Actualización en el Diagnóstico de las Enfermedades Priónicas

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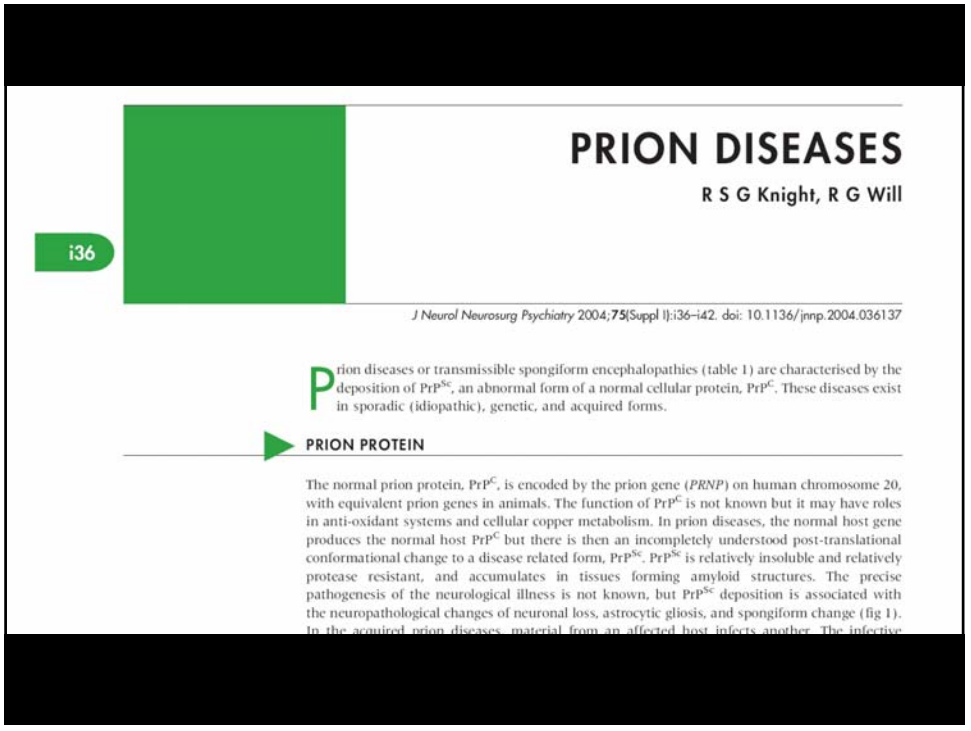

i36

PRION DISEASES

R S G Knight, R G Will

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Prion diseases or transmissible spongiform encephalopathies (table 1) are characterised by the deposition of PrP^{Sc}, an abnormal form of a normal cellular protein, PrP^{C}. These diseases exist in sporadic (idiopathic), genetic, and acquired forms.

PRION PROTEIN

The normal prion protein, PrP^{C}, is encoded by the prion gene (*PRNP*) on human chromosome 20, with equivalent prion genes in animals. The function of PrP^{C} is not known but it may have roles in anti-oxidant systems and cellular copper metabolism. In prion diseases, the normal host gene produces the normal host PrP^{C} but there is then an incompletely understood post-translational conformational change to a disease related form, PrP^{Sc}. PrP^{Sc} is relatively insoluble and relatively protease resistant, and accumulates in tissues forming amyloid structures. The precise pathogenesis of the neurological illness is not known, but PrP^{Sc} deposition is associated with the neuropathological changes of neuronal loss, astrocytic gliosis, and spongiform change (fig 1). In the acquired prion diseases, material from an affected host infects another. The infective

Proteína Priónica
Celular normal (PrP)

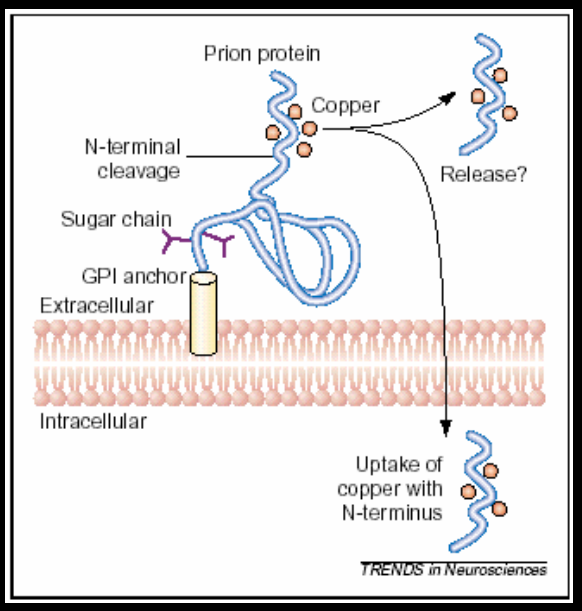


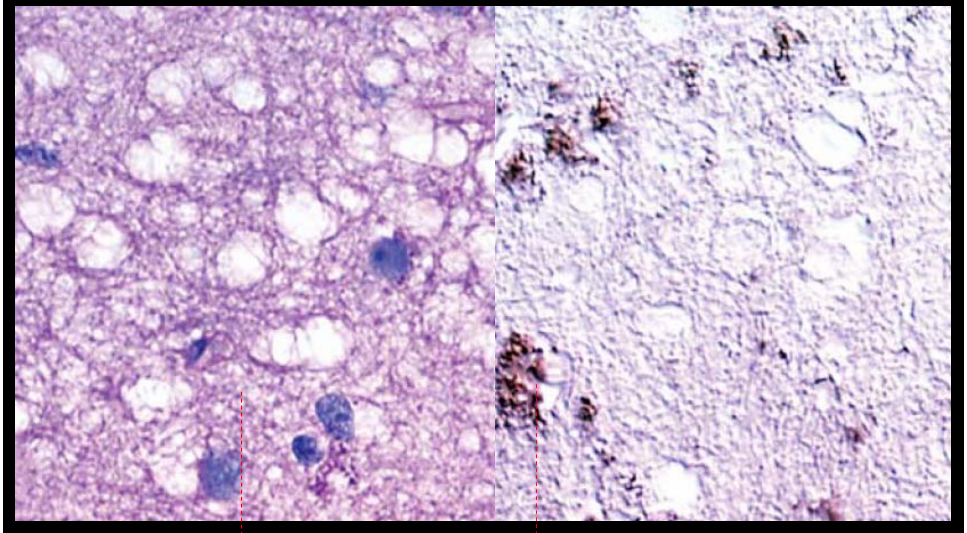
Table 1 Classification of human prion disease

