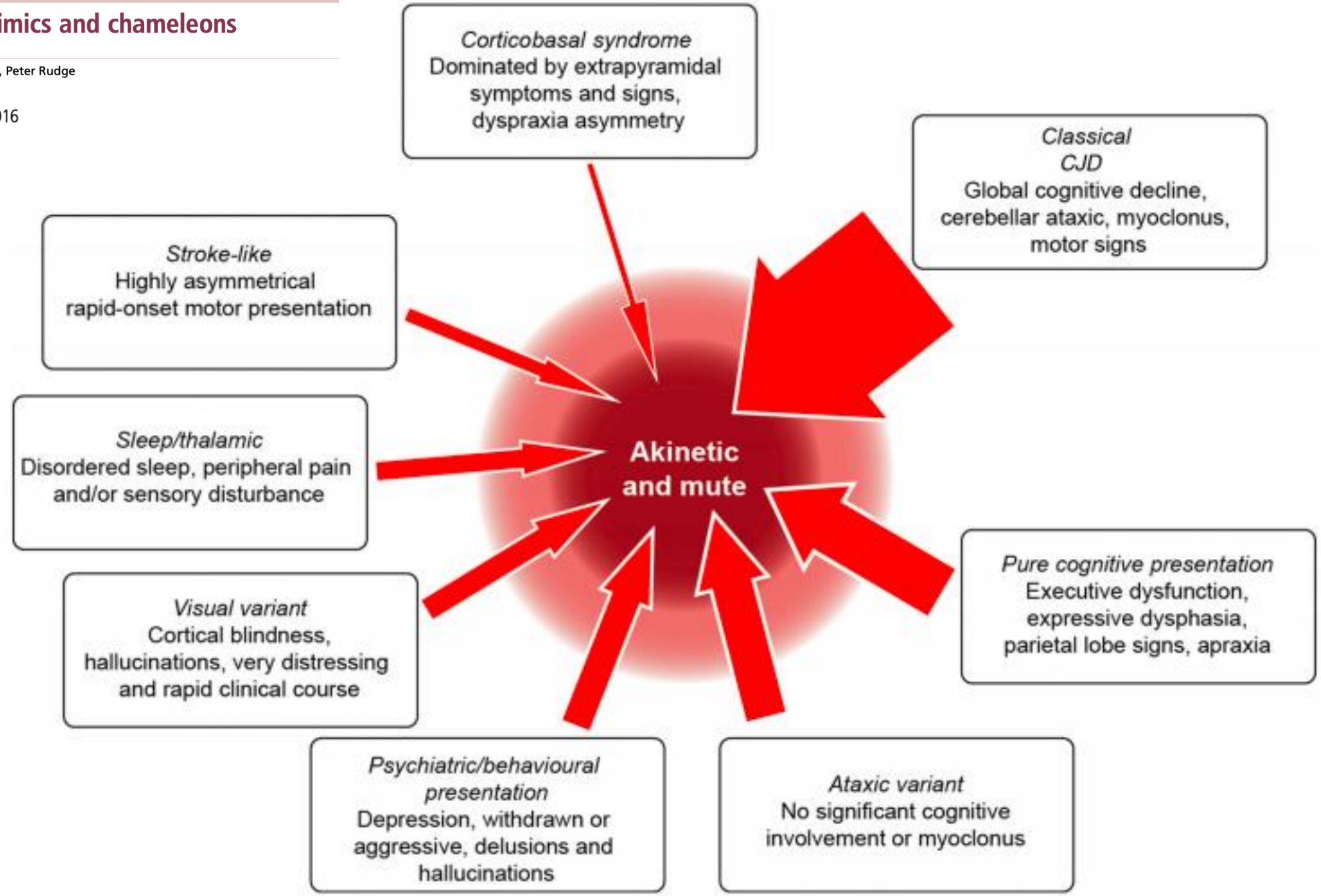
Zerr e Parchi, 2018

# CJD mimics and chameleons

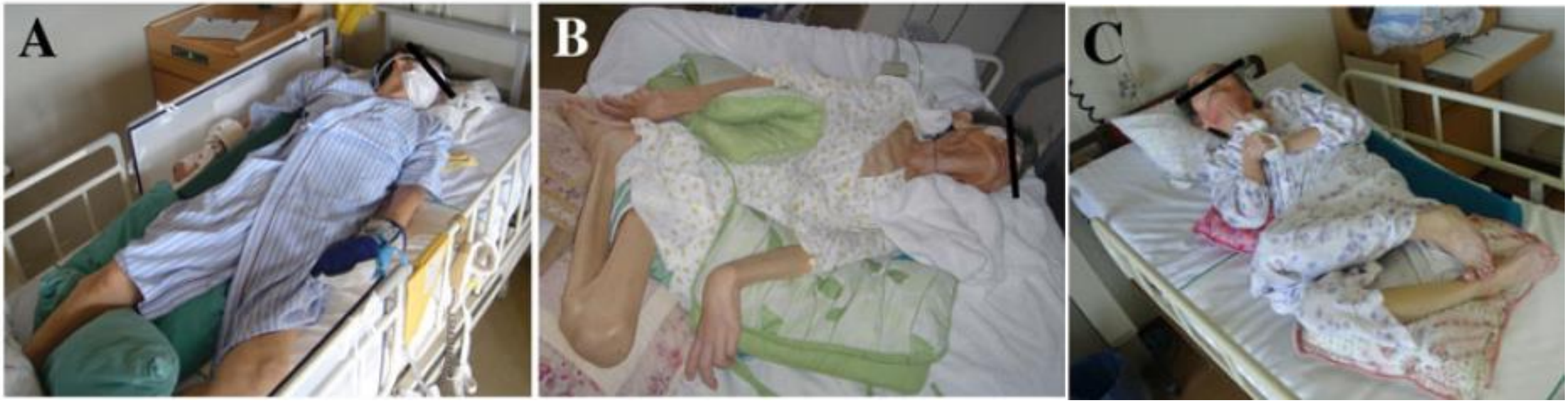
Simon Mead, Peter Rudge

OPEN ACCESS

Accepted 21 December 2016
Published Online First
2 February 2017



# Fasi Terminali



**M, 62 aa**

**Anamnesi personale:** ndr.

**Giunge al PS per:**

• crisi: pdc >deviazione dello sguardo e del capo verso destra>clonie ai 4 arti, frequenti negli ultimi 3 giorni.

**Inoltre, da 3 settimane:**

• "stato di confusione" (disorientato, non riconosce i familiari)

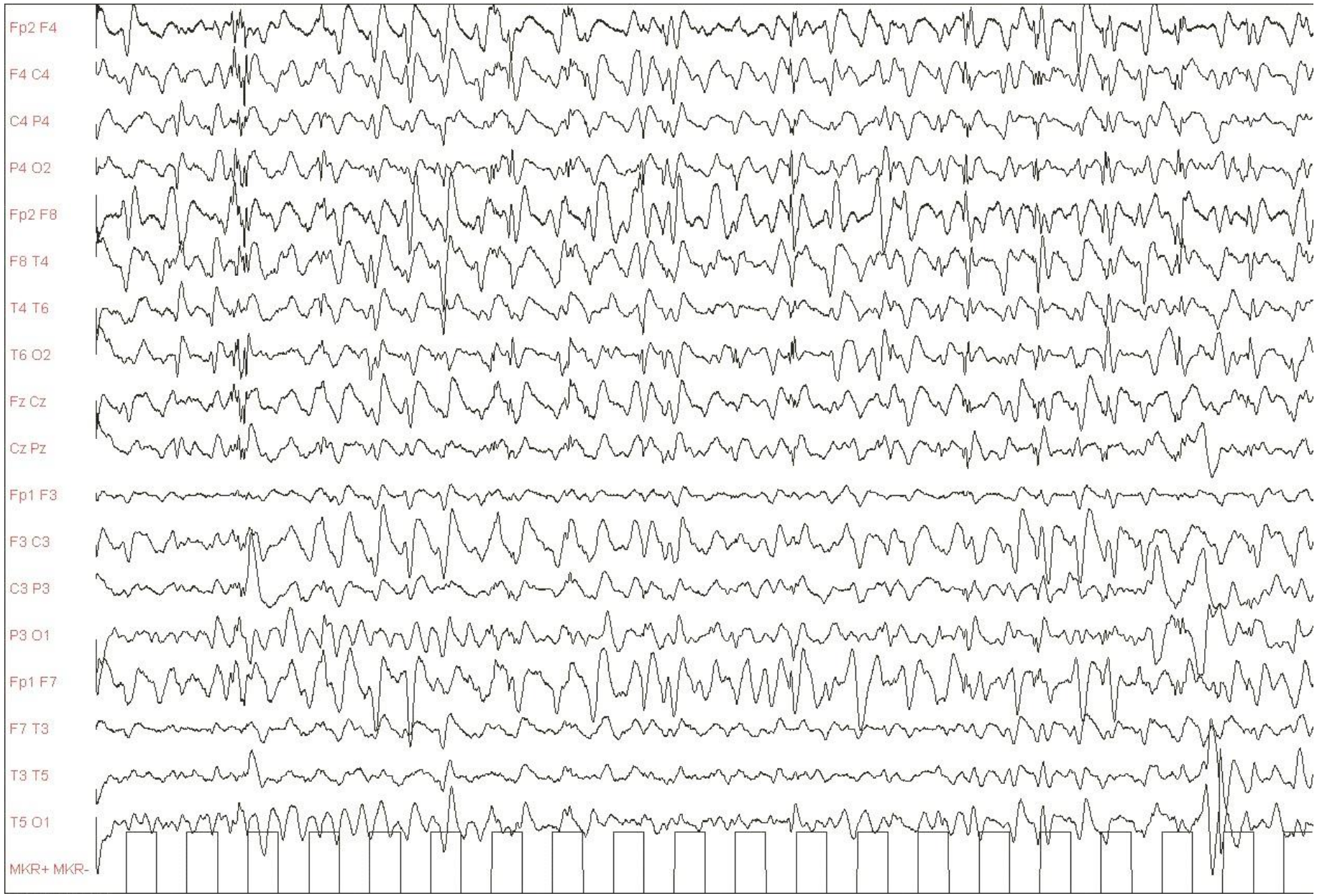
• "visione di immagini terrifiche"

• **EOG:** nella norma, afebbrile.

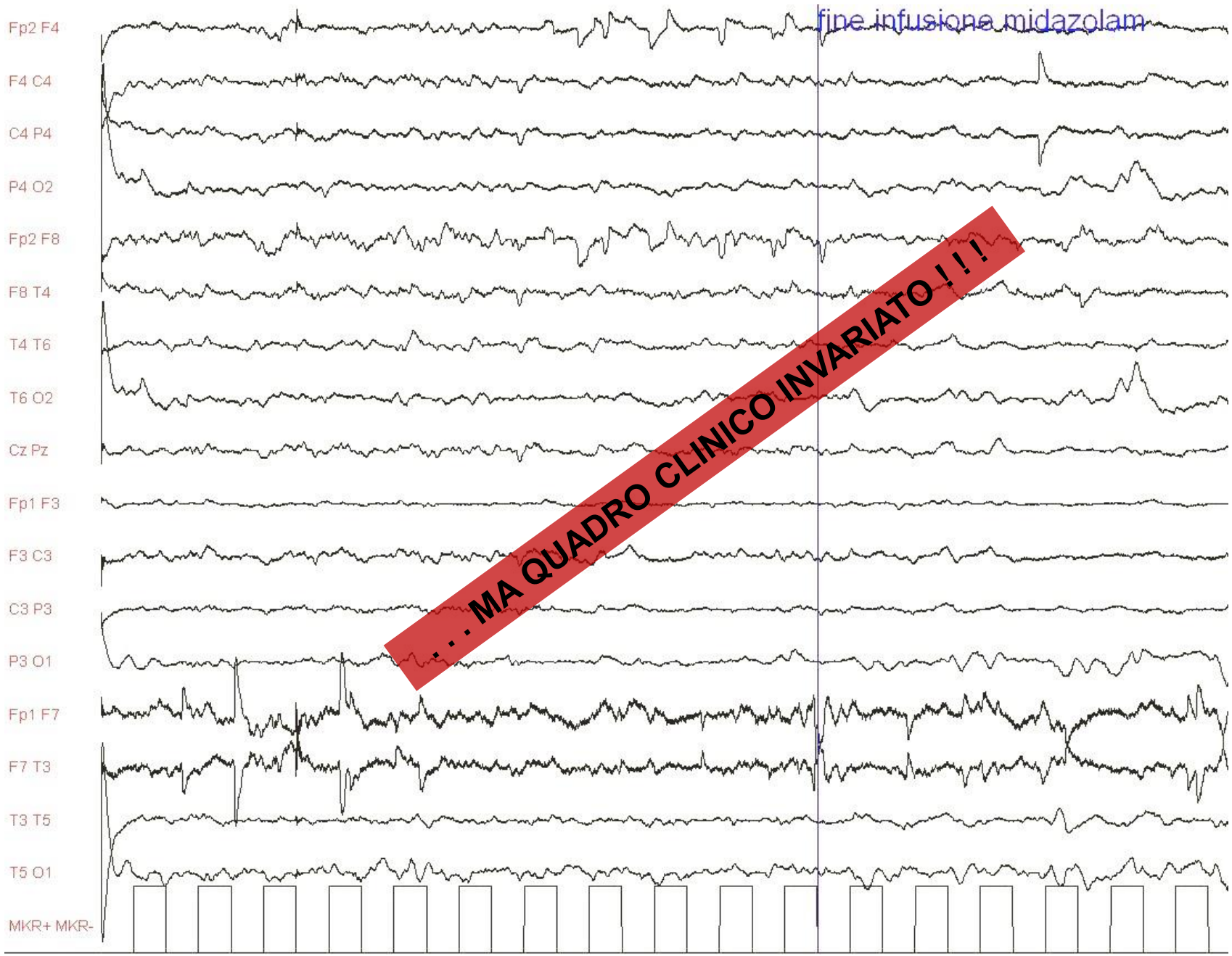
• **EN:** vigile, non collaborante, disorientato, non deficit forza, non segni meningei.

• **TC cranio:** normale.

# SENC?


Fp2 F4
F4 C4
C4 P4
P4 O2
Fp2 F8
F8 T4
T4 T6
T6 O2
Fz Cz
Cz Pz
Fp1 F3
F3 C3
C3 P3
P3 O1
Fp1 F7
F7 T3
T3 T5
T5 O1
MKR+ MKR-

# Midazolam 10 mg ev



•**es. ematochimici** (emocromo, elettroliti, screening tiroideo, vit. B12 e folati, markers epatite B e C, TPHA e VDRL, PCR e VES): nella norma

• **Tc total body, markers tumorali**: negativi.

• **anticorpi anti-antigeni neuronali su CSF e sangue**: negativi

•**screening autoimmune**: negativo.

• **esame liquor (chimico-fisico, citologico e colturale):** normale

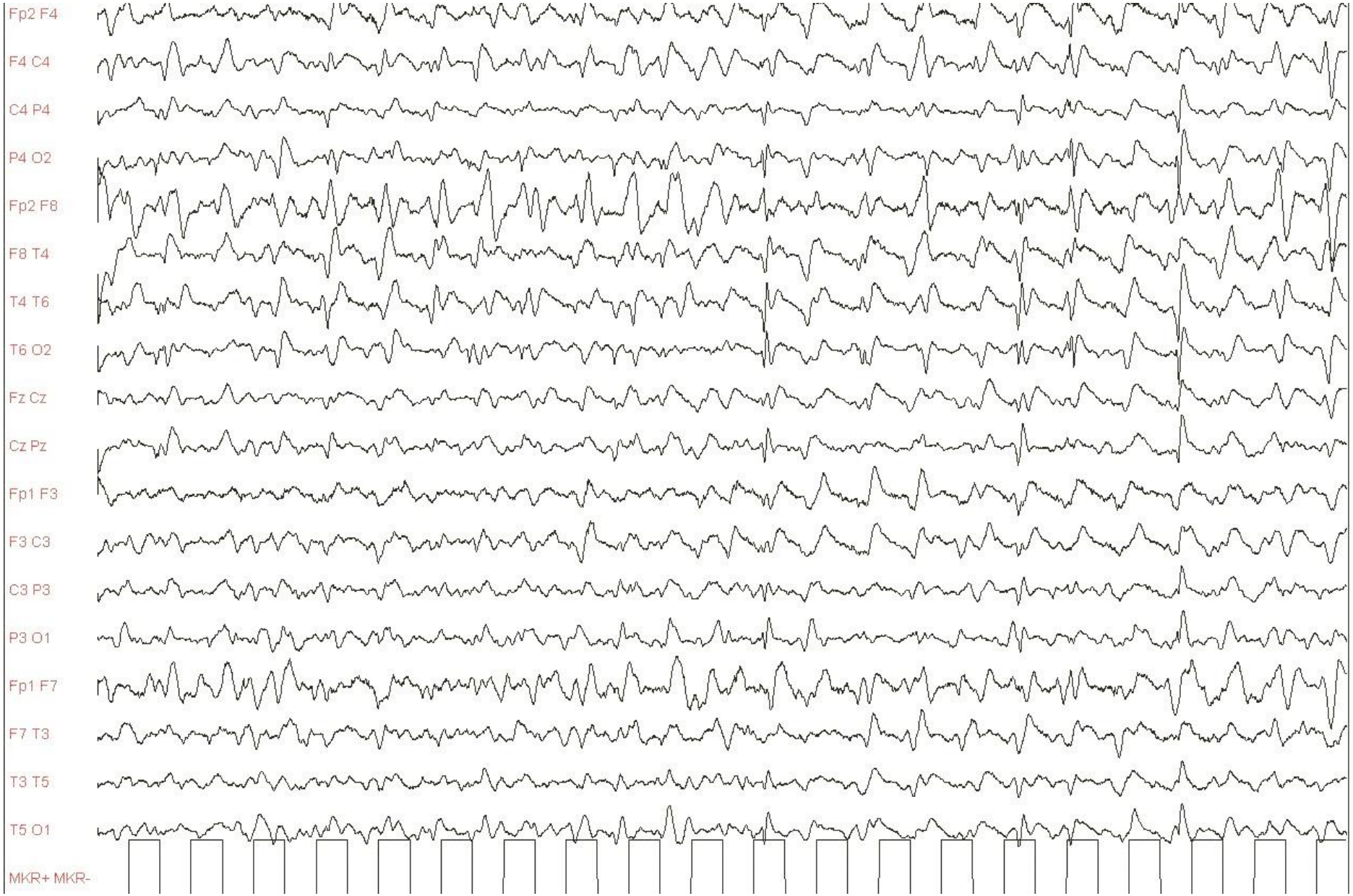
**Terapia eseguita:**

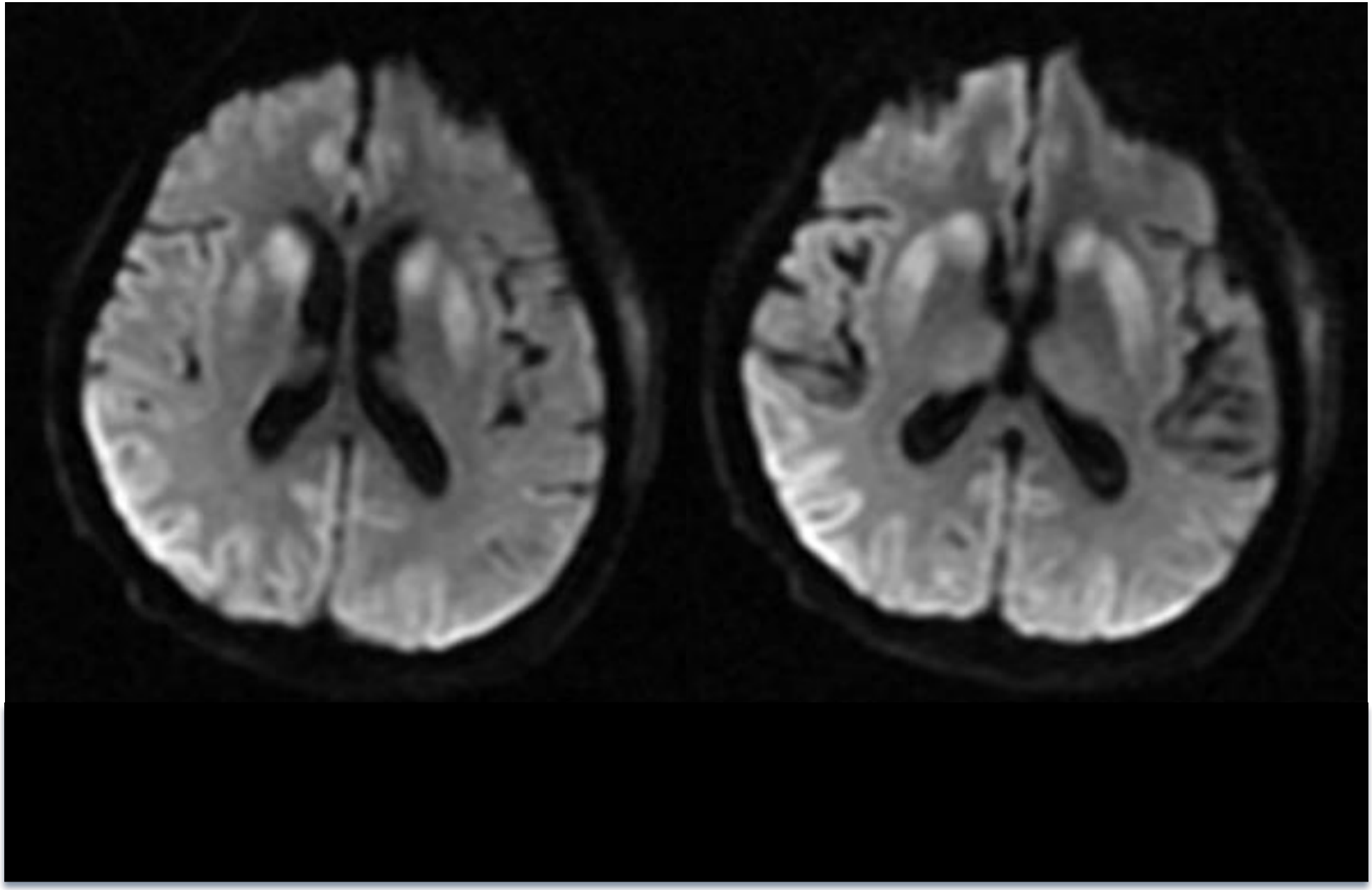
- Midazolam 5 mg
- Lacosamide fino a 400 mg