Aetiology	Phenotype	Frequency
Sporadic		
Unknown: random distribution worldwide; incidence of 1–2 per million per annum	Sporadic CJD: sub-acute myoclonic form and range of atypical forms; multiple distinct prion strains associated with distinct clinicopathological phenotypes which include sporadic fatal insomnia	~85%
Inherited		
Autosomal dominantly inherited conditions with high penetrance; all forms have germline *PRNP* coding mutations	Extremely variable: readily mimics familial Alzheimer's disease and other neurodegenerative conditions; over 30 mutations identified; includes GSS, familial CJD. and fatal familial insomnia	~10–15%
Acquired		
Iatrogenic infection with human prions via medical or surgical procedures: human cadaveric derived pituitary hormones, tissue grafts, and contaminated neurosurgical instruments	Iatrogenic CJD: typical CJD when direct central nervous system (CNS) exposure; ataxic onset when peripheral infection	<5% (most from USA, UK, France, and Japan)
Exposure to human prions via endocannibalism	Kuru	Unique to small area of Papua New Guinea; major epidemic in 1950s with gradual decline since cessation of cannibalism
Environmental exposure (presumed dietary) to BSE prion strain; probable secondary transmission via blood transfusion	Variant CJD	Mainly UK (total to date ~150), 7 in France, individual patients in several other countries

Diagnóstico de las EETH

- El diagnóstico definitivo:
  - detección en el tejido de PrP^{sc} (prión) o sus alteraciones AP
- No prueba pre-mortem de absoluta certeza
- ECJe no enfermedad homogénea,
  - varios subtipos diferentes, según el tipo PrP (W-B) y de la variante alélica del codón 129 (M/V)……..*probable Nueva Clasificación de esta enfermedad…..*
  - MM1 y MV1 más frecuentes (mayoría casos ECJe)
- Riesgo real de transmisión de alguna EETH (ECJv)
  - pruebas diagnósticas específicas y precoces
  - resolver potenciales problemas para la salud publica

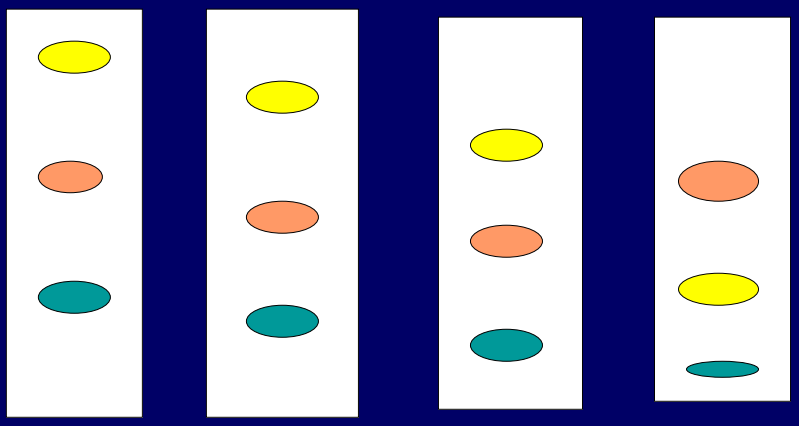
Neuropatología de ECJ



Espongiosis

Inmunohistoquimia de PrP

Western blot en ECJ



ECJ esporadico tipo 1 | **ECJ esporadica tipo 2** | **ECJ yatrogena periférica tipo 3** | **ECJ nv, BSE tipo 4**

Modificado de Aguzzi A. Nature, 1996

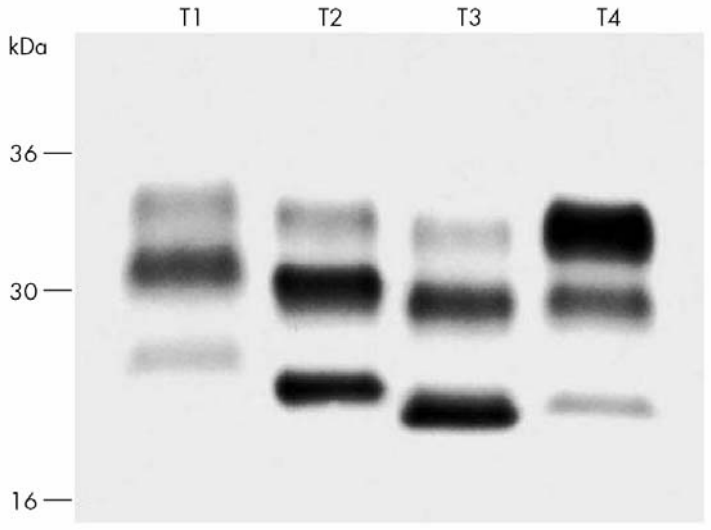
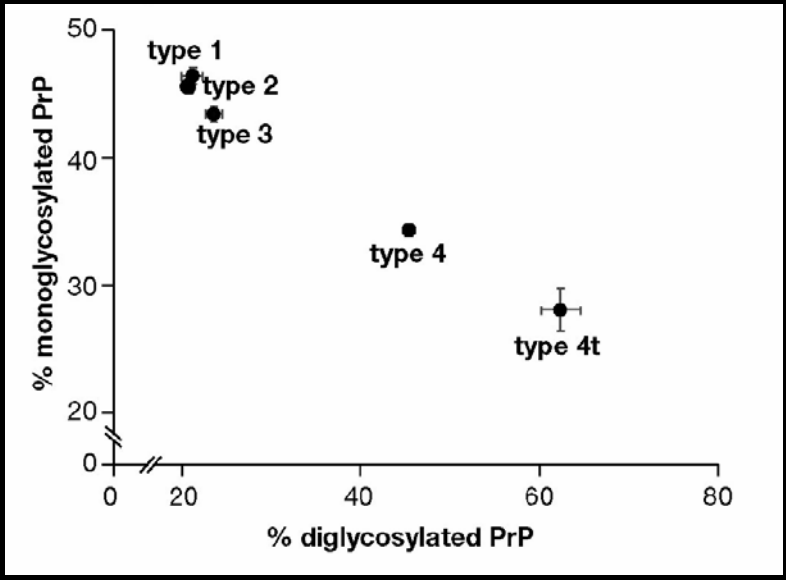


Figure 3 Molecular strain typing of human prions. Western blot of brain homogenate after treatment with proteinase K shows different apparent molecular mass and glycoform ratios in patients with forms of sporadic or iatrogenic (T1–3) or vCJD (T4).



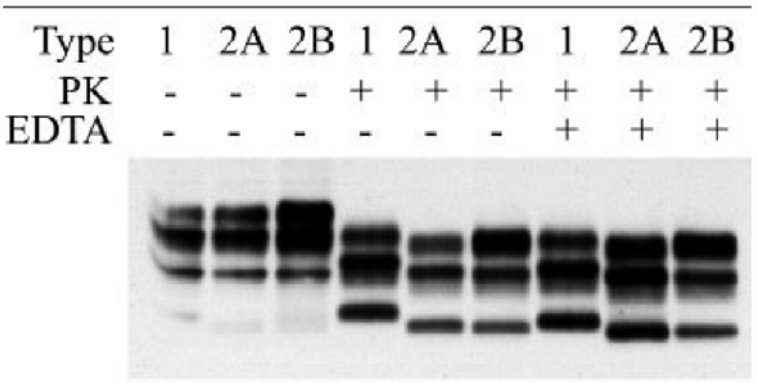


Fig 1. Western blot of PrP^{res} type standards type 1 (1), type 2A (2A), and type 2B (2B) analyzed with (+) or without (−) digestion with proteinase K (PK) in the presence (+) or absence (−) of EDTA.

Tipo 1 y 2 de Collinge = Tipo 1 de Parchi
Tipo 3 y 4 = 2 A y 2 B

Tipo 1: 21 kDa
Tipo 2: 19 kDa

Gen de la Proteina Priónica Humana

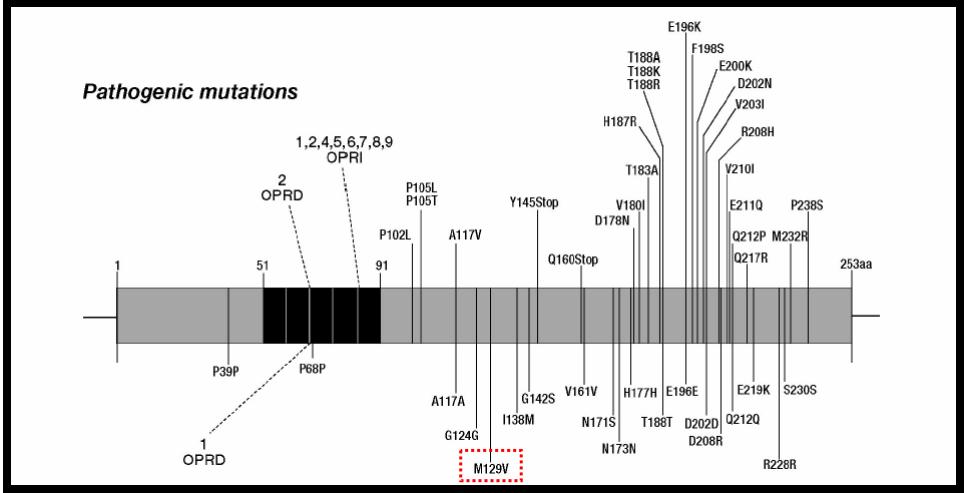


Table 3 Percentage of codon 129 PrP genotypes in CJD and in the normal population

	Met/Met	Met/Val	Val/Val
Normal population	39%	50%	11%
Sporadic CJD	68%	15%	18%
hGH-related CJD	48%	20%	32%
vCJD	100%	–	–

Table 3 *Molecular subtypes of sporadic CJD with corresponding phenotypic features*

sCJD type	Variant	% of cases*	Key features
MM1, MV1	Classic, typical	56	Rapid progression, short duration, periodic sharp waves on EEG, prominent and early myoclonus
VV2	Ataxic	21	Ataxia at onset, dementia late, no periodic sharp waves on EEG
MM2†	Slowly progressive	11	Progressive dementia, no periodic sharp waves on EEG, large vacuoles on histology
MV2	Ataxic with Kuru plaque	8	Ataxia and dementia, no periodic sharp waves EEG, some with long duration, Kuru plaques in cerebellum
VV1	Early onset	3	Progressive dementia, no periodic sharp waves, younger patients