- Metilprednisolone 1 g in 500 cc di sol. fis. ev per 5 gg

Risultato dopo 5 giorni:

- ✓ quadro clinico invariato
- ✓ EEG invariato





**Analisi genetica e liquorale presso Istituto Superiore di Sanità**

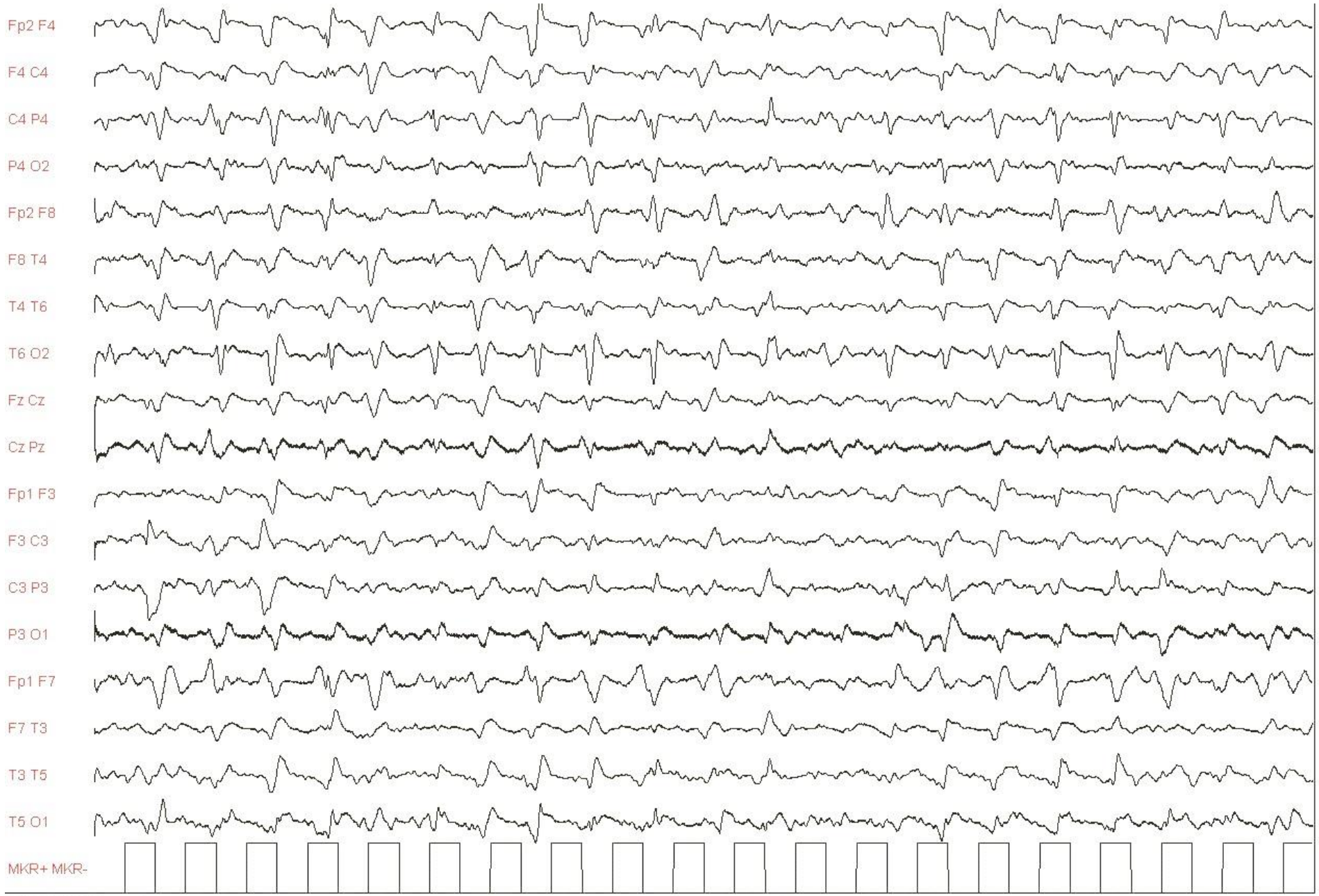
- **Analisi del liquor**: proteina 14-3-3 (Western blot): positiva

- **Analisi del gene della proteina PrP (PRNP):**
  - *Mutazioni puntiformi E200K*
  - Polimorfismo al codone 129 (MV) Met/Met

**Conclusioni diagnostiche:**

**Malattia di Creutzfeldt-Jacob, genetica**

# Dopo 1 mese: mutismo acinetico + EEG tipico



Neurology, 2018

Published Ahead of Print on June 22, 2018 as 10.1212/WNL.0000000000005860
ARTICLE CLASS OF EVIDENCE

**Validation and utilization of amended diagnostic criteria in Creutzfeldt-Jakob disease surveillance**

Peter Hermann, MD, Mareike Laux, MD, Markus Glatzel, MD, Jakob Matschke, MD, Tobias Knipper, MD, Stefan Goebel, MD, Johannes Treig, MD, Walter Schulz-Schaeffer, MD, Maria Cramm, PhD, Matthias Schmitz, PhD, and Inga Zerr, MD

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epicjd@med.uni-goettingen.de

*Neurology*® 2018;0:1-8. doi:10.1212/WNL.0000000000005860

# Malattia di CJD - Criteri

- **Clinica:**

I. Demenza rapidamente progressiva

II.
   a. Mioclono
   b. Disturbi visivi o segni cerebellari
   c. Segni Piramidali o Extrapiramidali
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- **Strumentali**

1) RM encefalo tipica
2) EEG Tipico
3) 14-3-3 nel liquor.
4) RT QuIC

- **Possibile:** I + 2 tra i criteri clinici 2 e durata < 2 anni
- **Probabile:**

Criterio clinico I e 2 tra criteri clinici II + 1 esame strumentale «positivo» (1-3)
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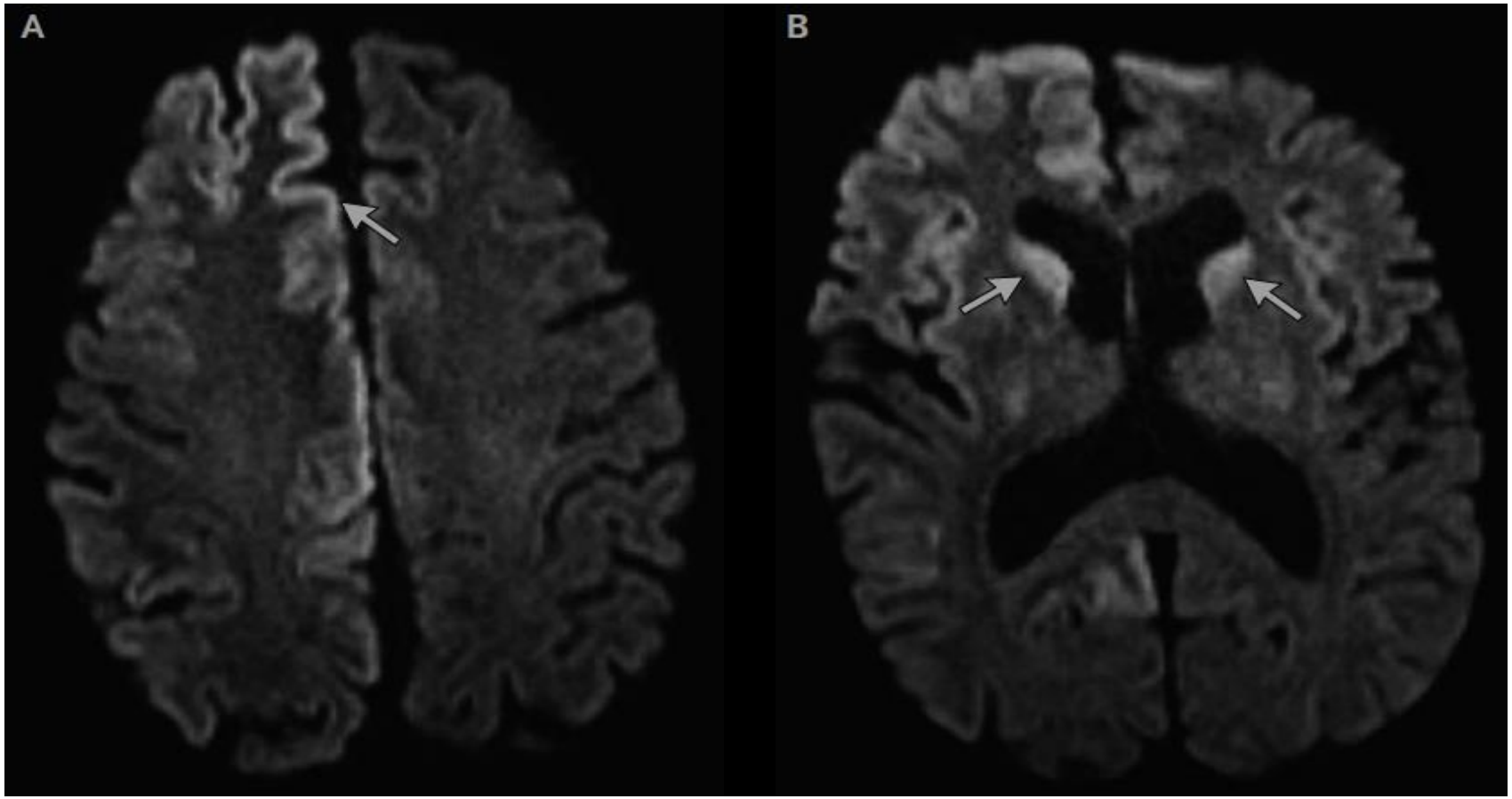
# RM tipica

- Iperintensità DWI/FLAIR di nucleo caudato/putamen e/o almeno 2 regioni corticali.

*Tschampa et al., 2005*



RESIDENT & FELLOW SECTION

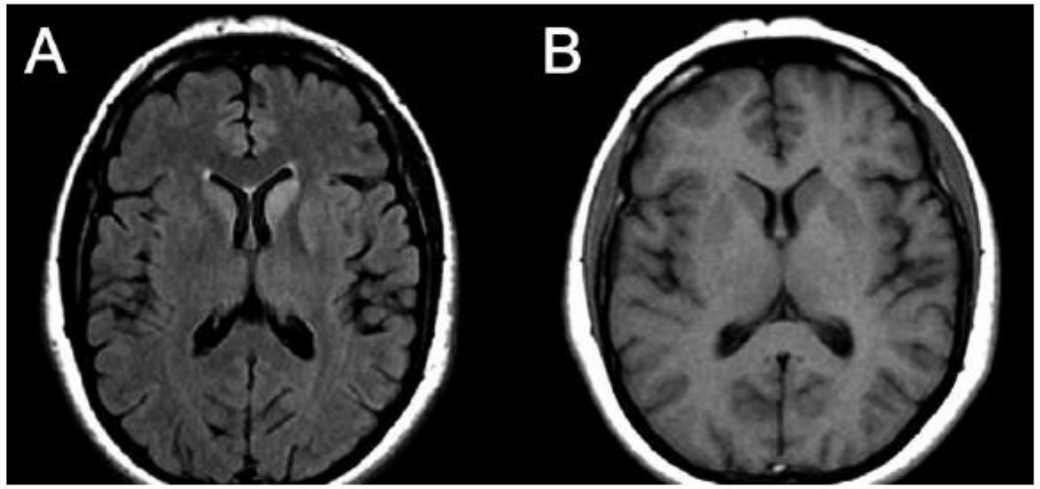
Section Editor
Mitchell S.V. Elkind, MD, MS

# Teaching NeuroImages: Pseudohypertrophic cerebral cortex in end-stage Creutzfeldt-Jakob disease

Sara Gasparini, MD
Edoardo Ferlazzo, PhD
Damiano Branca, MD
Angelo Labate, MD
Vittoria Cianci, PhD
Maria Adele Latella, PhD
Umberto Aguglia, MD

*Neurology* January 8, 2013 vol. 80 no. 2 e21

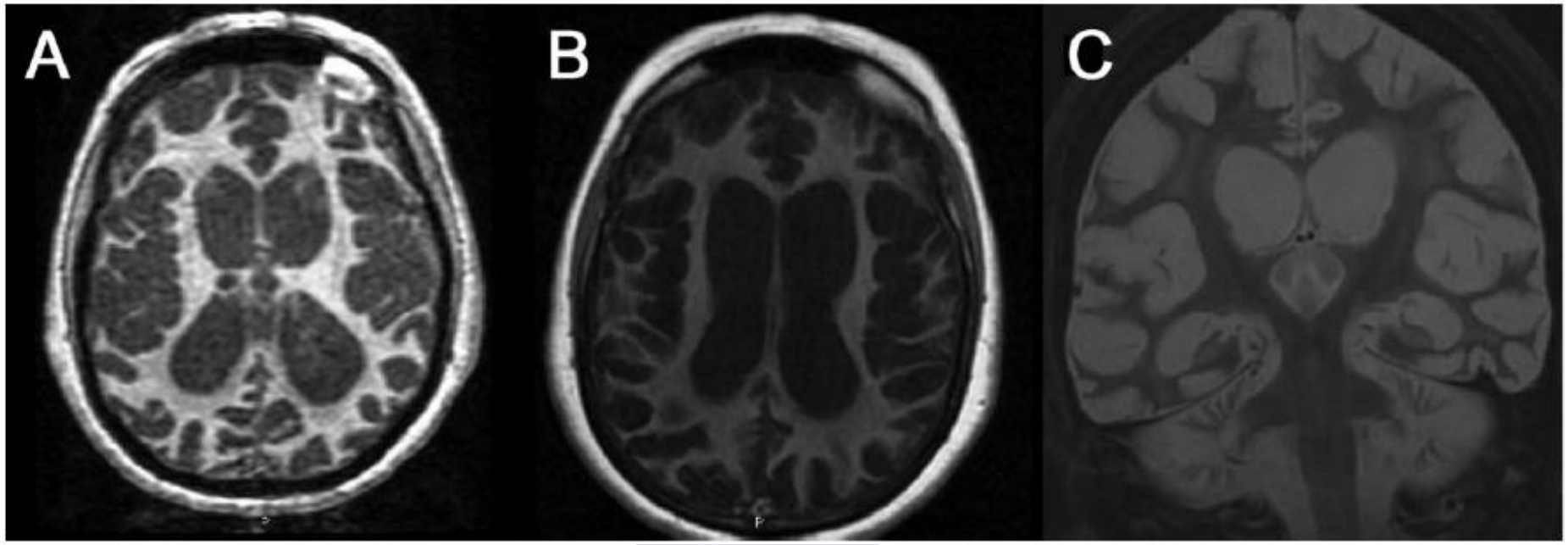
MRI at admission (*PRNP* E200K mutation).




FLAIR

T1-weighted

MRI 1 year later




FLAIR

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T2-weighted

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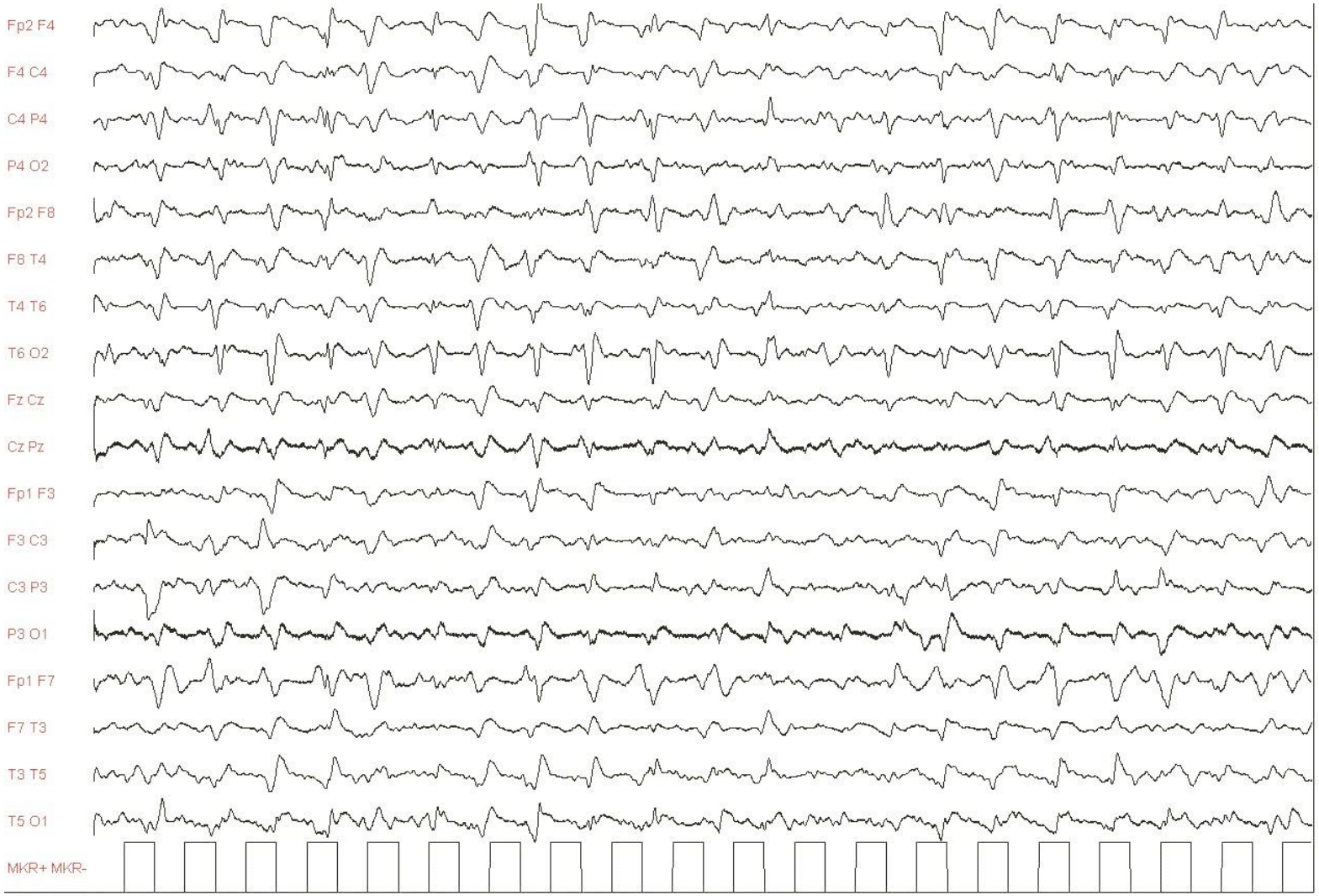
# EEG tipico




Può mancare in fasi precoci!!

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ORIGINAL ARTICLE

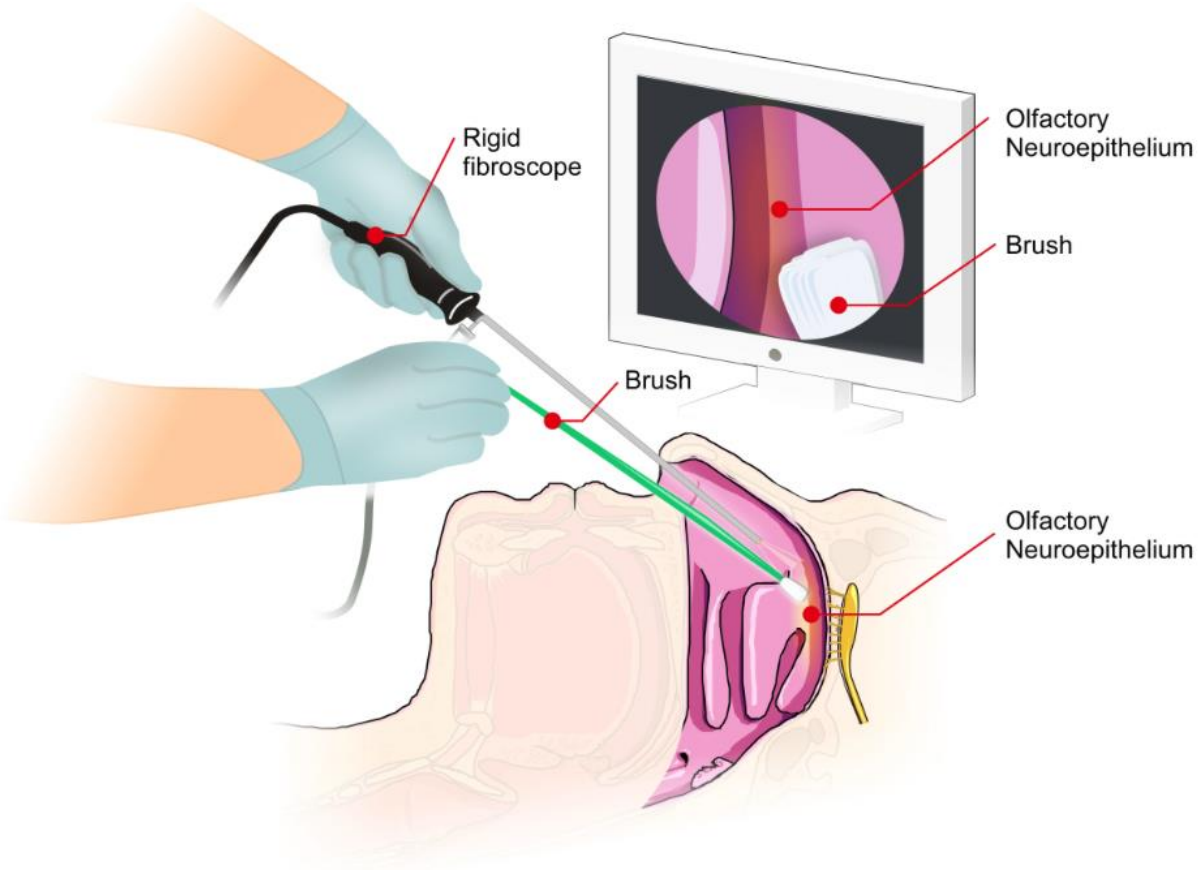
August 7, 2014
N Engl J Med 2014; 371:519-529
DOI: 10.1056/NEJMoa1315200

# A Test for Creutzfeldt–Jakob Disease Using Nasal Brushings

Christina D. Orrú, Ph.D., Matilde Bongianni, Ph.D., Giovanni Tonoli, M.D., Sergio Ferrari, M.D., Andrew G. Hughson, M.S., Bradley R. Groveman, Ph.D., Michele Fiorini, Ph.D., Maurizio Pocchiari, M.D., Salvatore Monaco, M.D., Byron Caughey, Ph.D., and Gianluigi Zanusso, M.D., Ph.D.