Table 8. Molecular and Phenotypic Features of the Sporadic Creutzfeldt-Jakob Disease (sCJD) Variants

sCJD Variant	Previous Classification	% of Cases	Duration (mo)	Clinical Features	Neuropathological Features
MM1 or MV1	Myoclonic, Heidenhain variants	70	3.9	Rapidly progressive dementia, early and prominent myoclonus, typical EEG; visual impairment or unilateral signs at onset in 40% of cases 14-3-3 + : 95 %	"Classic CJD" distribution of pathology; often prominent involvement of occipital cortex; "synaptic type" PrP staining; in addition, one-third of cases shows confluent vacuoles and perivacuolar PrP staining
VV2	Ataxic variant	16	6.5	Ataxia at onset, late dementia, no typical EEG in most cases 14-3-3 + : 80 %	Prominent involvement of subcortical, including brain stem nuclei; in neocortex, spongiosis is often limited to deep layers; PrP staining shows plaque-like, focal deposits, as well as prominent perineuronal staining
MV2	Kuru-plaques variant	9	17.1	Ataxia in addition to progressive dementia, no typical EEG, long duration (>2 yr) in some cases	Similar to VV2 but with presence of amyloid-kuru plaques in the cerebellum, and more consistent plaque-like, focal PrP deposits
MM2-thalamic	Thalamic variant	2	15.6	Insomnia and psychomotor hyperactivity in most cases, in addition to ataxia and cognitive impairment, no typical EEG	Prominent atrophy of the thalamus and inferior olive (no spongiosis) with little pathology in other areas; spongiosis may be absent or focal, and PrP^{Sc} is detected in lower amount than in the other variants
MM2-cortical	Not established	2	15.7	Progressive dementia, no typical EEG	Large confluent vacuoles with perivacuolar PrP staining in all cortical layers; cerebellum is relatively spared
VV1	Not established	1	15.3	Progressive dementia, no typical EEG	Severe pathology in the cerebral cortex and striatum with sparing of brain stem nuclei and cerebellum; no large confluent vacuoles, and very faint synaptic PrP staining

PrP = prion protein; PrP^{Sc} = protease-resistant PrP.

Clasificación de las EETHs en España
Período 1993-2002

Tipo de EETHS	N (%)
ECJe	439 (88,6)
ECJg	23 (4,6)
ECJta	3 (0,6)
ECJ total	465 (94,4)
IFF	28 (5,6)
No Casos	70 (12,5)
Total notificaciones	565

Diagnóstico Clínico de las EETH

- ECJe es una *demencia mioclónica* de rápida evolución
  - signos neurológicos focales + demencia
  - duración media 4 m; 75 % < 6 m; 95 % < 12 m (excepcional 2 a.)
- Fase de Inicio:
  - Deterioro cognitivo o alteración cerebelosa progresiva
  - Alteraciones visuales o extrapiramidales menos frecuente
- Fase de Estado:
  - La demencia imprescindible para diagnóstico
    - Sino al principio, aparece en su evolución
  - mioclonías (85 %) seguido de alteraciones cerebelosas y extrapiramidales.
  - Empeora rápido a una demencia severa y/o un mutismo acinético

Table 3 Diagnosis of sporadic CJD

- Awareness of sCJD
- A rapidly progressive dementia (75 % < 6 m; 95 % < 12 m)
- Other early neurological features (especially cerebellar or visual)
- Myoclonus
- Exclusion of other diagnoses (including other forms of CJD)
- MRI — Exclusion of other diagnoses; Findings suggestive of sCJD
- EEG — Periodic discharges
- CSF — Exclusion of other diagnoses (e.g. no pleocytosis); Positive 14-3-3

Características de la Series de ECJ definitivo en la Literatura

Grupo	USA [11] N = 232	España N= 191	Francia [10] N = 232
Sexo V / H	**1,05**	**0,86**	**0,83**
Edad media	**60 ± 9**	**67,6 ± 0,66**	**61,5 ± 9,7**
Duración (m)	**8 ± 11**	**6,55**	**7,6 ± 12,4**
Formas heredita.	**14 %**	**4,9 %**	**5 %**
Debut clínico rápido gradual	 **13 %** **80 %**	 **36 %** **64 %**	 **20 %** **80 %**

Patrón de Inicio de la EETHs en España

Grupo	EETHs (N= 565)	ECJ def (N= 191)
Demencia rápida	**35,4**	**36,13**
Cerebelosa	**9,73**	**10,99**
Demencia progresiva	**8,5**	**9,95**
Heidenhein	**2,65**	**4,19**
Psiquiátrica	**4,25**	**2,09**
Extrapiramidal	**2,12**	**2,09**
Vascular	**1,24**	**2,09**
No consta	**36**	**32,4**

Patrón de Inicio de la ECJ definitiva en diversas series

Grupo	España 1993-02 N = 191	USA [11] 1963-93 N = 232	UK [2] 1990-94 N = 144	Francia [10] 1968-82 N = 232
Demencia	**45,2**	**48**	**19**	**31**
Cerebelosa / Ataxia	**11**	**33**	**39**	**34**
T. del Comportamiento	**15**	**29**	**2**	**29**
Visual	**4,2**	**19**	**10**	**17**
Extrapiramidal	**2**	**4**	**2**	**2**
Mareo	**ND**	**13**	**ND**	**7**
Sensitiva	**ND**	**5**	**ND**	**6**

Clínica en fase de Estado en España

Grupo	EETHs (N= 565)	ECJ def (N= 191)
Demencia	100	100
Mioclonias	78,6	85,9
Cerebelo	57,7	62,3
Visual	41,4	47,6
Psiquiátrica	17,35	22
Extrapiramidal	48,5	49,2
Mutismo	40,5	42,4
Piramidal	36	35,6
Sensitivo	1,6	1