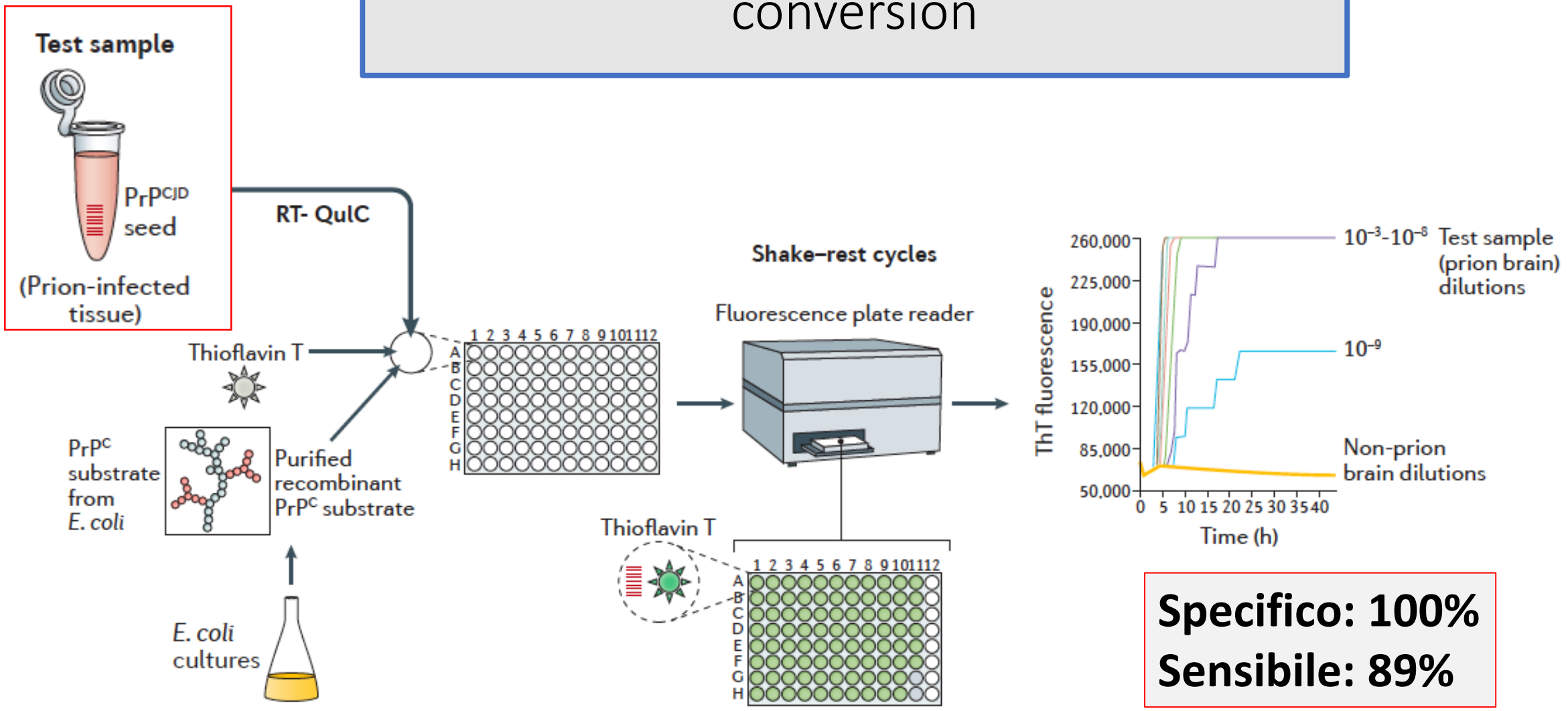
Breve vasocostrizione, visualizzare il turbinato medio ed inserire il tampone ruotato delicatamente per il brushing. Il tampone viene quindi immerso in una provetta contenente fisiologica.

**Durata**: 5 min.



1) Liquor
2) Neuroepitelio olfattivo

# **RT-QuIC:** real-time quaking-induced conversion




**Specifico: 100%**
**Sensibile: 89%**

RESIDENT & FELLOW SECTION

# Pearls & Oy-sters: Challenging diagnosis of Gerstmann-Sträussler-Scheinker disease

## Clinical and imaging findings

Min Ju Kang, MD, Jeewon Suh, MD, Seong Soo An, PhD, SangYun Kim, MD, PhD, and Young Ho Park, MD, PhD

*Neurology*® 2019;92:101-103. doi:10.1212/WNL.0000000000006730

**Correspondence**
Dr. Park
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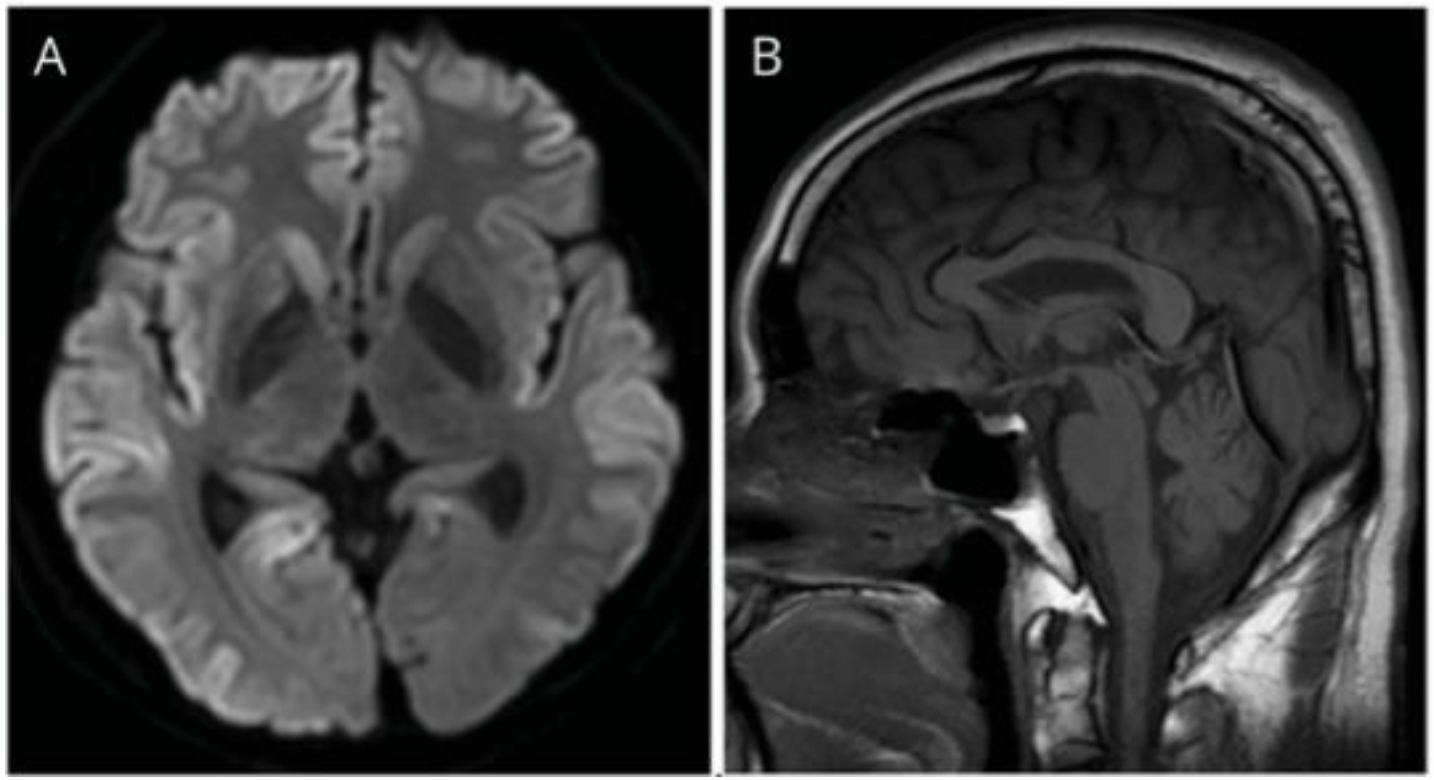
**59 casi in Italia dal 1993 ad oggi**




- ✓ **Età esordio**: 5-6 decade
- ✓ **Durata media malattia**: 5-6 anni (range: 3 mesi-13 anni)
- ✓ **Storia familiare**: negativa in 16.5%
- ✓ **RM tipica** (iperintensità di segnale in corteccia, nucleo caudato o putamen): 20.6%.
- ✓ **EEG pseudoperiodico**: raro.
- ✓ **Proteina 14.3.3. in CSF**: 50%
- ✓ **Analisi molecolare PRNP**: mutazione più comune P102L.

**Sospettare sempre in pz con atassia di n.d.d., con o senza familiarità. Probabilmente sotto diagnosticata.**

# Malattia di CJ Variante – Criteri

Health et al., 2010

**3 casi in Italia, ultimo 2016!**

I

- **a) Disturbo neuropsichiatrico progressivo**
- b) Durata della malattia > 6 mesi
- c) Indagini di routine non suggeriscono una diagnosi alternativa
- d) Anamnesi negativa per eventuali fattori iatrogeni
- e) Indagine genetica o anamnesi familiare negativa per EST genetiche o familiari

IV

- **a) Biopsia tonsillare positiva**

II

- a) Sintomi psichiatrici precoci
- b) Sintomi sensoriali di dolore persistente
- c) Atassia
- d) Mioclono o corea o distonia
- e) Demenza

III

- **a) EEG non tipico** per MCJc nelle fasi precoci di malattia
- **b) Iperintensità bilaterale del segnale nel pulvinar** alla RMN

- Possibile:

Criterio I + 4/5 di II + 3 A

- Probabile:

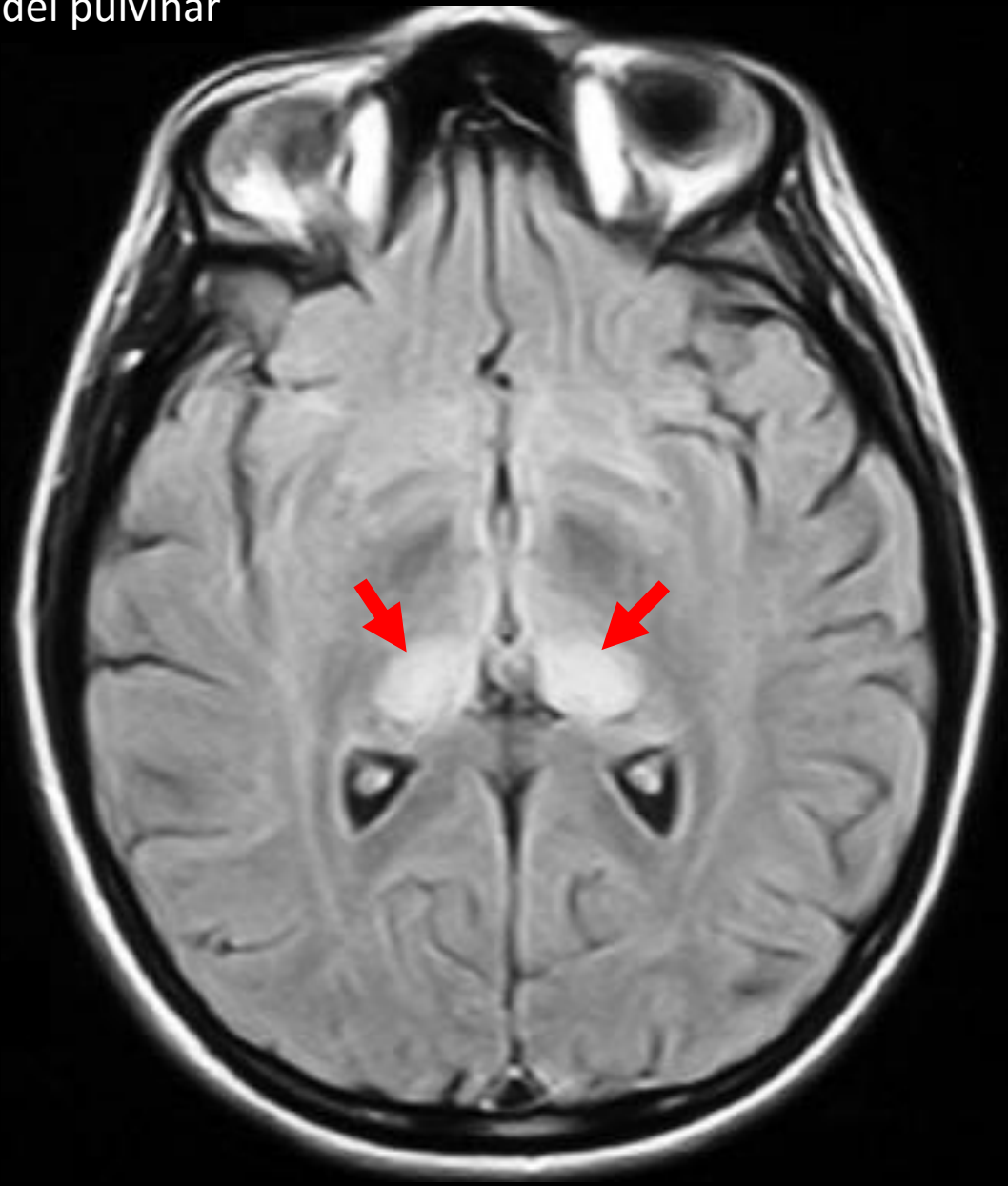
Criterio I e 4 di II e IIIAa e IIIb

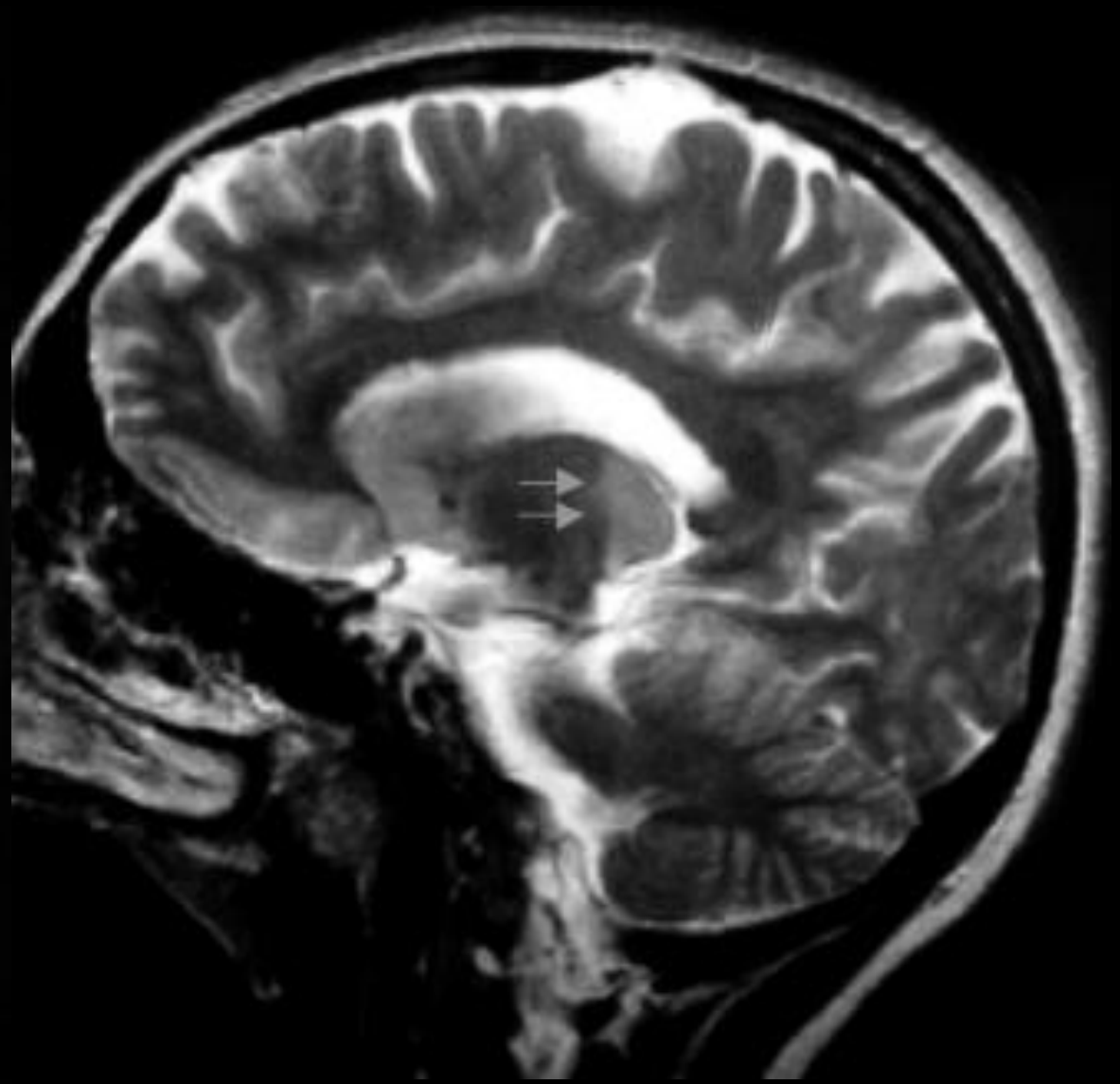
Criterio I e IVa

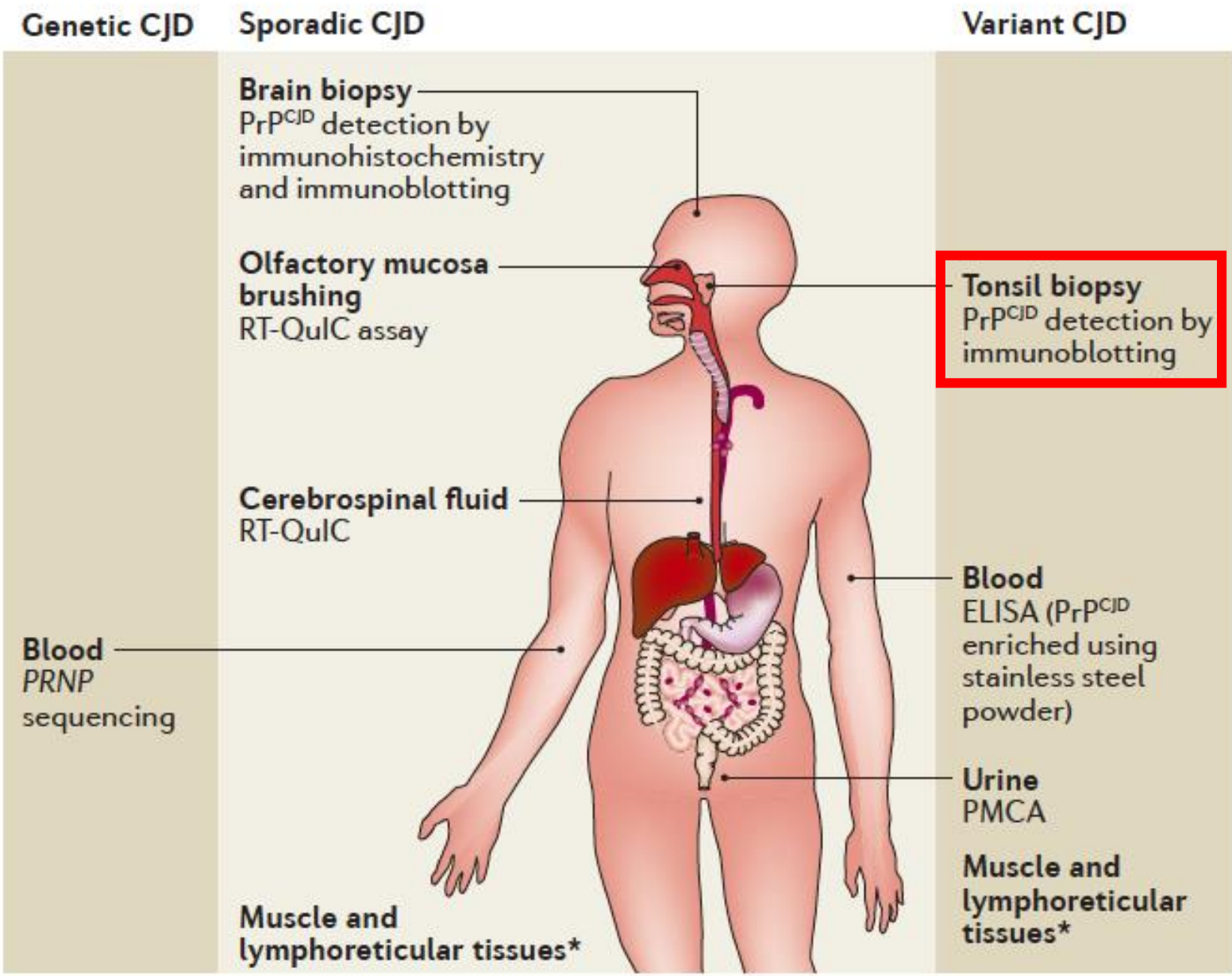
- **Certa:**

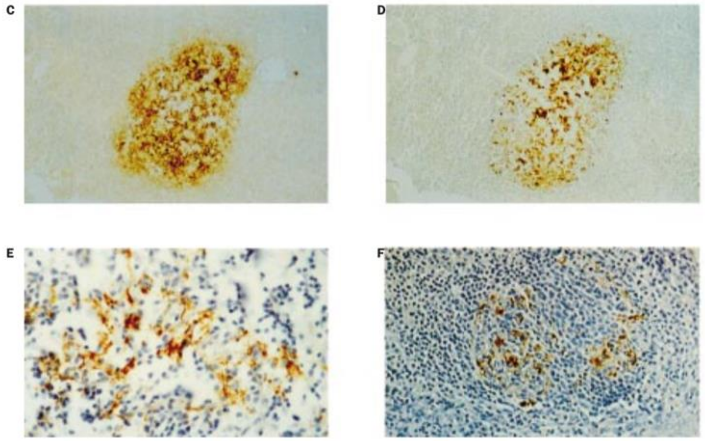
Criterio I più conferma neuropatologica

Segno del pulvinar



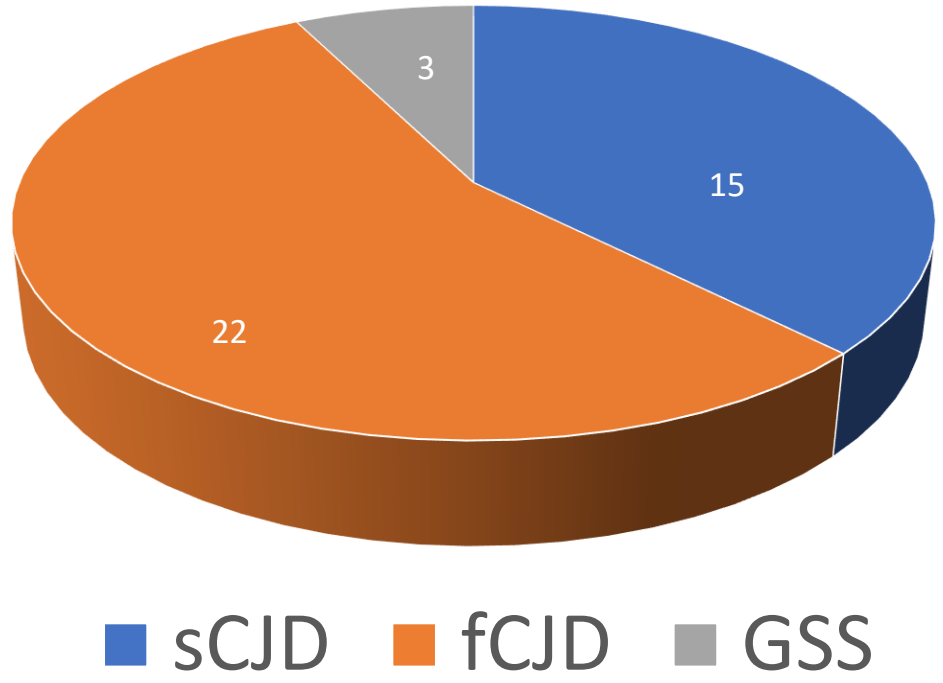



Genetic CJD
Sporadic CJD
Variant CJD
Brain biopsy
PrP^CJD detection by immunohistochemistry and immunoblotting
Olfactory mucosa brushing
RT-QuIC assay
Cerebrospinal fluid
RT-QuIC
Blood
PRNP sequencing
Muscle and lymphoreticular tissues*
Tonsil biopsy
PrP^CJD detection by immunoblotting
Blood
ELISA (PrP^CJD enriched using stainless steel powder)
Urine
PMCA
Muscle and lymphoreticular tissues*


C
D
E
F

# Malattie da Prioni GOM/RC periodo 2000-2019: 40 pazienti

17 M, 23F



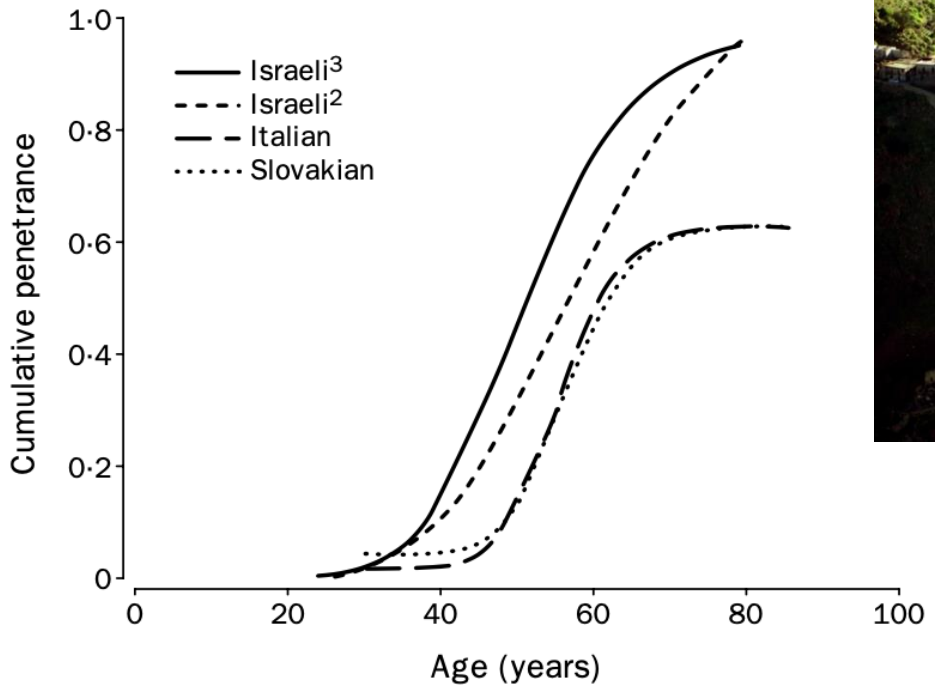

- sCJD: CJD sporadica
- fCJD: CJD familiare (mutazione codone 200, gene PRNP)
- GSS: sindrome di Gerstmann-Straussler-Scheinker (mutazione codone 102, gene PRNP)

THE LANCET • Vol 352 • December 19/26, 1998

# High incidence of Creutzfeldt-Jakob disease in rural Calabria, Italy

*Marco D'Alessandro, Rosella Petraroli, Anna Ladogana, Maurizio Pocchiari*

**Cluster di 17 casi di CJD familiare in pz di piccola area rurale (142000 m2 ) della Calabria**




**Cumulative age-dependent probability of developing CJD**

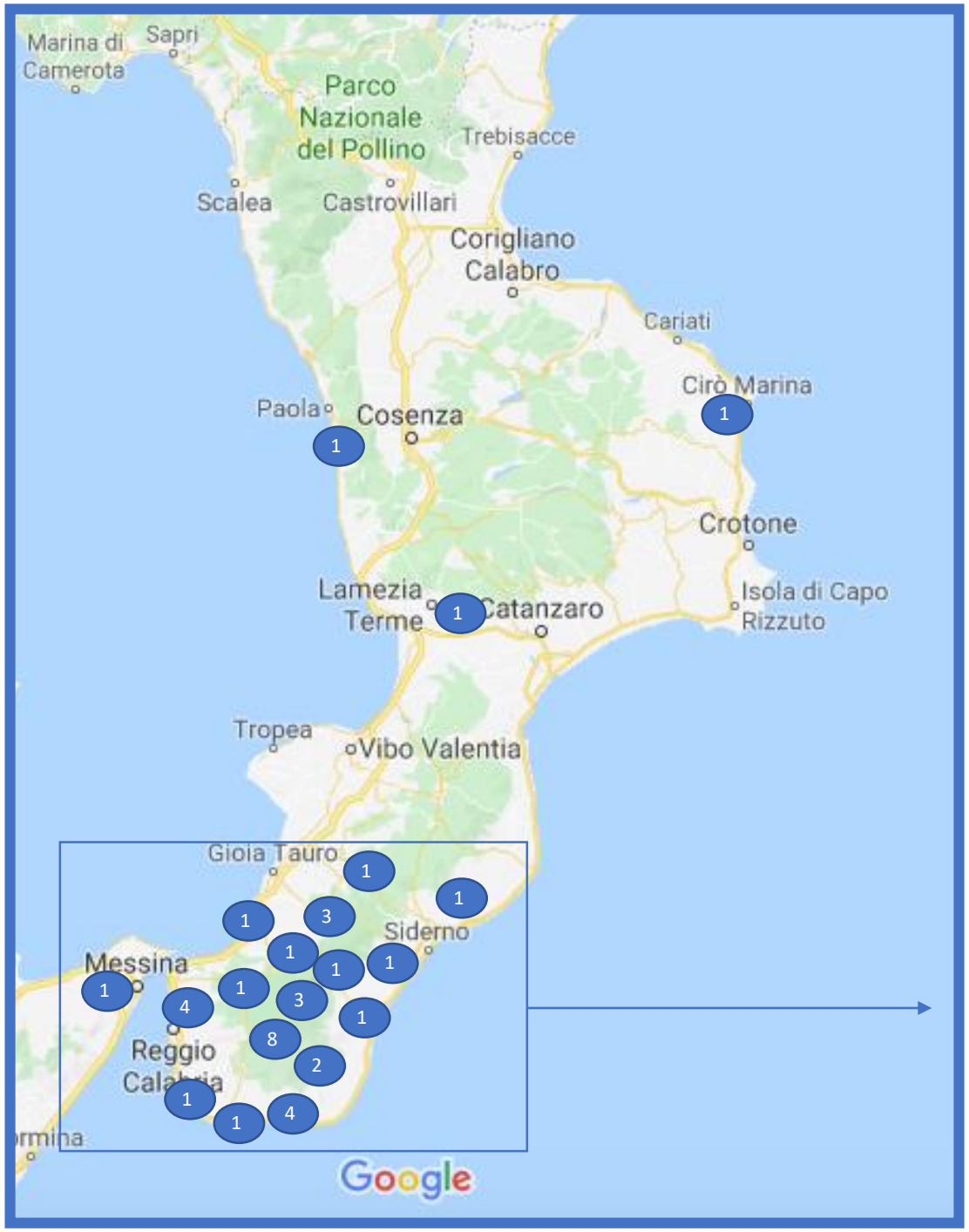
**Probabilità per i portatori della mutazione E200K di sviluppare malattia a 70 ani: 61%**

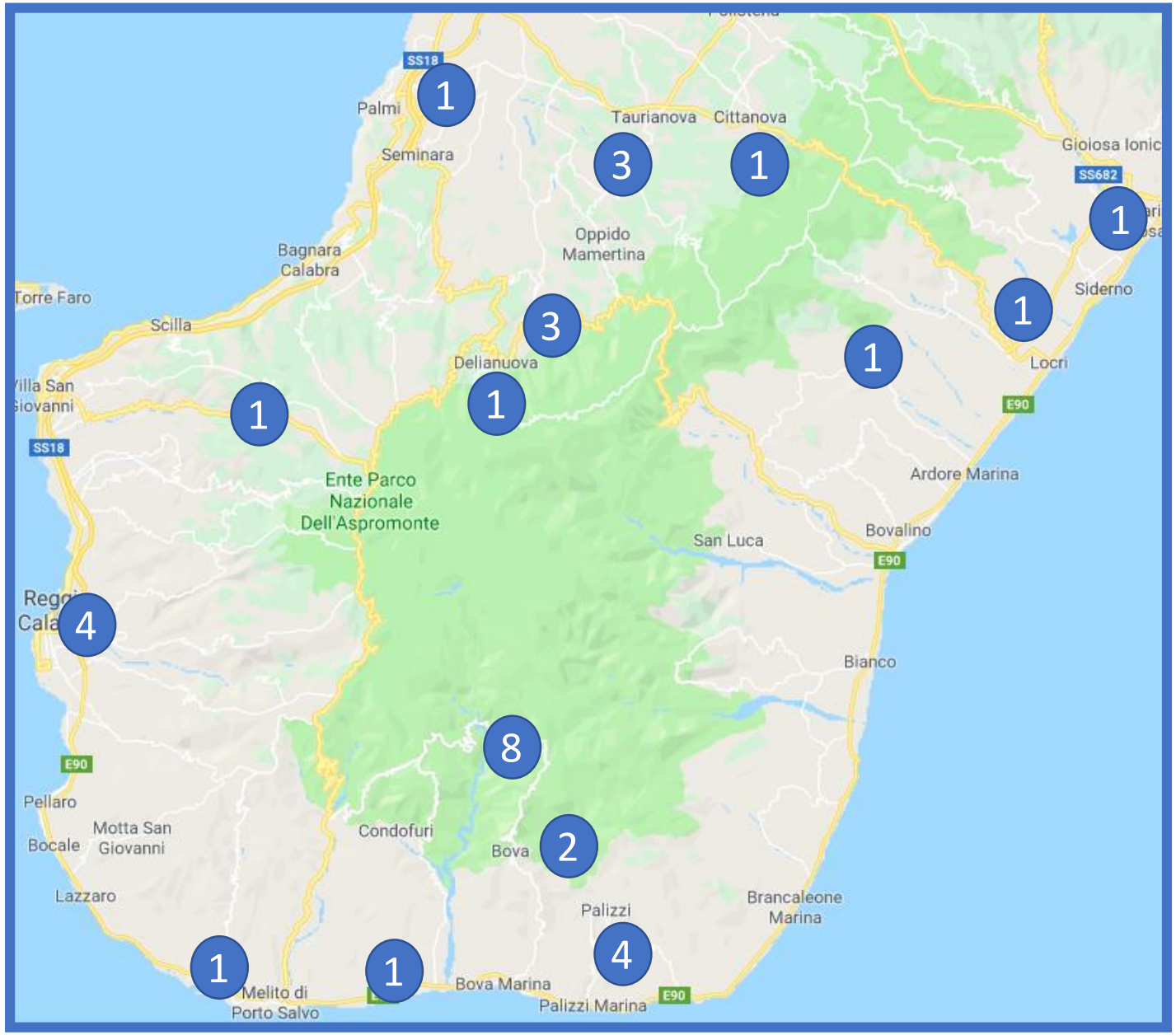
# GRAZIE!

Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

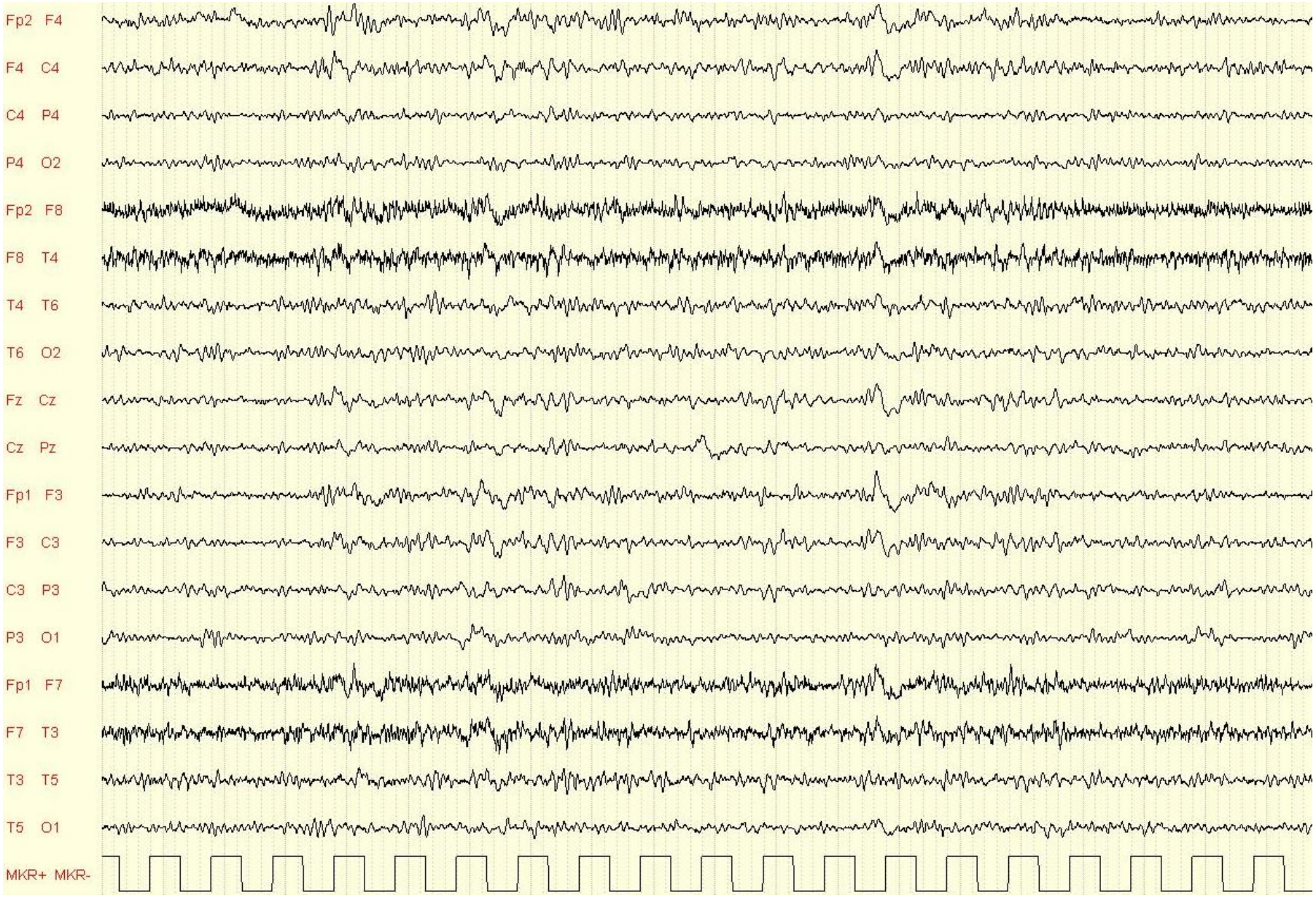
*Riunione annuale SIN Calabria*

***23 novembre 2019***


Marina di Camerota
Sapri
Parco Nazionale del Pollino
Trebisacce
Scalea
Castrovillari
Corigliano Calabro
Cariati
Cirò Marina
Paola
Cosenza
Crotone
Lamezia Terme
Catanzaro
Isola di Capo Rizzuto
Tropea
Vibo Valentia
Gioia Tauro
Siderno
Messina
Reggio Calabria
Google


SS18
Palmi
Seminara
Taurianova
Cittanova
Gioiosa Ionic
SS682
Siderno
Oppido Mamertina
Bagnara Calabra
Torre Faro
Scilla
Delianuova
Locri
E90
Ente Parco Nazionale Dell'Aspromonte
Ardore Marina
San Luca
Bovalino
Bianco
Pellaro
Motta San Giovanni
Bocale
Condofuri
Bova
Lazzaro
Palizzi
Brancaleone Marina
Melito di Porto Salvo
Bova Marina
Palizzi Marina

# EEG: CJD FASI PRECOCI

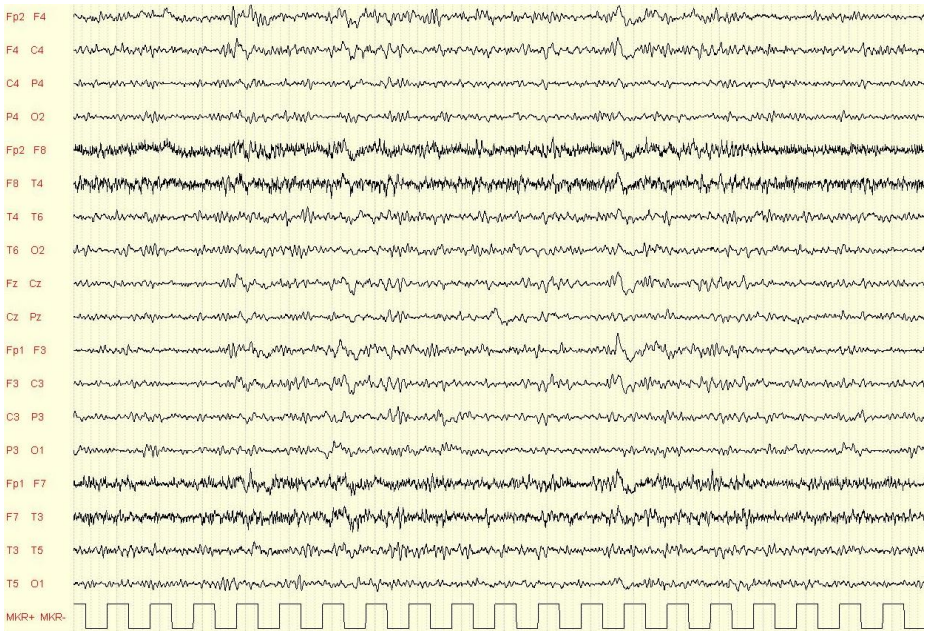


International Journal of Neural Systems, Vol. 26, No. 0 (2016) 1650039

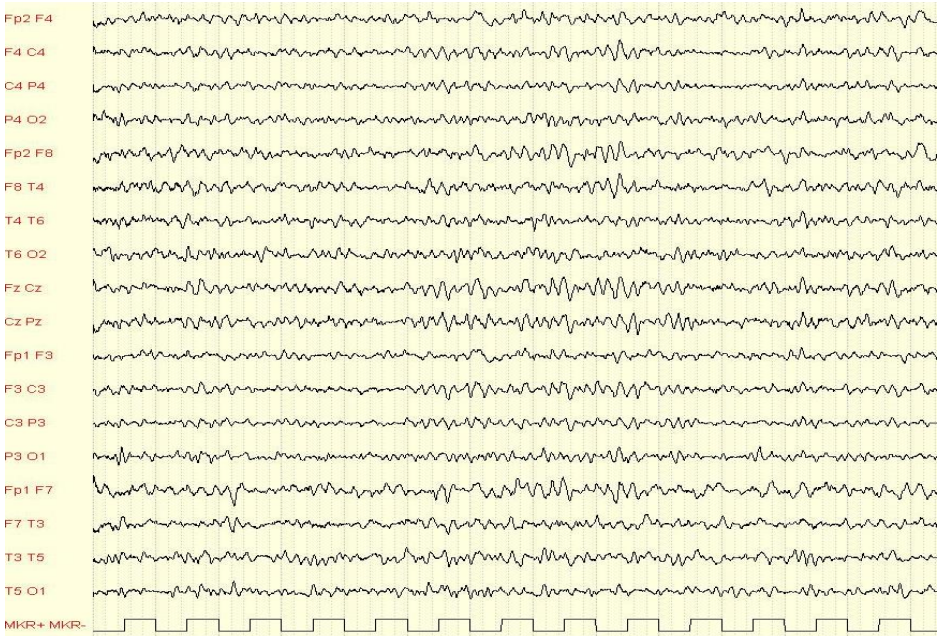
# Deep Learning Representation from Electroencephalography of Early-Stage Creutzfeldt-Jakob Disease and Features for Differentiation from Rapidly Progressive Dementia

Francesco Carlo Morabito*,**, Maurizio Campolo*, Nadia Mammone‖, Mario Versaci*, Silvana Franceschetti†, Fabrizio Tagliavini†, Vito Sofia‡, Daniela Fatuzzo‡, Antonio Gambardella§, Angelo Labate§, Laura Mumoli§, Giovanbattista Gaspare Tripodi¶, Sara Gasparini§,¶, Vittoria Cianci¶, Chiara Sueri¶, Edoardo Ferlazzo§,¶ and Umberto Aguglia§,¶

A: EEG di paziente con CJD.