Clínica de la fase de Estado de la ECJ definitiva

Grupo	España 1993-02 (N= 191)	USA [11] 1963-93 N = 232	UK [2] 1990-94 N = 144	Francia [10] 1968-82 N = 232
Demencia	100	100	100	100
Mioclonias	86	78	85	88
Cerebelosa / Ataxia	62,3	71	85	61
Piramidal	36	62	62	43
Visual	48	ND	52	42
Extrapiramidal	49,2	56	34	67
Mutismo	42,4	ND	75	ND
Disfasia	ND	ND	58	ND
Comportamiento	ND	49	ND	49

Diagnóstico Clínico de las EETH

- ECJ como diagnóstico de exclusión
- Clásicamente solo el EEG como ± típico y específico
- Ahora otras pruebas permiten diagnóstico + específico
- ECJ hereditarias:
  - clínica variada (edad + tempranas y evolución + prolongada)
  - Alto grado de alerta para solicitar análisis genéticos
    - aquellos sin historia familiar
    - pasar desapercibido (ECJe u otra demencia)
- ECJ yatrógena:
  - formas = ECJe (contagio vía central) y otras cuadro cerebeloso progresivo (vía periférica)
  - Antecedentes personales nos alertarán de los grupos de riesgo

Clínica Inicial en los diversos tipos moleculares de ECJ esporádica

Table 5. Symptoms and Signs at Onset (in %)

sCJD Group (No. of Cases)	MM1 (199)	MV1 (8)	VV1 (3)	MM2-C (6)	MM2-T (6)	MV2 (27)	VV2 (45)
Cognitive[a]	70	50	100	100	67	74	27
Aphasia	23	25	33	33	0	11	0
Visual[b]	26	12	0	0	0	0	0
Oculomotor	6	12	0	0	17	19	32
Gait or limb ataxia	33	75	0	0	67	81	100
Dysarthria	5	12	0	0	33	11	13
Myoclonus	18	12	0	0	0	0	0
Other dyskinesias	4	0	0	0	0	0	0
Pyramidal	6	0	0	0	0	0	0
Sensory	7	25	0	0	0	7	15
"Psychiatric"[c]	28	12	0	0	50	34	19
Insomnia	8	0	0	0	17	15	9
Unilateral	25	25	0	0	0	7	4

P Parchi et al. Ann Neurol 1999; 46: 224-233

Clínica en los diversos tipos moleculares de ECJ esporádica

Table 6. Symptoms and Signs throughout the Entire Course of the Illness (in %)

sCJD Group (No. of Cases)	MM1 (203)	MV1 (8)	VV1 (3)	MM2-C (6)	MM2-T (6)	MV2 (27)	VV2 (47)
Cognitive[a]	94[b]	75[b]	100	100	100	100	100
Aphasia	36	25	100	83	0	37	0
Apraxia	10	0	67	33	0	26	0
Visual[c]	42	12	0	0	0	0	0
Oculomotor	8	12	33	0	33	19	32
Limb or gait ataxia	52	87	33	17	100	100	100
Dysarthria	7	37	0	0	67	26	48
Myoclonus (mo)	97 (1.8)	100 (2)	67 (7.5)	67 (10.5)	50 (9)	77 (9)	66 (4.2)
Seizures	19	12	0	33	0	11	2
Other dyskinesias	18	12	0	17	17	22	20
Parkinsonism	7	0	33	33	17	22	6
Pyramidal[d]	60	62	67	83	50	81	50
Sensory	7	25	0	0	0	7	15
"Psychiatric"[e]	34	12	0	0	67	44	21
Insomnia	8	0	0	0	67	15	15

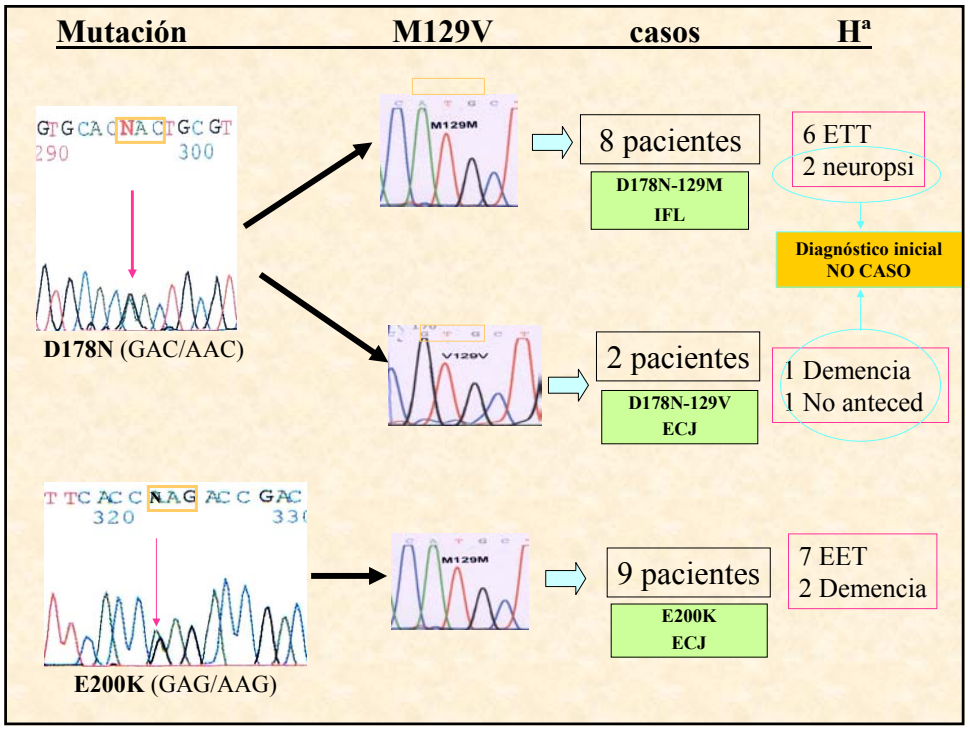
P Parchi et al. Ann Neurol 1999; 46: 224-233