B: EEG di paziente con encefalopatia cortisono-sensibile.



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| Patients | Sample | Gender (M) | Mean age (SD) |
|---|---|---|---|
| CJD | 20 | 8 M | 59.4 (14.8) |
| AD | 13 | 8 M | 79.2 (7.0) |
| RPD | 17 | 9 M | 63.1 (8.1) |
| HC | 26 | 11 M | 59.5 (12.4) |

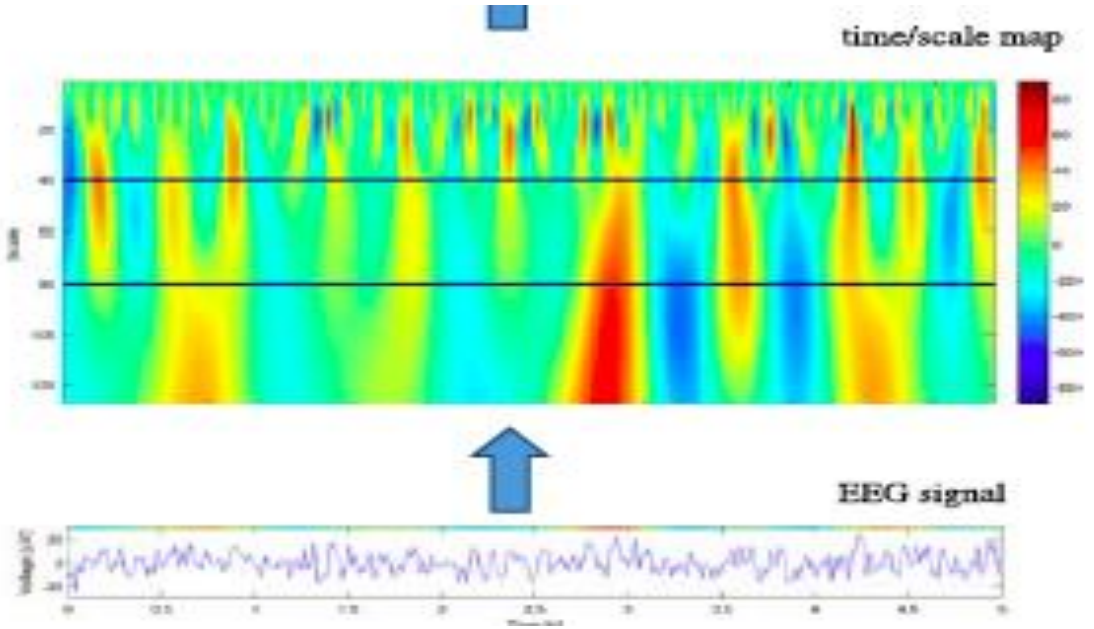

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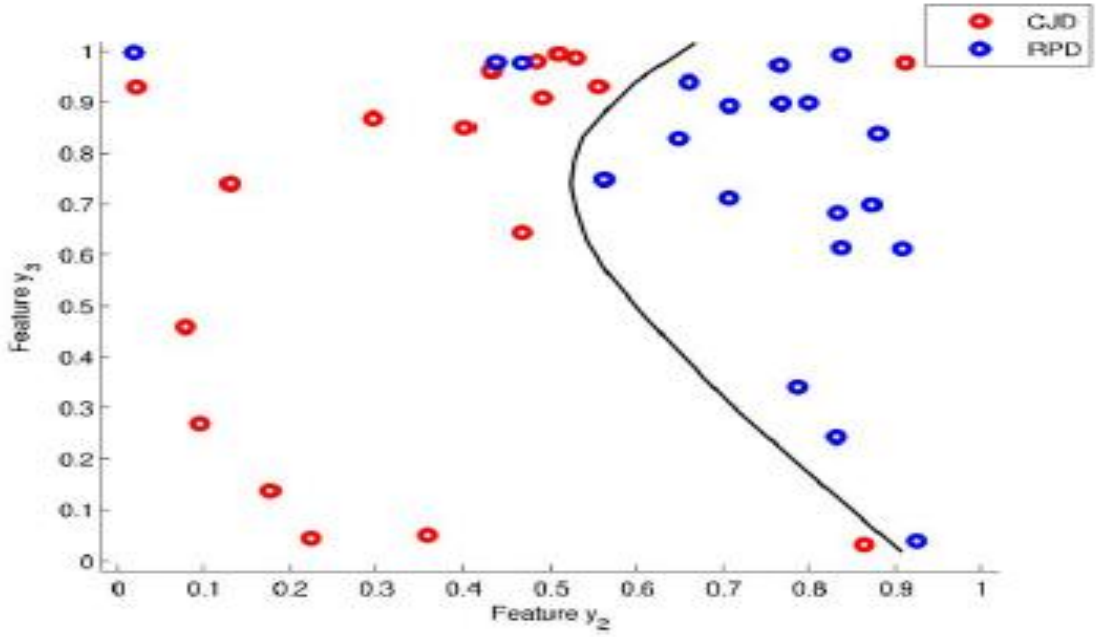
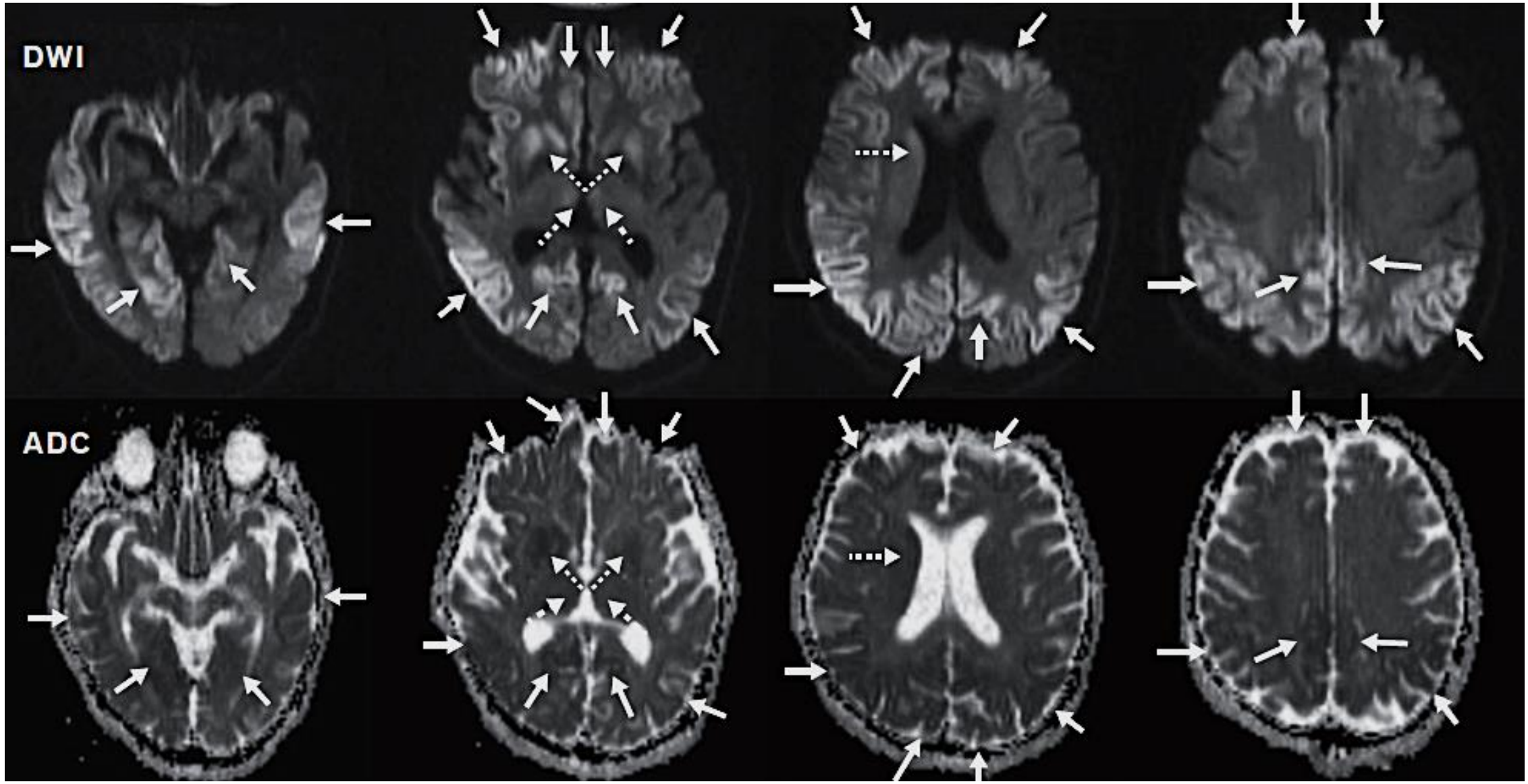
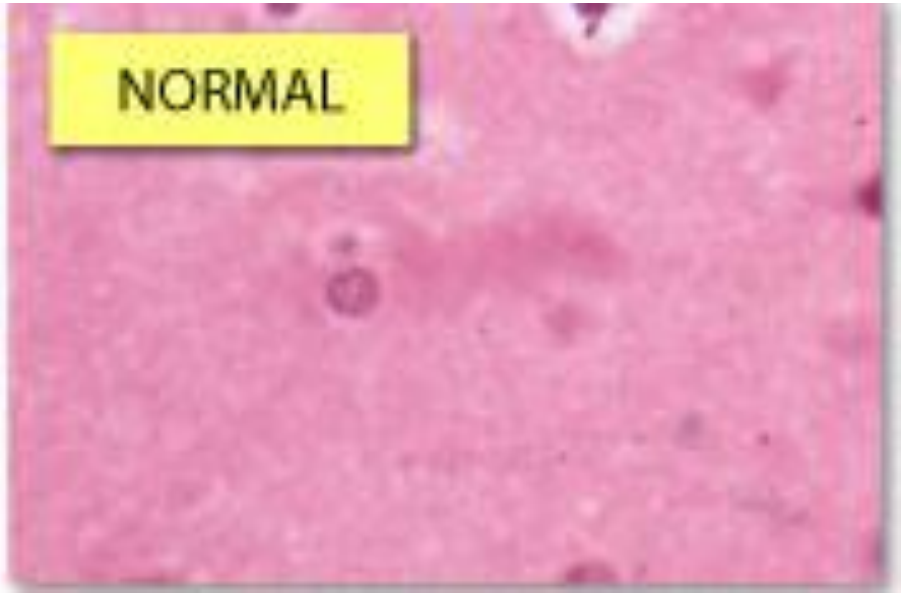
Table 4. Performance on the validation step of the 20-10-2 classifier for the three problems at hand, with supervised fine tuning step.

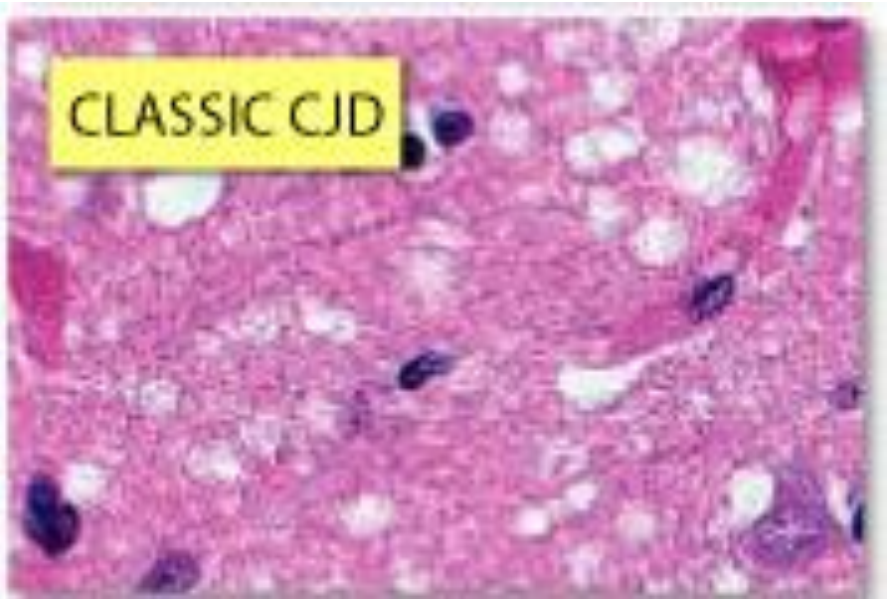
| | MLP (20-10-2 classifier, test results) | | |
|---|---|---|---|
| | Avg Acc (%) | Avg Sens (%) | Avg Spec (%) |
| CJD versus RPD | 89 | 92 | 89 |
| CJD versus AD | 88 | 94 | 85 |
| CJD versus HC | 87 | 86 | 84 |




DWI
ADC

# Alterazioni spongiformi nella malattie da prioni umane

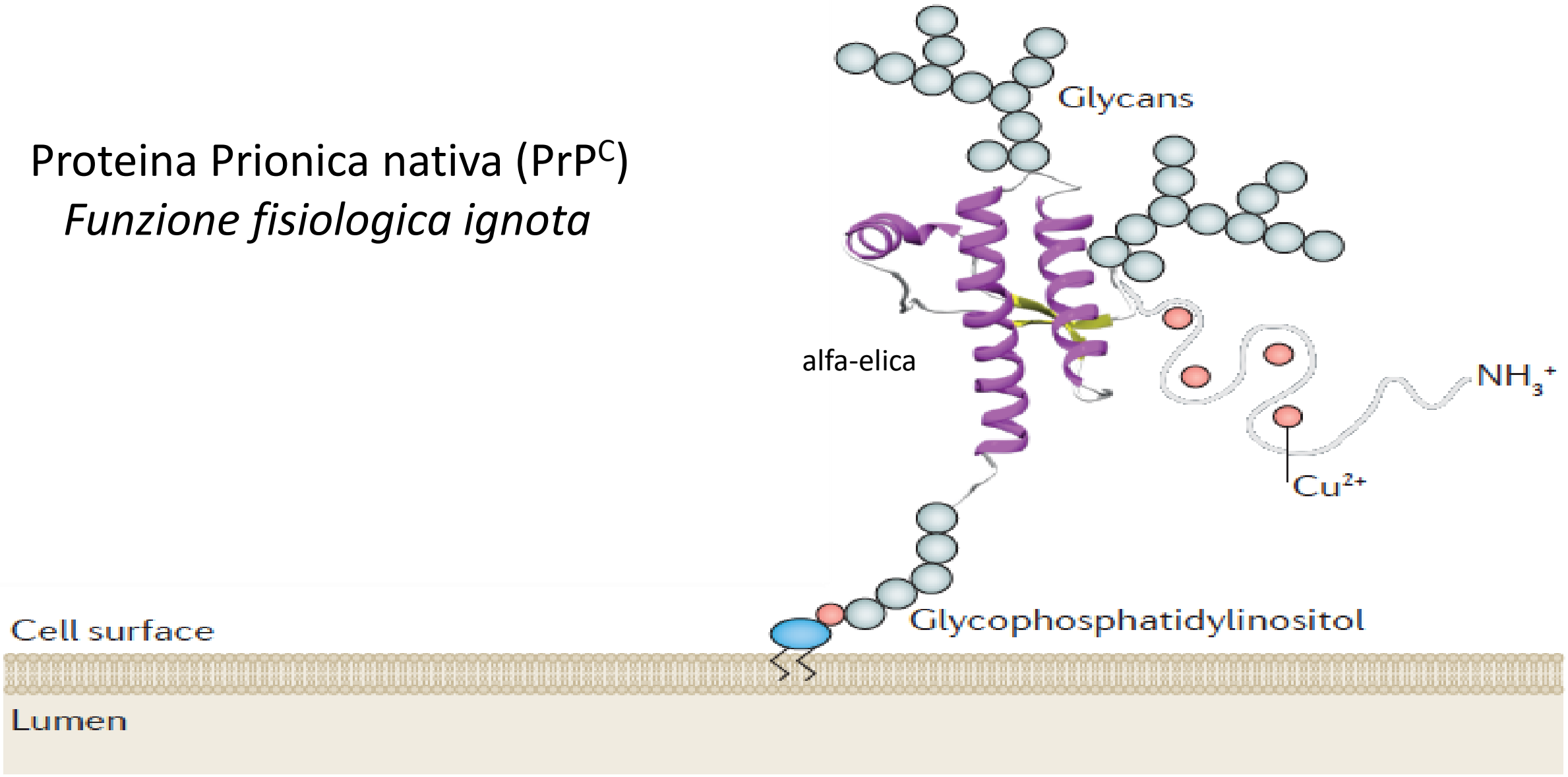


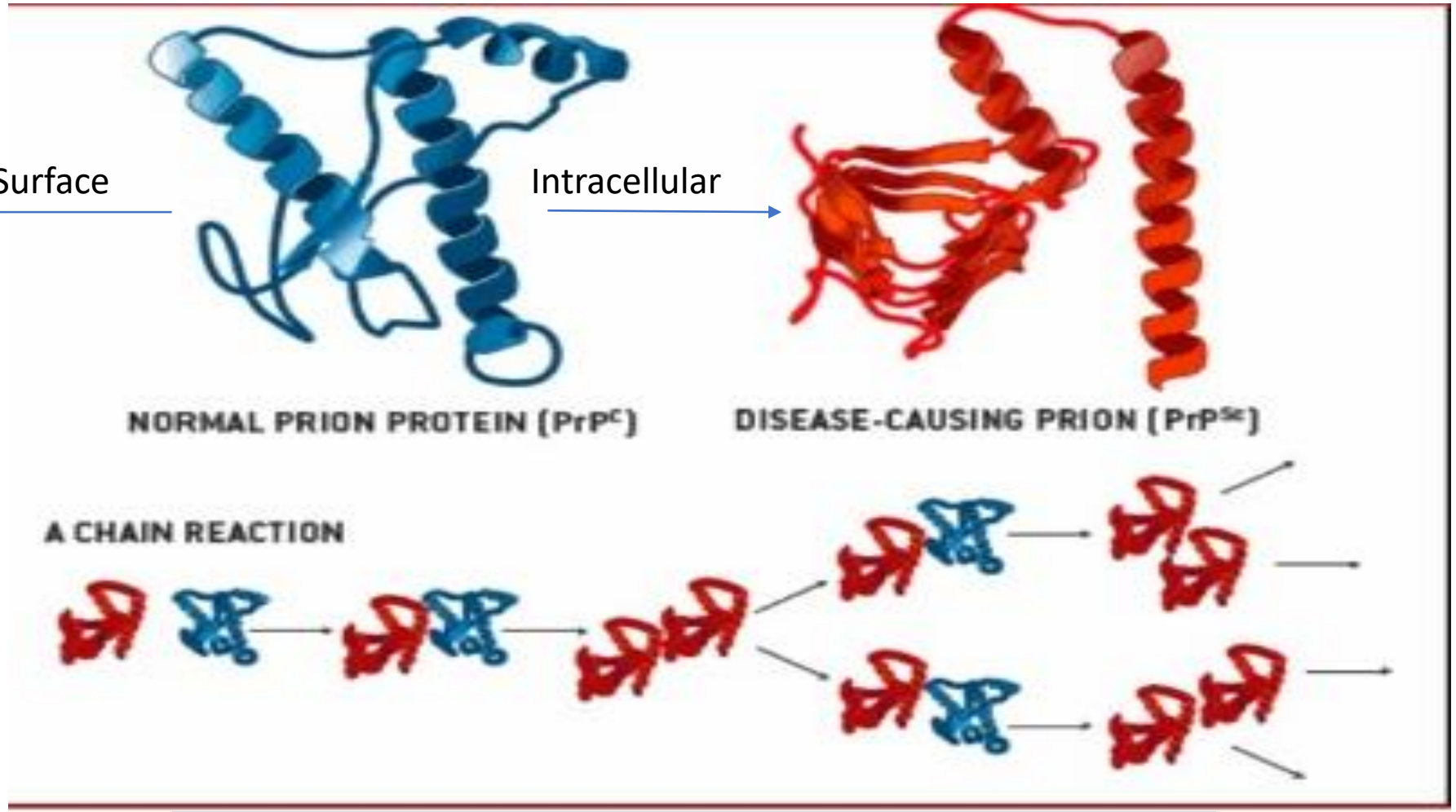




Colorazione ematossilina-eosina: vacuoli nel tessuto cerebrale, perdita di neuroni, gliosi.