Table 5 Diagnosis of genetic prion disease

Awareness of possibility
Awareness of clinical phenotypic variability
Exclusion of other diagnoses

Diagnosis of a prion disease (clinically or neuropathologically)

Family history
Blood test: PRNP mutation screening



Diagnóstico de la ECJv

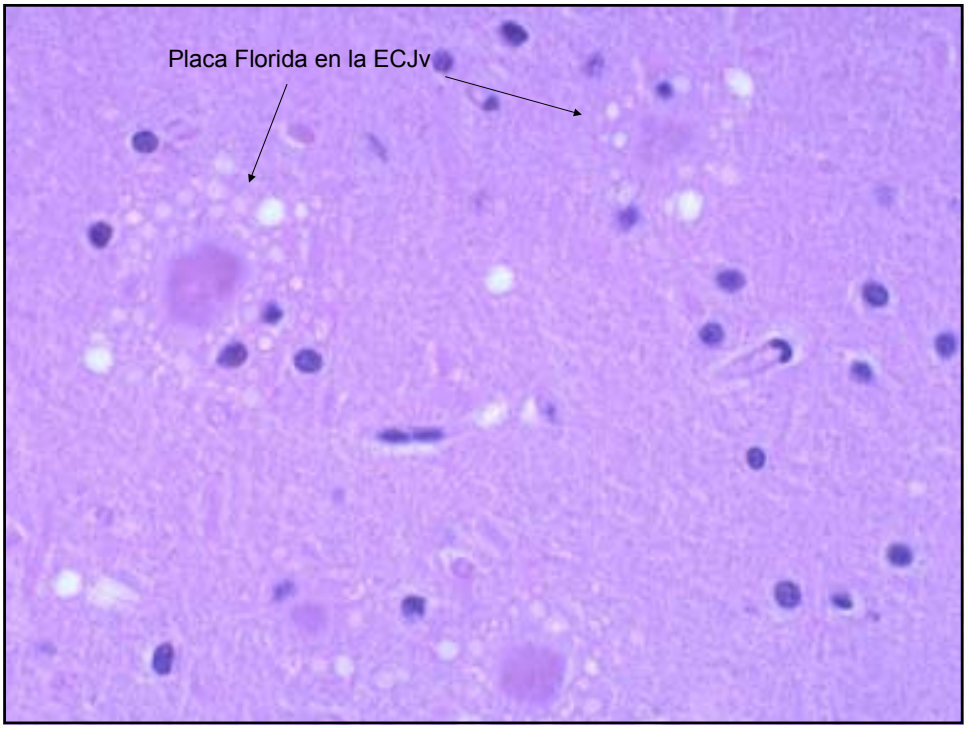
- Características clínicas propias (diferentes de la ECJe)
  - edad de presentación más precoz (media de 28 a.), aunque hay algún caso tardío descrito
  - mayor duración (media de 14 meses) de la enfermedad
  - clínica inicial con sintomatología psiquiátrica (sobre todo depresión) o con trastornos del comportamiento y la posterior aparición de un cuadro de ataxia y déficit cognitivo.
  - EEG no presenta el patrón periódico típico
  - proteína 14-3-3 + en un porcentaje menor (41 %) que ECJe.
  - RM con hiperintensidad en el tálamo (signo del pulvinar)
  - PrPsc en una biopsia de amígdala (papel diagnóstico debatido)

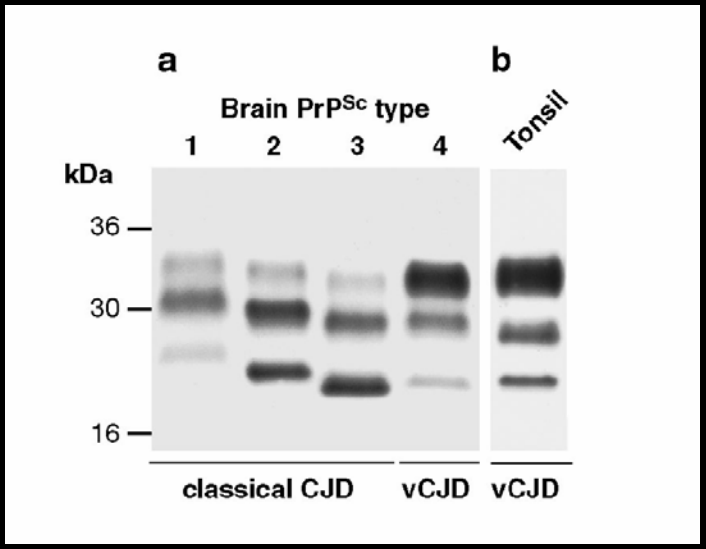
Table 6 Differences between sporadic and variant CJD

	sCJD	vCJD
Mean age at death	66 years	29 years
Median duration of illness	4 months	14 months
Thalamic MRI high signal	Caudate/putamen 60%	Pulvinar 90%
EEG	"Typical" 70%	"Typical" 0%
Neuropathology	Plaques 10%	Florid plaques 100%