Proteina Prionica nativa ($PrP^C$)

*Funzione fisiologica ignota*






PrPsc: PrPc cambia conformazione e ha capacità di auto-propagarsi: la proteina mutata “infetta” le molecole fisiologiche causandone la trasformazione

# Malattie da prioni umane

- ✓ Malattia di Creutzfeldt-Jakob (sporadica, genetica, iatrogena).
- ✓Sindrome di Gerstmann-Sträussler-Scheinker
- ✓Variante della Malattia di Creutzfeldt-Jakob
- ✓Insonnia Fatale Familiare
- ✓Kuru

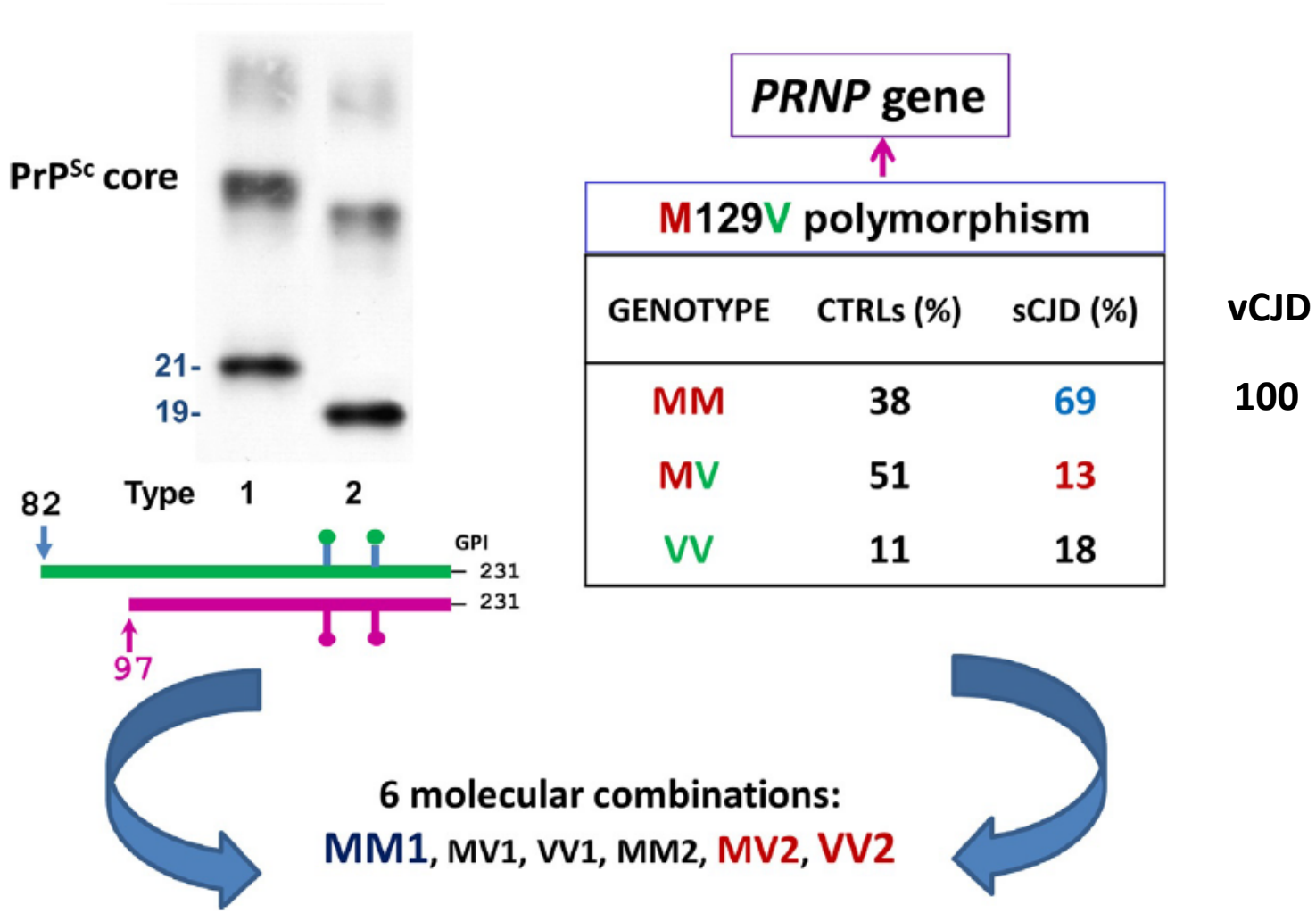



**Fig. 9.2.** Molecular basis of phenotypic variability in sporadic Creutzfeldt–Jakob disease (sCJD). $PrP^{TSE}$ core fragments type 1 and type 2 differ for the primary site of cleavage by PK (in position 82 and 97, respectively). The relative percentage of codon 129 genotypes in both controls (CTRLs) and sCJD refers to the Caucasian population. The combination of each of the two $PrP^{TSE}$ types with the three codon 129 genotypes generate six molecular groups, with MM1, VV2, and MV2 accounting for the large majority of cases.

**Distinctive clinical and pathological features of sporadic Creutzfeldt–Jakob disease subtypes**

| | Molecular disease subtype | Median age at onset (range) (years) | Median duration (range) (months) | Most prominent clinical signs/ symptoms | Distinctive histopathologic features |
|---|---|---|---|---|---|
| Frequent | MM1(V)1 | 68 (31–86) | 4 (1–24) | Dementia, cortical anopsia, ataxia, myoclonus | Neocortex (especially in occipital lobe), striatum, thalamus, and cerebellum constantly affected "synaptic type" PrP staining |
| | MV2K | 65 (36–83) | 17 (4–48) | Ataxia, dementia, extrapyramidal | Similar to VV2 with more involvement of the cerebral cortex, amyloid kuru plaques in the cerebellum, plaque-like focal PrP deposits |
| | VV2 | 64 (40–83) | 6.5 (3–18) | Prominent ataxia, late dementia | Prominent pathology in cerebellum and subcortical areas, late cortical involvement, plaque-like and perineuronal PrP staining |

Zerr e Parchi, 2018

# Distribuzione: Luogo di nascita

- 37 Calabria
- 2 Sicilia
- 1 Piemonte

2013

OPEN ACCESS

RESEARCH PAPER

# A proposal of new diagnostic pathway for fatal familial insomnia

A Krasnianski,[1,2] P Sanchez Juan,[3,4] Claudia Ponto,[1] M Bartl,[1] U Heinemann,[1] D Varges,[1] W J Schulz-Schaeffer,[5] H A Kretzschmar,[6] I Zerr[1]

15 casi in Italia dal 1993 ad oggi!

A) Obligatory **organic sleep disturbances**. If not yet clinically apparent, a polysomnography has to be performed.

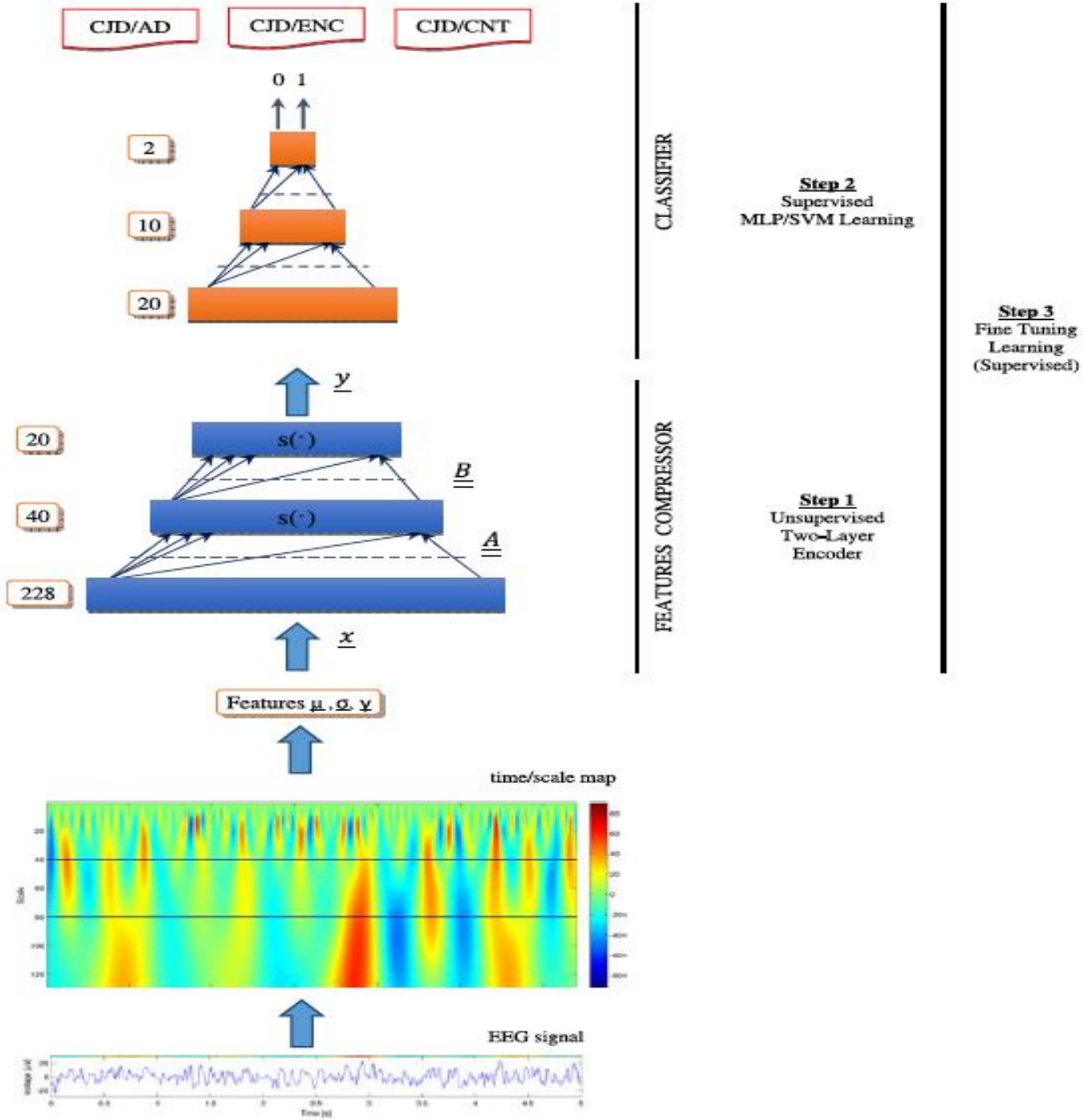
B) At least **two** of the following "**CJD-like symptoms/signs**"
1. Psychiatric*
2. Ataxia
3. Visual
4. Myoclonus
5. Cognitive/mnestic deficits

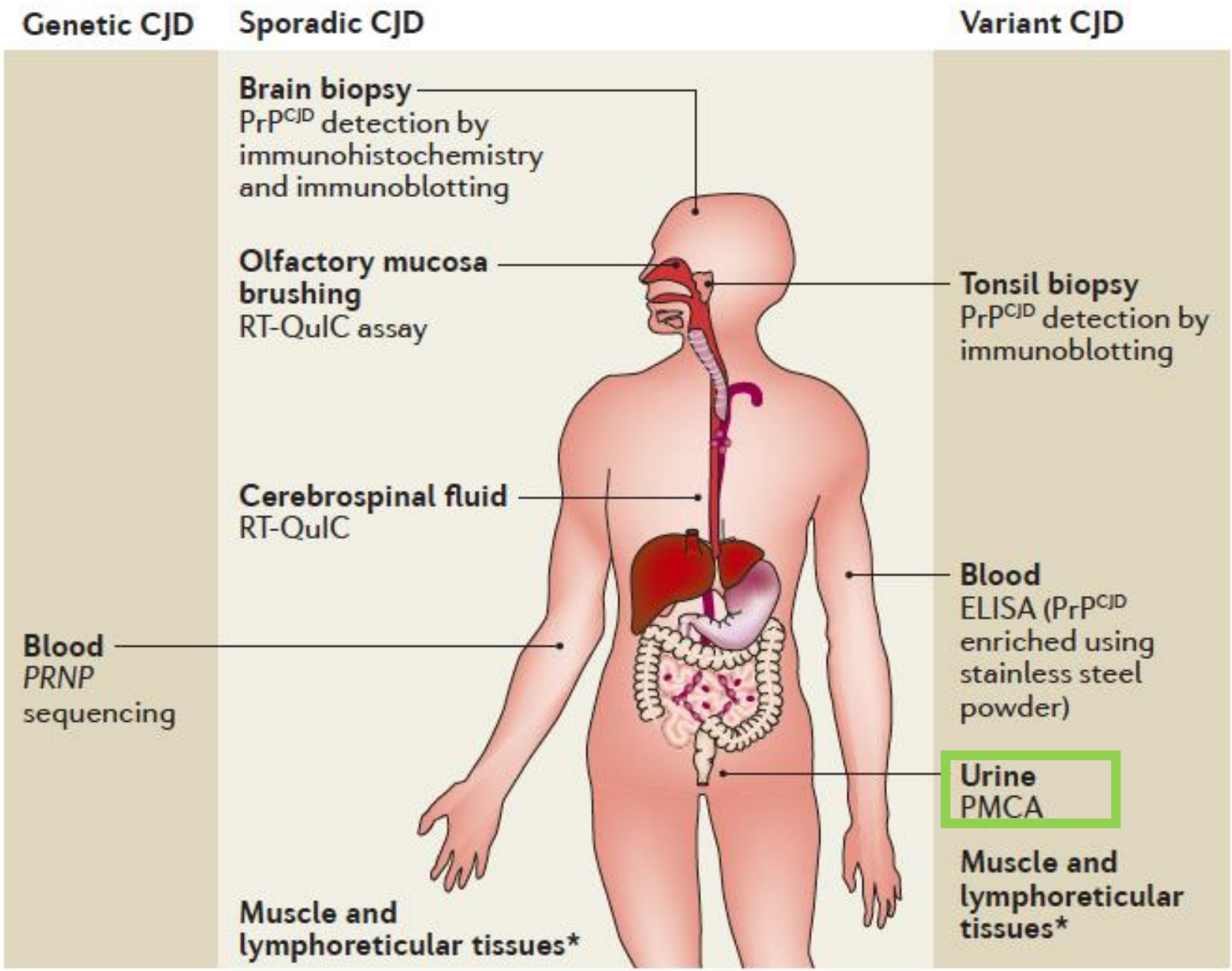
Mutazione Codone 178: D178N

Codone 129: M129M o M129V

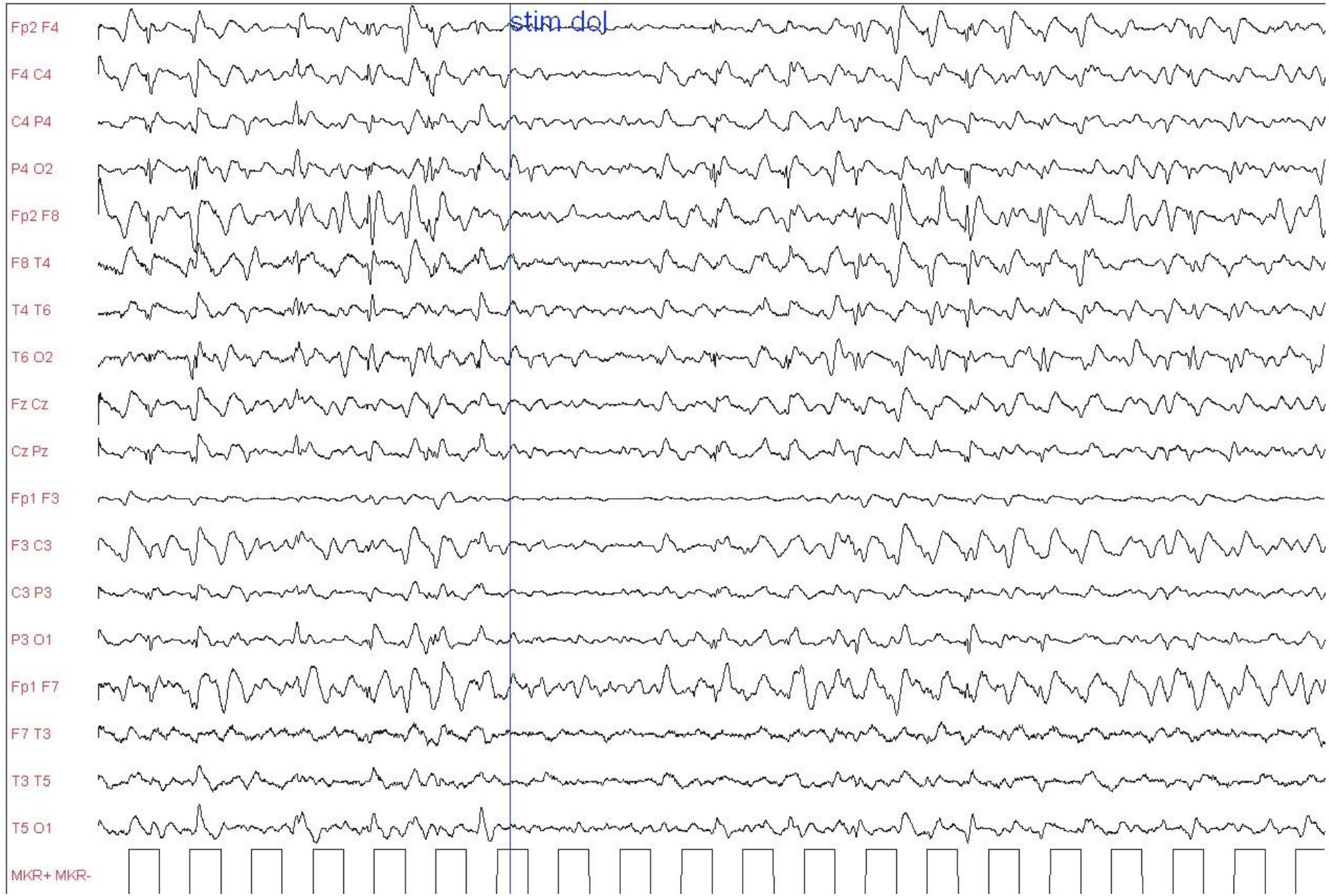
C) At least **one** of the following "**relatively disease-specific symptoms/signs**"
1. Loss of weight with a cutoff point of > 10 kg during the last 6 months
2. Vegetative**
3. Husky voice

*Visual hallucinations, personality change, depression, anxiety, aggressiveness, disinhibition, listlessness
**Hyperhidrosis, newly diagnosed arterial hypertonia, tachycardia, obstipation, hyperthermia


CJD/AD
CJD/ENC
CJD/CNT
0 1
2
10
20
CLASSIFIER
Step 2
Supervised
MLP/SVM Learning
Step 3
Fine Tuning
Learning
(Supervised)
y
20
s(·)
B
40
s(·)
A
228
x
FEATURES COMPRESSOR
Step 1
Unsupervised
Two-Layer
Encoder
Features μ , σ, γ
time/scale map
EEG signal




N.B.: Non inserita in criteri


stim dol
Fp2 F4
F4 C4
C4 P4
P4 O2
Fp2 F8
F8 T4
T4 T6
T6 O2
Fz Cz
Cz Pz
Fp1 F3
F3 C3
C3 P3
P3 O1
Fp1 F7
F7 T3
T3 T5
T5 O1
MKR+ MKR-