Hallazgos Clínicos en la ECJ / ECJnv

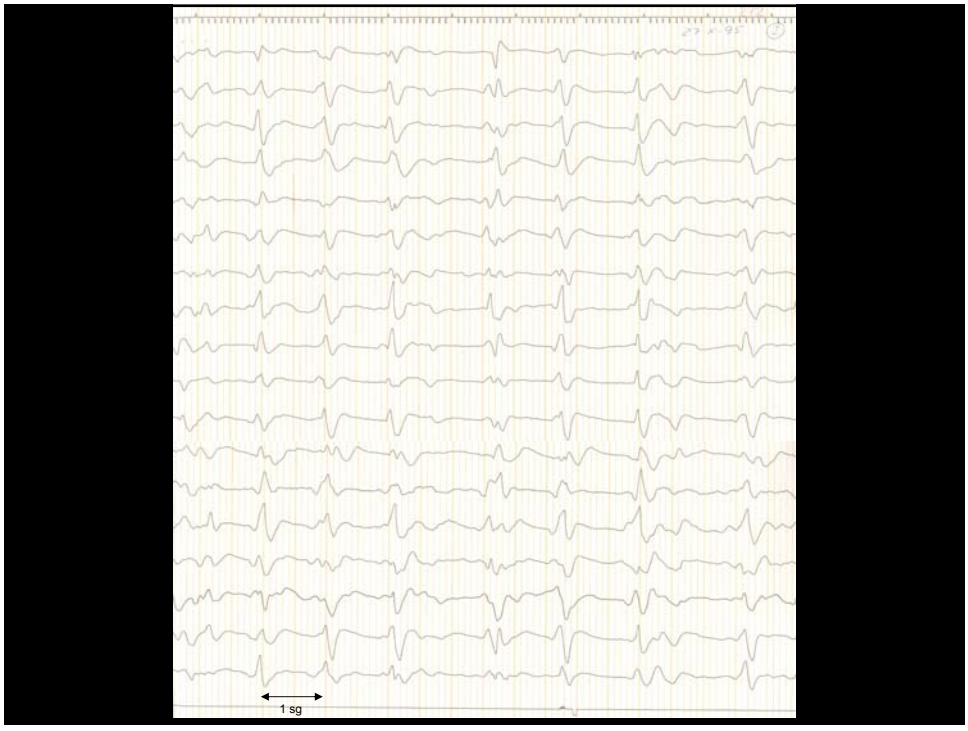
F. Inicio / F. Estado	ECJ	ECJnv
Stº Psiquiátrica	29 / 49 %	63 / 97 %
Stº Sensitiva (parestesias, dolor..)	5 / 11 %	24 / 68 %
Ataxia	34 / 61 %	80 / 100 %
Demencia	31 / 96 %	0 / 100 %
Mov. involuntarios **mioclonias**	2 / 67 % 0 / 88 %	6 / 94 % 0 / 71 %
Edad	62 (19-83) a.	28 (12-79) a.
Duración	7,6 (1-30) m	12 (8-23) m


Placa Florida en la ECJv


a
b
Brain PrPSc type
1
2
3
4
Tonsil
kDa
36
30
16
classical CJD
vCJD
vCJD

EEG

- Jones y Nevin en 1954
- 1ª prueba con alteraciones + específicas en la ECJ
- proteína 14-3-3 y RM ↓ protagonismo
- fácil acceso y reproducibilidad, conocimiento neurólogos
- En el trazado típico:
  - complejos de ondas agudas periódicas
  - síncronos y simétricos,
  - frecuencia de 1/segundo aproximadamente
  - sobre ambos hemisferios cerebrales
- Los resultados = nº de EEGs y evolución del caso



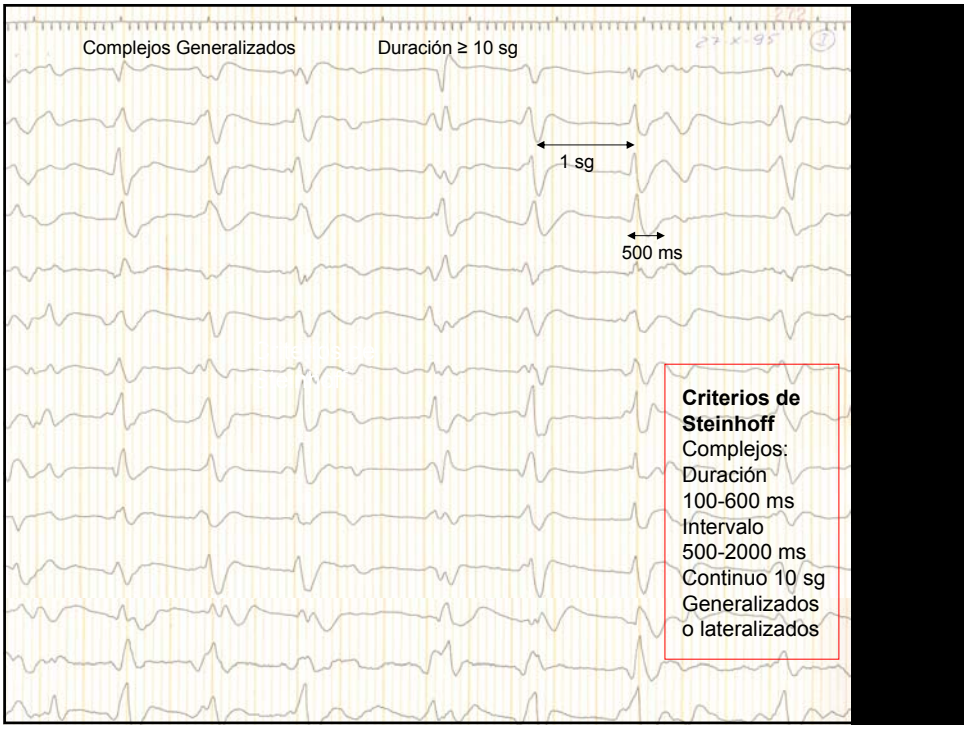


Table 1. Objective Diagnostic Criteria of Periodic Sharp-Wave Complexes Typical for Sporadic Creutzfeldt–Jakob Disease

- Strictly periodic cerebral potentials, the majority with a duration between 100 and 600 milliseconds and an intercomplex interval between 500 and 2,000 milliseconds
- Generalized and lateralized complexes accepted
- At least five repetitive intervals with a duration difference of less than 500 milliseconds to rule out semiperiodic activity