# Sporadic Creutzfeldt-Jakob disease mimicking nonconvulsive status epilepticus

Neurology® 2010;74:1995-1999

B. Lapergue, MD
S. Demeret, MD
V. Denys, MD
J.L. Laplanche, PharmD, PhD
D. Galanaud, MD, PhD
M. Verny, MD
V. Sazdovitch, MD
M. Baulac, MD
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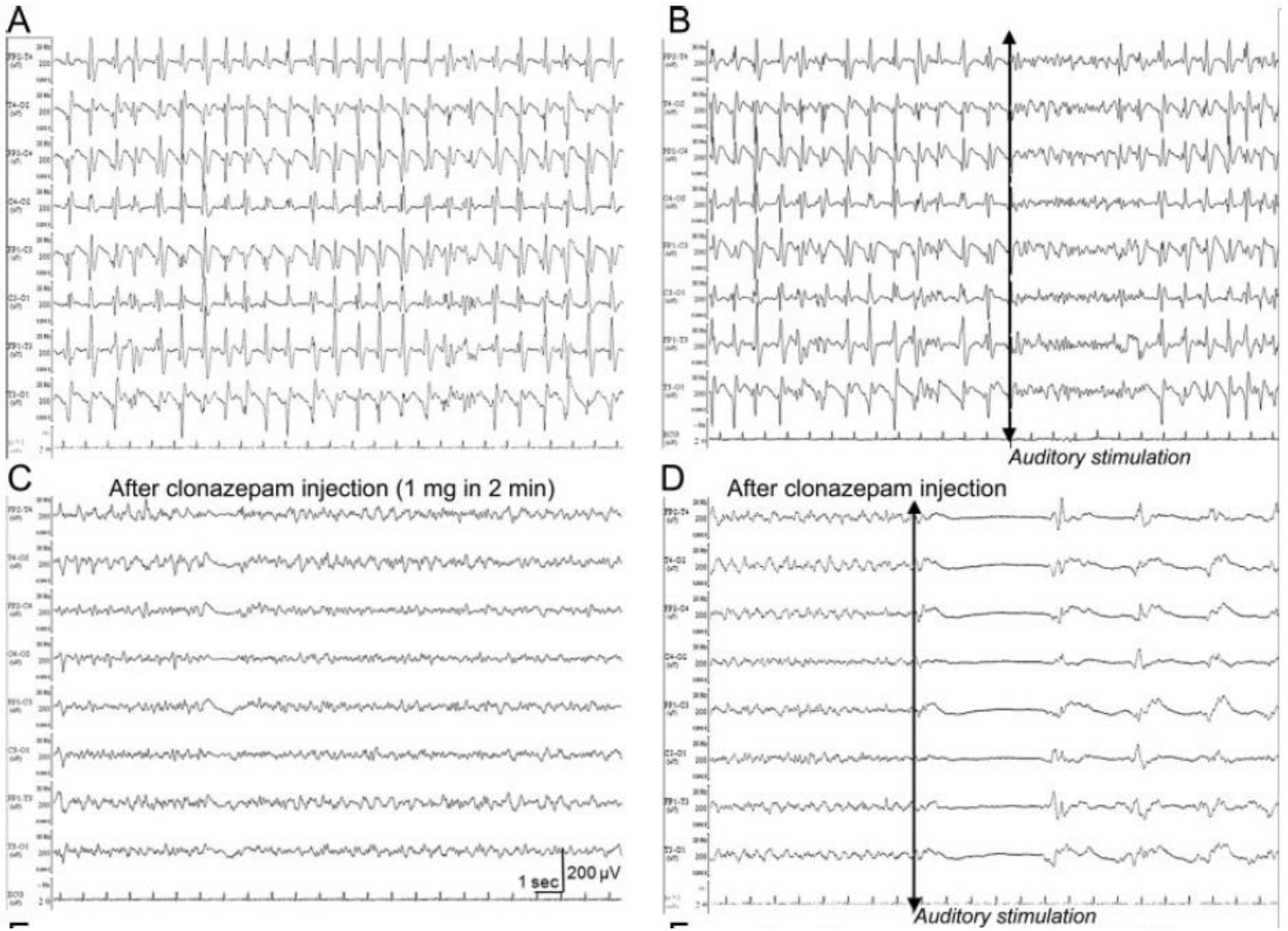
J.J. Hauw, MD
F. Bolgert, MD
J.P. Brandel, MD
V. Navarro, MD, PhD



# CJD sporadica: clinica

| | Onset (%) | Course (%) |
|---|---|---|
| Dementia | 72 | 91 |
| Ataxia | 72 | 83 |
| Pyramidal signs | 40 | 77 |
| Myoclonus | 40 | 84 |
| Visual/oculomotor | 38 | 58 |
| Extrapyramidal signs | 36 | 75 |
| Akinetic mutism | 9 | 45 |
| Paresthesia | 13 | 16 |
| Epileptic fits | 3 | 12 |

Zerr e Parchi, 2018

**Distinctive clinical and pathological features of sporadic Creutzfeldt–Jakob disease subtypes**

| | Molecular disease subtype | Median age at onset (range) (years) | Median duration (range) (months) | Most prominent clinical signs/ symptoms | Distinctive histopathologic features |
|---|---|---|---|---|---|
| Rare | MM2T | 52 (26–71) | 16 (8–36) | Ataxia, diplopia, psychiatric signs, sleep loss, late cognitive impairment | Atrophy of the thalamus and inferior olive, focal spongiosis limited to the cerebral cortex |
| | MM2C | 64 (49–77) | 16 (9–36) | Progressive dementia for several months | Spongiosis with large confluent vacuoles; perivacuolar PrP staining |
| | VV1 | 44 (19–55) | 21 (17–42) | Dementia at onset, later ataxia and extrapyramidal | Severe pathology in the cerebral cortex and striatum with sparing of brainstem nuclei and cerebellum |
| | p-MM1[a] | 58 (48–70) | 22 (13–38) | Progressive dementia and neurologic signs for several months | Moderate to severe pathology. MM1-like lesion profile. Widespread PrP amyloid plaques in subcortical and deep nuclei white matter |

Zerr e Parchi, 2018

Avicenna Journal of Medicine

Wolters Kluwer -- Medknow Publications

# Creutzfeldt–Jakob disease with unusual presentation of peripheral neuropathy and ophthalmoplegia

Mais Arwani, Abhishek Purohit, [...], and Sandeep Rana

# Alice in Wonderland Syndrome as a Presenting Manifestation of Creutzfeldt-Jakob Disease

CASE REPORT
published: 09 May 2019
doi: 10.3389/fneur.2019.00473

*Tirza Naarden [1], Bastiaan C. ter Meulen [1,2], Sarah I. van der W*

*[1] Department of Neurology, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands, [2] Medisch Centrum, Zaandam, Netherlands, [3] Outpatient Clinic for Uncommon Psychi*

# Supranuclear Gaze Abnormality in Spor

*Sporadik Creutzfeldt-Jacob Hastalığında Supranükleer Bak*

Selen GÜR ÖZMEN[1], Hakan GÜRVİT[2], Haşmet A. HANAĞASI[2], Meltem Ha

[1]Iğdır State Hospital, Department of Neurology, Iğdır, Turkey

[2]İstanbul University İstanbul Faculty of Medicine, Department of Neurology, İstanbul, Turkey

[3]Anadolu Health Center, Department of Neurology, İstanbul, Turkey

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Novel Prion Disease Associated with Diarrhea and Autonomic Neuropathy

Simon Mead, M.D., Sonia Gandhi, M.D., Jon Beck, B.Sc., Diana Caine, Ph.D., Dillip Gallujipali, M.D., Christopher Carswell, M.D., Harpreet Hyare, M.D., Susan Joiner, M.Sc., Hilary Ayling, B.Sc., Tammaryn Lashley, Ph.D., Jacqueline M. Linehan, B.Sc., Huda Al-Doujaily, M.Sc., Bernadette Sharps, B.Sc., Tamas Revesz, M.D., Malin K. Sandberg, Ph.D., Mary M. Reilly, M.D., Martin Koltzenburg, M.D., Alastair Forbes, M.D., Peter Rudge, M.D., Sebastian Brandner, M.D., Jason D. Warren, M.D., Jonathan D.F. Wadsworth, Ph.D., Nicholas W. Wood, M.D., Janice L. Holton, M.D., and John Collinge, M.D.

# A Case of Creutzfeldt-Jakob Disease Mimicking Corticobasal Degeneration: FDG PET, SPECT, and MRI Findings

Yuyan

# Epilepsia partialis continua as the presenting symptom in probable sporadic Creutzfeldt-Jakob disease

# Sporadic MM-1 Type Creutzfeldt-Jakob Disease With Hemiballic Presentation and No Cognitive Impairment Until Death: How New NCJDRSU Diagnostic Criteria May Allow Early Diagnosis

*Lorenzo Saraceno [1], Vito A. G. Ricigliano [1], Michele Cavalli [1], Alessandro Cagol [1], Giovanna Bosco [2], Fabio Moda [3], Paola Caroppo [3] and Giovanni Meola [1,2]*

*[1] Department of Biomedical Sciences for Health, University of Milan, IRCCS Policlinico San Donato, Milan, Italy, [2] Department of Neurology, IRCCS Policlinico San Donato, Milan, Italy, [3] Carlo Besta Neurological Institute, IRCCS Foundation, Milan, Italy*

**Table 2** Descriptive data and diagnostic accuracies

| | Definite sCJD (n = 65)[a] | Controls (n = 118)[b] |
|---|---|---|
| **Age, median (minimum–maximum), y** | 67 (47–85) | 75 (17–91) |
| **Female, % (n)** | 40% (26) | 62% (70) |
| | **Sensitivity, % (95% CI)** | **Specificity, % (95% CI)** |
| **RT-QuIC (n = 183)** | 89 (79.1–95.6) | 100 (96.9–100) |
| **14-3-3 (n = 183)** | 86 (75.3–93.5) | 27 (19.4–36.1)[c] |
| **MRI (n = 154)** | 79 (66.7–88.8) | 96 (89.7–98.9) |
| **EEG (n = 142)** | 44 (30.1–58.6) | 98 (92.0–99.7) |
| **WHO criteria (n = 183)** | 74 (58.6–82.6) | 99 (95.4–99.9) |
| **Amended protocol (n = 183)** | 97 (89.3–99.6) | 99 (95.4–99.9) |

Abbreviations: CI = confidence interval; RT-QuIC = real-time quaking-induced conversion assay; sCJD = sporadic Creutzfeldt-Jakob disease; WHO = World Health Organization.
[a] MRI diffusion-weighted imaging available in 58 and EEG in 54 cases.
[b] MRI diffusion-weighted imaging available in 96 and EEG in 88 cases.
[c] Highly biased cohort.

# Clinica

**Sintomi iniziali** più frequenti (INSIDIOSI e progressivi):

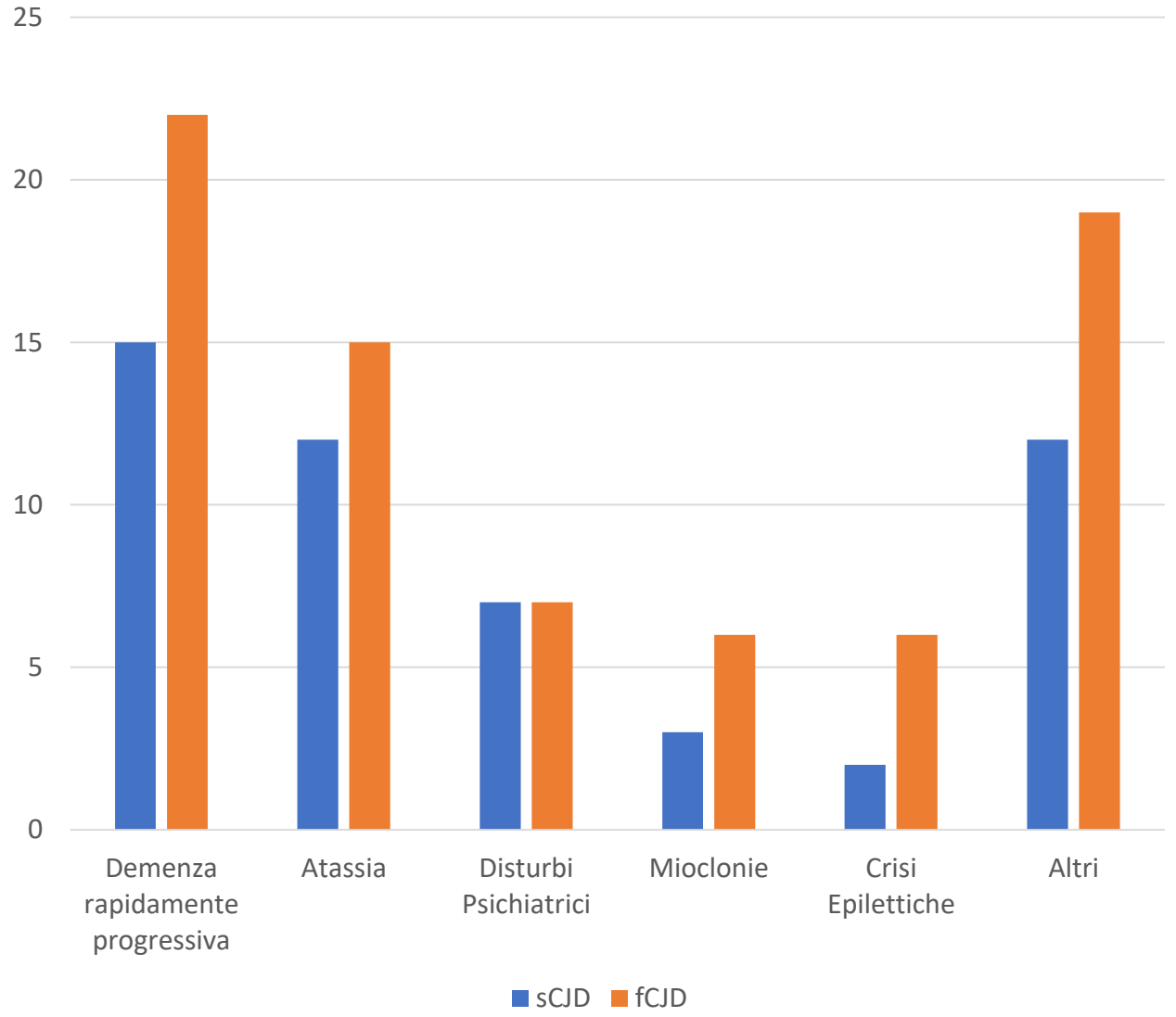
- Demenza
- Atassia
- Disturbi psichiatrici (allucinazioni)

**Fasi avanzate:**

- Mutismo acinetico
- Crisi epilettiche
- Mioclono

**Altri sintomi:**

- Piramidali
- Riduzione acuità visiva
- Disartria



ONLINE FIRST

# Contribution of Cerebrospinal Fluid Thymosin β4 Levels to the Clinical Differentiation of Creutzfeldt-Jakob Disease

*Maria Le Pera, PhD; Elena Urso, PhD; Teresa Sprovieri, PhD; Sabrina Bossio, PhD; Umberto Aguglia, MD; Ida Manna, PhD; Chiara Cupidi, MD; Tiziana Ferraro, PhD; Antonio Gambardella, MD; Antonio Qualtieri, PhD; Aldo Quattrone, MD*

ARCHIVES OF NEUROLOGY

Arch Neurol. 2012 Jul;69(7):868-72.

**Table 2. Sensitivity, Specificity, PPV, NPV, and Efficiency for Each Marker**

| | 14-3-3 Protein | Tau Protein | Thymosin β4 Protein |
|---|---|---|---|
| CJD[a] | 16/21 | 19/21 | 21/21 |
| Other dementia[a] | 3/67 | 1/63 | 1/67 |
| Sensitivity, % | 71 | 90 | 100 |
| Specificity, % | 95 | 98.4 | 98.5 |
| PPV, % | 84 | 95 | 95 |
| NPV, % | 93 | 97 | 100 |
| Efficiency, % | 91 | 96 | 99 |

Abbreviations: CJD, Creutzfeldt-Jakob disease; NPV, negative predictive value; PPV, positive predictive value.

[a]The numbers indicate the positive samples divided by the total samples investigated.

# Gene PRP: mutazione D178N

(sostituzione ac. aspartico con arginina)

## Codone 129

**Met/Met** → **FFI**

**Met/Val** → Met in allele mutato → **FFI**

**Met/Val** → Val in allele mutato → **fCJD**

**Val/Val** → **fCJD**

# Gene PRP: no mutazioni

## Codone 129

Met/Met (40%)

Met/Val (50%)

Val/Val (10%)

Suscettibilità MCJ sporadica (sCJD)

# Sporadic Creutzfeldt-Jakob disease mimicking nonconvulsive status epilepticus

B. Lapergue, MD
S. Demeret, MD
V. Denys, MD
J.L. Laplanche, PharmD, PhD
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S. Haïk, MD, PhD
J.J. Hauw, MD
F. Bolgert, MD
J.P. Brandel, MD
V. Navarro, MD, PhD

## ABSTRACT

**Background:** Nonconvulsive status epilepticus (NCSE) in patients with confusion may be difficult to distinguish from nonepileptic (metabolic/toxic, postanoxic, and spongiform) encephalopathies. This study aimed to describe the misleading presentation of patients with sporadic Creutzfeldt-Jakob disease (sCJD) who were initially diagnosed with a refractory NCSE (rNCSE).

**Methods:** We retrospectively reviewed the clinical characteristics, EEG records, brain MRI scans, 14-3-3 protein detection in CSF, genotype of the prion protein gene, and neuropathologic data of patients referred to our neurologic intensive care unit (NICU) with this presentation.

**Results:** Ten patients with a final diagnosis of definite (n = 7) or probable (n = 3) sCJD were referred to our NICU with an initial diagnosis of rNCSE. Reanalysis of the EEG ruled out ictal rhythmic activities, but showed diffuse, periodic, or semiperiodic sharp-wave complexes (PSWC) with short period. PSWC were briefly attenuated by auditory (n = 5) or painful (n = 3) stimuli and by IV injection of antiepileptic drugs (n = 5) but without clinical improvement. In addition, PSWC showed fluctuations according to the vigilance level (n = 5). Brain MRI showed hyperintensities in basal ganglia (n = 9/10) and in cortical areas (n = 7/10). 14-3-3 Protein was detected in CSF (n = 10). Only 2 sCJD subtypes were found (MM1 5/7, MV1 2/7).

**Conclusions:** This series of patients suggests that sporadic Creutzfeldt-Jakob disease should be considered as a differential diagnosis, rather than as a cause, of apparent refractory nonconvulsive status epilepticus. Criteria for nonconvulsive status epilepticus diagnosis should rely on careful examination of both EEG parameters and clinical state so that aggressive, unnecessary treatments can be avoided. *Neurology*® 2010;74:1995–1999

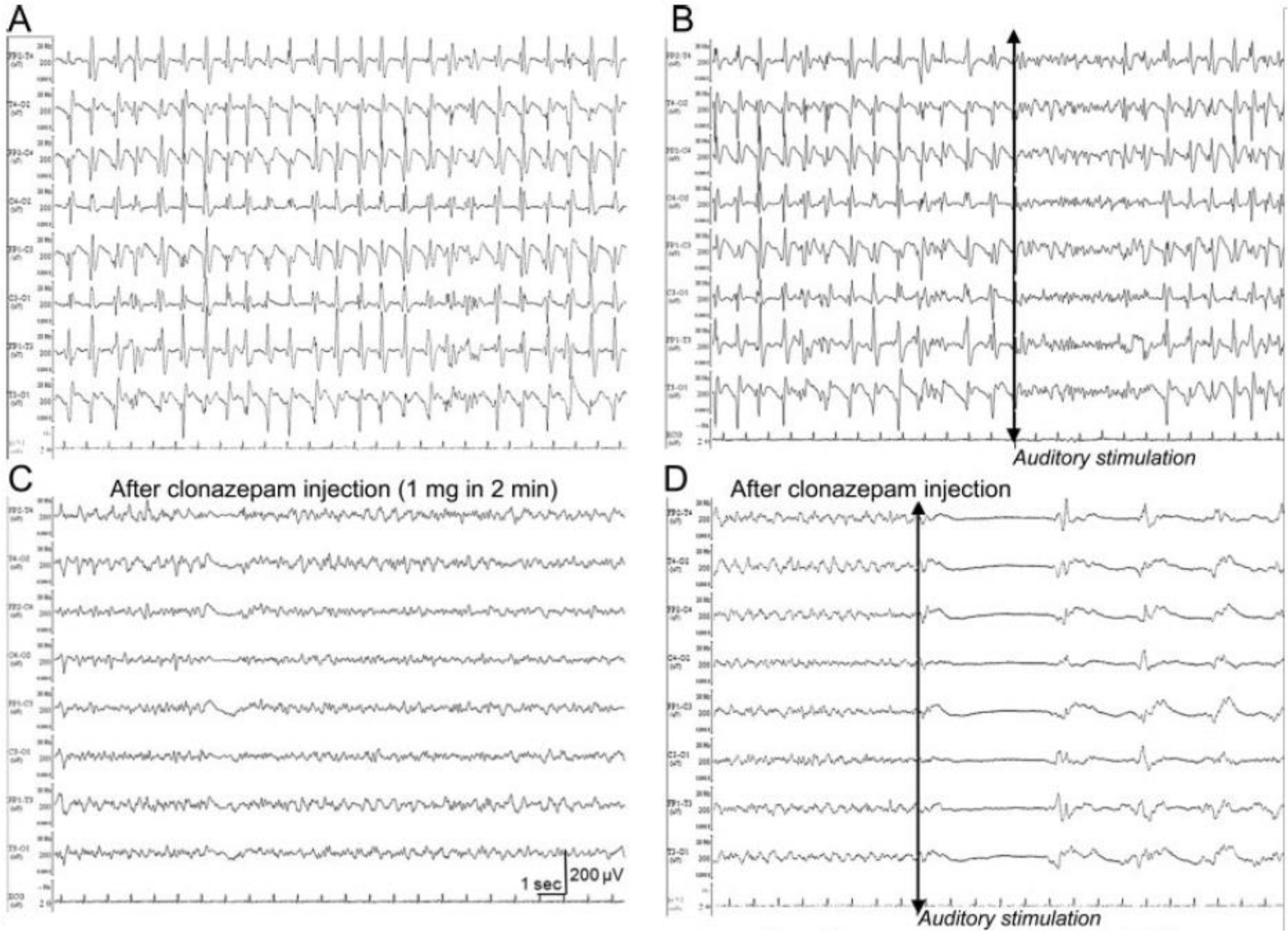
A
B
Auditory stimulation
C
After clonazepam injection (1 mg in 2 min)
1 sec
200 µV
D
After clonazepam injection
Auditory stimulation

**Table 2** Discriminating factors between sCJD and NCSE

| | sCJD | NCSE with confusion |
|---|---|---|
| Previous clinical events | Myoclonus, gait ataxia, visual or cognitive disturbance | No |
| EEG criteria for PSWC[3] (periodic activities) | Yes | No |
| EEG criteria for ictal NCSE[4] (rhythmic activities) | No | Yes |
| Reactivity of EEG activities to external stimuli and attenuation with drowsiness | Yes (inconstant) | No |
| Clinical improvement after rapid onset antiepileptic drug injection | No | Yes, in generalized NCSE<br>Inconstant, in partial NCSE |
| Synchronization of the myoclonias with paroxysmal EEG complexes | No | Yes |
| Positive 14-3-3 protein in CSF | Yes | May be positive in partial lesional NCSE |
| Brain MRI hypersignal | Cortex (wide) and basal ganglia (caudate and putamen) | Cortex (focal) and sometimes thalamus (pulvinar) in partial NCSE |

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# CJD mimics and chameleons

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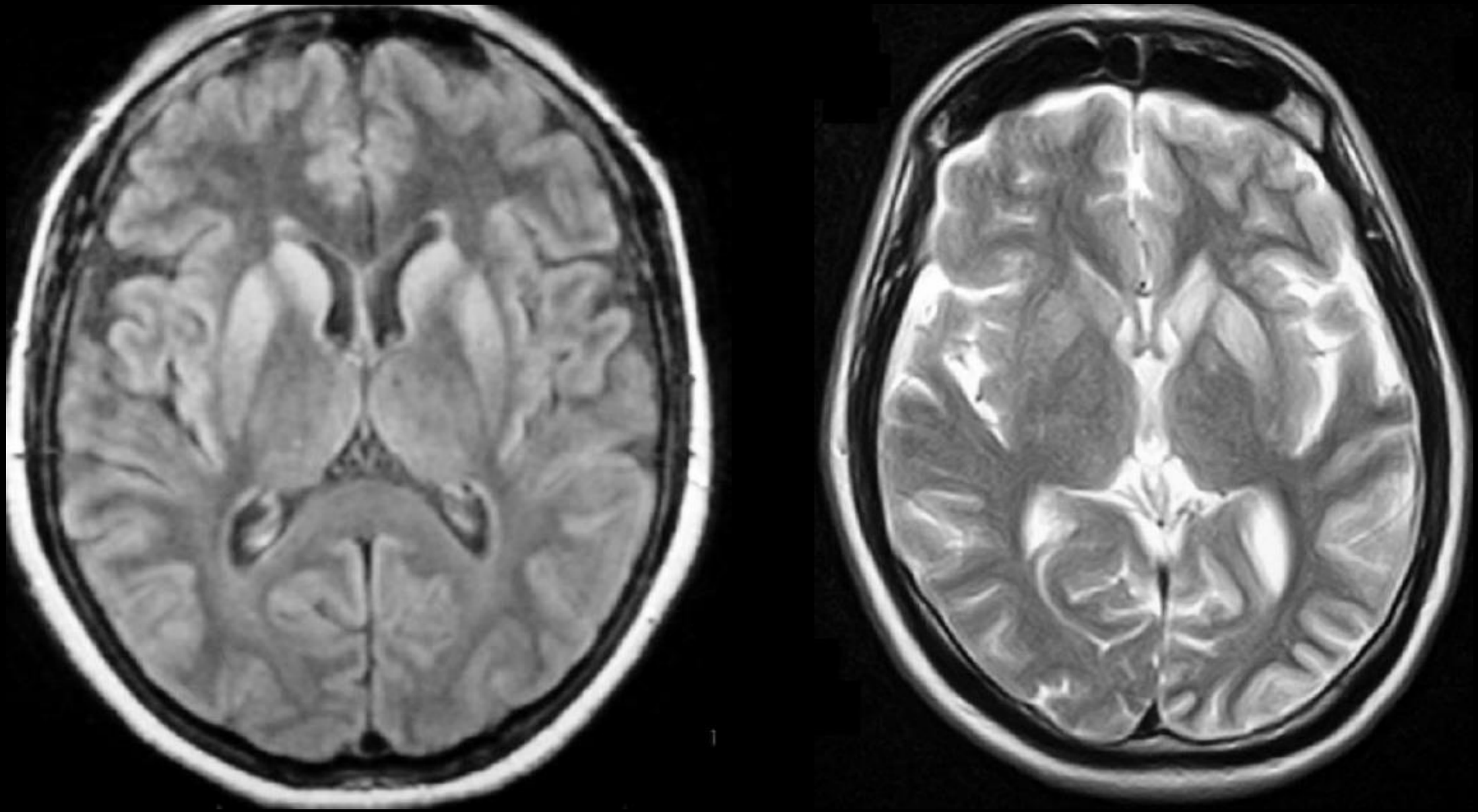
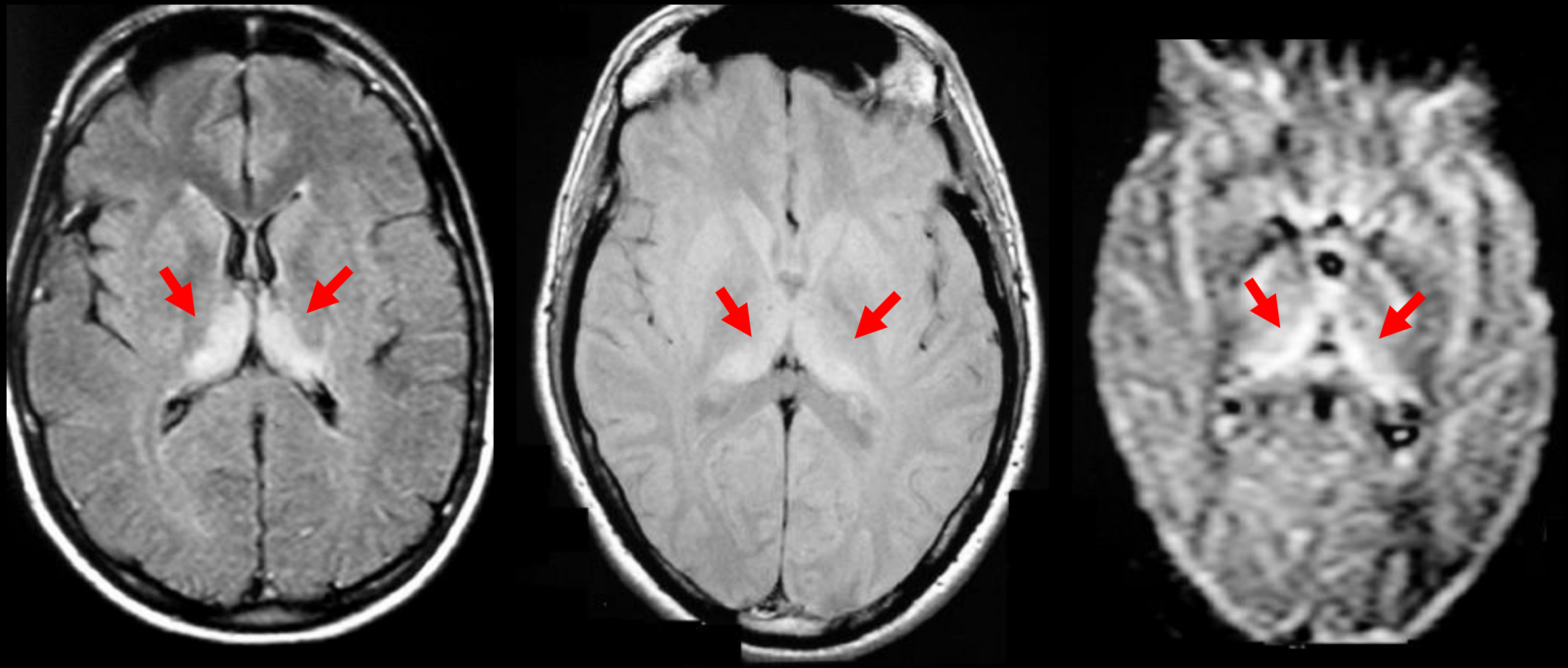
**Table 2** Differential diagnosis checklist

| Common disorders with rare presentation that mimic CJD | Rare but potentially treatable/reversible mimics | Rare and untreatable mimics of CJD |
|---|---|---|
| Rapidly progressive forms of common neurodegenerative diseases | Limbic and other immune-mediated encephalitis | Unusual infections: subacute sclerosing panencephalitis |
| Delirium and pre-existing dementia | Metabolic and endocrine conditions (hyperammonaemia, electrolyte disturbance, hypoglycaemia/hyperglycaemia, uraemia) | Mitochondrial cytopathy |
| Viral encephalitis | Primary CNS vasculitis | Diffuse neoplastic disease (eg, carcinomatous meningitis, gliomatosis cerebri) |
| Hepatic failure and encephalopathy | Neurosarcoidosis | |
| Cerebrovascular disease (single or multiple strokes) or hypoxic encephalopathy | Primary CNS and intravascular lymphoma | |
| Wernicke's encephalopathy and related manifestations of alcohol-related dementia (eg, extrapontine myelinolysis) | Unusual infections: progressive multifocal leukoencephalopathy, fungal encephalitis, Lyme disease, Whipple's disease, neurosyphilis | |
| Thyroid dysfunction | Large dural arteriovenous fistula | |
| | HIV-related dementia | |
| | Subacute combined degeneration | |
| | CNS manifestations of autoimmune disorders (eg, lupus, sarcoidosis) | |
| | Heavy metal toxicity (eg, lithium, mercury) | |
| | Toxicity related to medications (eg, lithium, valproate) | |
| | Non-convulsive status epilepticus | |
| | Psychiatric conditions: functional disorders, catatonia, depression | |

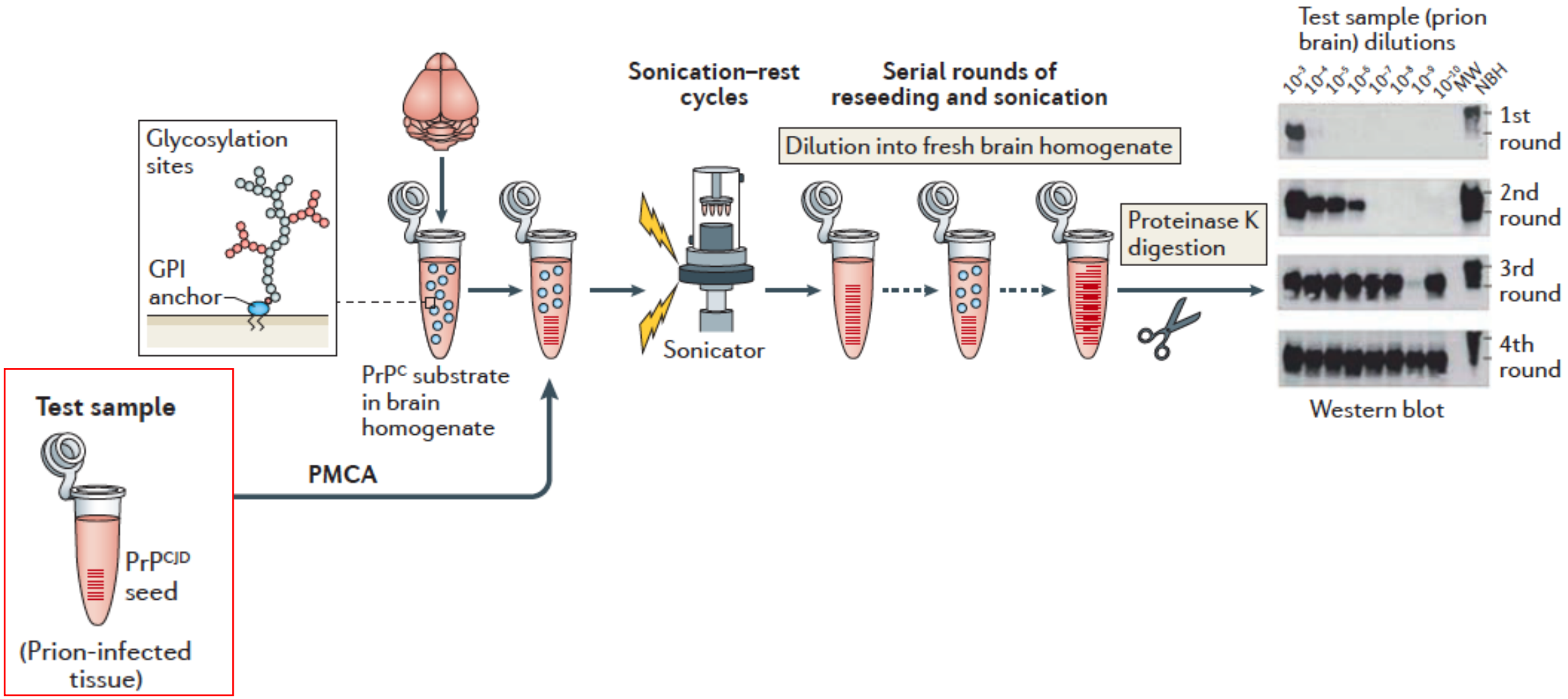
CJD, Creutzfeldt–Jakob disease; CNS, central nervous system.



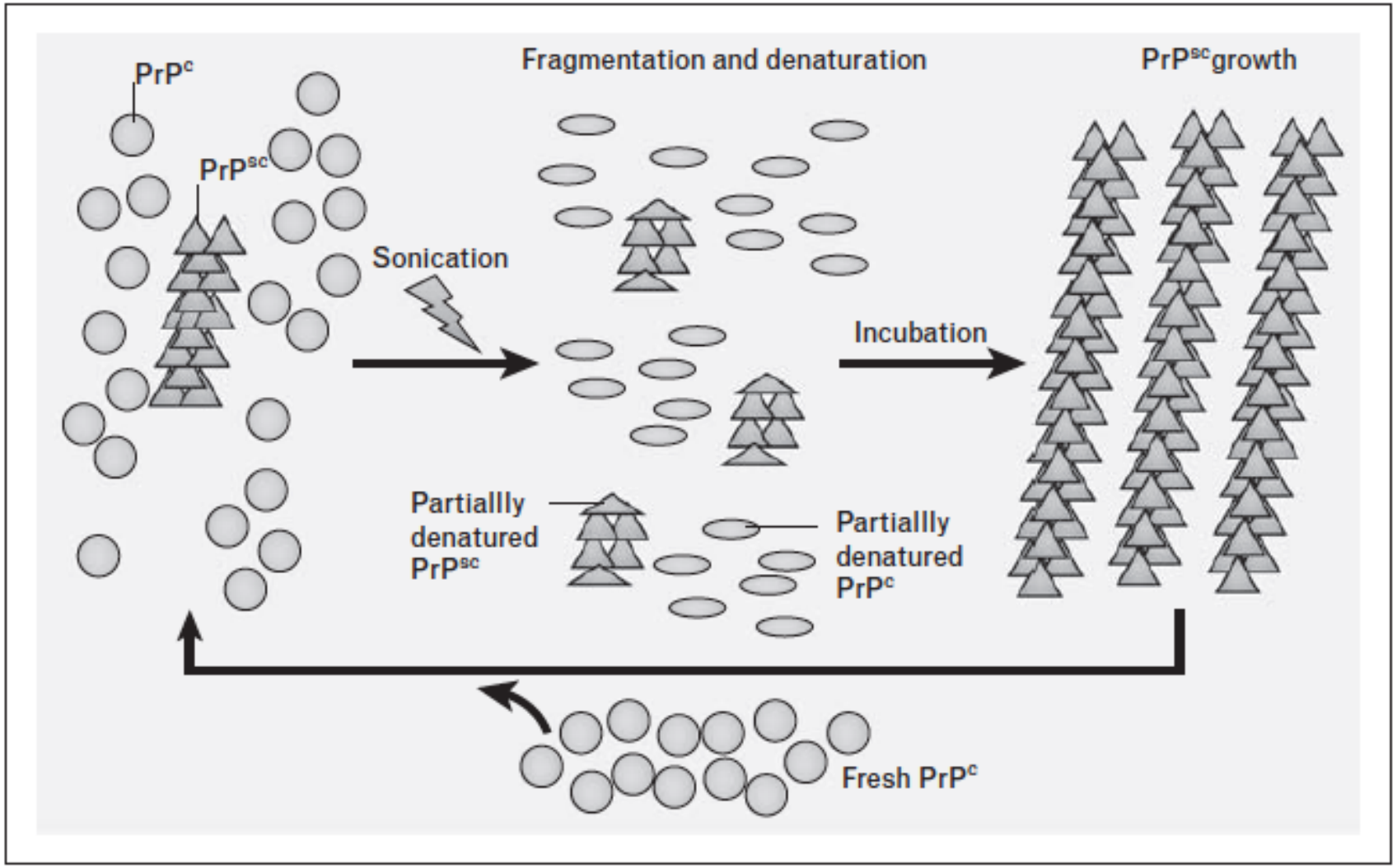
Hockey stick



# PMCA


Test sample
PrPCJD seed
(Prion-infected tissue)
PMCA
PrPC substrate in brain homogenate
Glycosylation sites
GPI anchor
Sonication–rest cycles
Sonicator
Serial rounds of reseeding and sonication
Dilution into fresh brain homogenate
Proteinase K digestion
Test sample (prion brain) dilutions
10-3 10-4 10-5 10-6 10-7 10-8 10-9 10-10 MW NBH
1st round
2nd round
3rd round
4th round
Western blot

# PMCA


PrP^c
PrP^sc
Sonication
Fragmentation and denaturation
Incubation
PrP^sc growth
Partiallly denatured PrP^sc
Partiallly denatured PrP^c
Fresh PrP^c

2013

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RESEARCH PAPER

# A proposal of new diagnostic pathway for fatal familial insomnia

A Krasnianski,[1,2] P Sanchez Juan,[3,4] Claudia Ponto,[1] M Bartl,[1] U Heinemann,[1] D Varges,[1] W J Schulz-Schaeffer,[5] H A Kretzschmar,[6] I Zerr[1]

A) Obligatory **organic sleep disturbances**. If not yet clinically apparent, a polysomnography has to be performed.

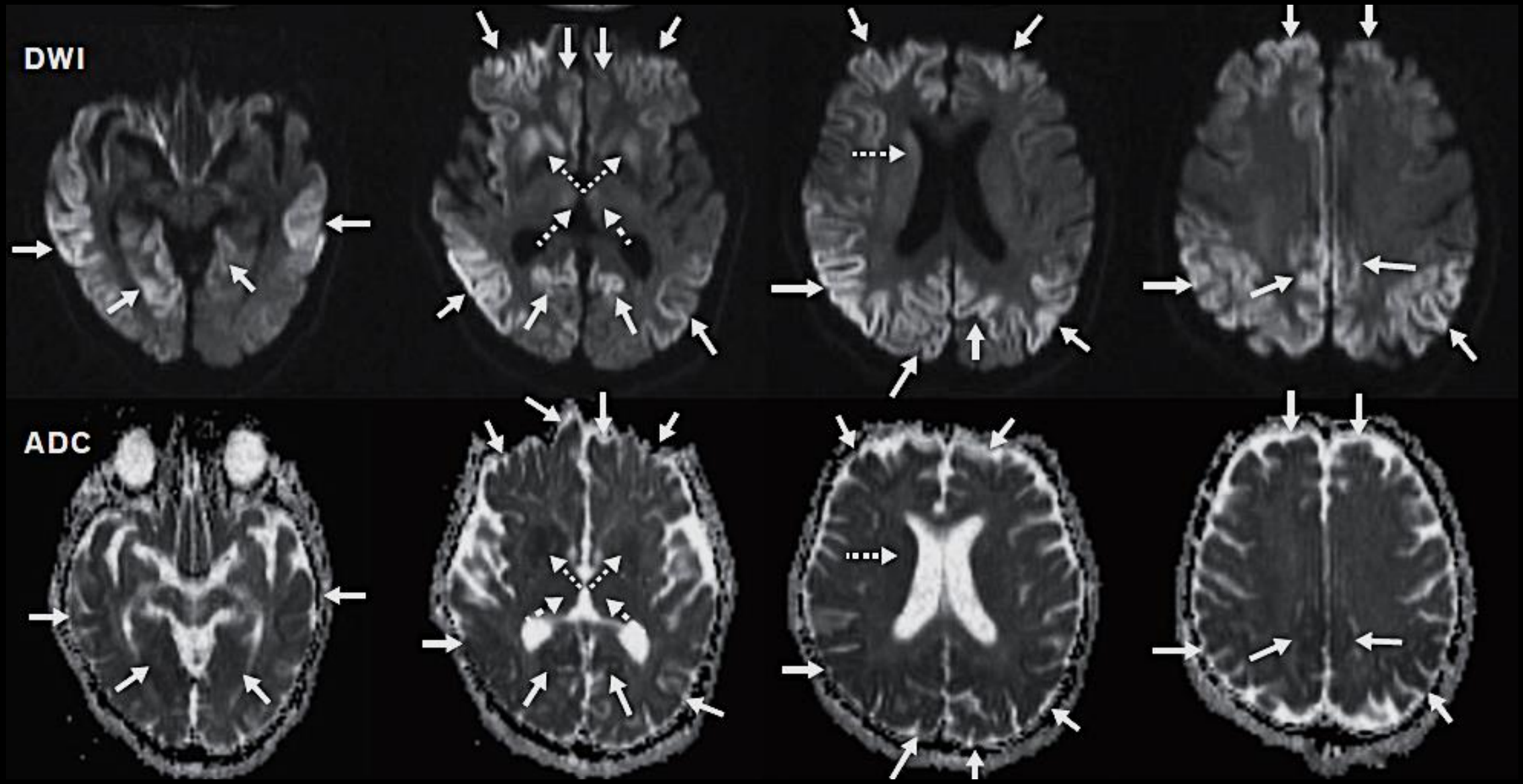
B) At least **two** of the following "**CJD-like symptoms/signs**"
1. Psychiatric*
2. Ataxia
3. Visual
4. Myoclonus
5. Cognitive/mnestic deficits

C) At least **one** of the following "**relatively disease-specific symptoms/signs**"
1. Loss of weight with a cutoff point of > 10 kg during the last 6 months
2. Vegetative**
3. Husky voice

*Visual hallucinations, personality change, depression, anxiety, aggressiveness, disinhibition, listlessness
**Hyperhidrosis, newly diagnosed arterial hypertonia, tachycardia, obstipation, hyperthermia

Mutazione Codone 178: D178N

Codone 129: M129M o M129V


DWI
ADC