From Steinhoff and colleagues.[8]

EEG en las EETHs en España

Grupo	EETHS (N= 565)	ECJ def (N= 191)
EEG		
Practicado	96, 3 (544)	99 (189)
Alterado (típico)	54, 8 (298)	67, 5 (129)
sensibilidad	55,6	-
especificidad	81,8	-

Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt–Jakob disease

I. Zerr, MD; M. Pocchiari, MD; S. Collins, MD, FRACP; J.P. Brandel, MD; J. de Pedro Cuesta, MD; R.S.G. Knight, FRCP(E); H. Bernheimer, MD; F. Cardone, PhD; N. Delasnerie-Lauprêtre, MD; N. Cuadrado Corrales, MD; A. Ladogana, MD; M. Bodemer; A. Fletcher, BSc; T. Awan, MD; A. Ruiz Bremón, MD; H. Budka, MD; J.L. Laplanche, PhD; R.G. Will, MD; and S. Poser, MD

Article abstract—*Objective:* To improve diagnostic criteria for sporadic Creutzfeldt–Jakob disease (CJD). *Methods:* Pooled data on initial and final diagnostic classification of suspected CJD patients were accumulated, including results of investigations derived from a coordinated multinational study of CJD. Prospective analysis for a comparison of clinical and neuropathologic diagnoses and evaluation of the sensitivity and specificity of EEG and 14-3-3 CSF immunoassay were conducted. *Results:* Data on 1,003 patients with suspected CJD were collected using a standard questionnaire. After follow-up was carried out, complete clinical data and neuropathologic diagnoses were available in 805 cases. In these patients, the sensitivity of the detection of periodic sharp wave complexes in the EEG was 66%, with a specificity of 74%. The detection of 14-3-3 proteins in the CSF correlated with the clinical diagnosis in 94% (sensitivity). The specificity (84%) was higher than that of EEG. A combination of both investigations further increased the sensitivity but decreased the specificity. *Conclusions:* Incorporation of CSF 14-3-3 analysis in the diagnostic criteria for CJD significantly increases the sensitivity of case definition. Amended diagnostic criteria for CJD are proposed.

NEUROLOGY 2000;55:811–815

Table 3 *Comparative diagnostic value of EEG and CSF analysis in cases of Creutzfeldt–Jakob disease (CJD) initially classified as "probable" or "possible" CJD*

Characteristic	n = 805	PSWC in EEG	14-3-3 in CSF	PSWC in EEG or 14-3-3 in CSF*	PSWC in EEG and 14-3-3 in CSF†
CJD		144/219	205/219	213/219	144/219
Not CJD		11/43	7/43	15/43	3/43
Sensitivity, %		66	94	97	66
Specificity, %		74	84	65	93
Positive predictive value, %		93	97	93	98
Negative predictive value, %		30	72	79	35

* Test positive: patients with either periodic sharp wave complexes (PSWC) in EEG or 14-3-3 in CSF. Test negative: patients without PSWC in EEG and without 14-3-3 in CSF.
† Test positive: only patients who had PSWC in EEG and 14-3-3 in CSF. Test negative: all other patients.

Table 3 *Comparative diagnostic value of EEG and CSF analysis in cases of Creutzfeldt–Jakob disease (CJD) initially classified as "probable" or "possible" CJD*

Characteristic	PSWC in EEG	14-3-3 in CSF	PSWC in EEG or 14-3-3 in CSF*	PSWC in EEG and 14-3-3 in CSF†
CJD	144/219	205/219	213/219	144/219
Not CJD	11/43	7/43	15/43	3/43
Sensitivity, %	66	94	97	66
Specificity, %	74	84	65	93
Positive predictive value, %	93	97	93	98
Negative predictive value, %	30	72	79	35

* Test positive: patients with either periodic sharp wave complexes (PSWC) in EEG or 14-3-3 in CSF. Test negative: patients without PSWC in EEG and without 14-3-3 in CSF.
† Test positive: only patients who had PSWC in EEG and 14-3-3 in CSF. Test negative: all other patients.

Table 3 *Comparative diagnostic value of EEG and CSF analysis in cases of Creutzfeldt–Jakob disease (CJD) initially classified as "probable" or "possible" CJD*

Characteristic	PSWC in EEG	14-3-3 in CSF	PSWC in EEG or 14-3-3 in CSF*	PSWC in EEG and 14-3-3 in CSF†
CJD	144/219	205/219	213/219	144/219
Not CJD	11/43	7/43	15/43	3/43
Sensitivity, %	66	94	97	66
Specificity, %	74	84	65	93
Positive predictive value, %	93	97	93	98
Negative predictive value, %	30	72	79	35

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† Test positive: only patients who had PSWC in EEG and 14-3-3 in CSF. Test negative: all other patients.

Diagnostic Value of Periodic Complexes in Creutzfeldt–Jakob Disease

Bernhard J. Steinhoff, MD,[1,2] Inga Zerr, MD,[2] Maya Glatting, MD,[2] Walter Schulz-Schaeffer, MD,[3] Sigrid Poser, MD,[2] and Hans A. Kretzschmar, MD[3,4]

In 1996, our group published objective electroencephalogram (EEG) criteria to define periodic sharp-wave complexes (PSWCs) suggestive for Creutzfeldt–Jakob disease (CJD). These criteria have since then been strictly applied in all cases reported to us as possible CJD in the course of the German CJD surveillance study. Furthermore, EEG analysis of the records was performed without any additional information on complementary clinical and laboratory data. In this study, we investigated sensitivity, specificity, and the predictive values of these EEG criteria exclusively in cases in which autopsy confirmed (n = 150) or excluded (n = 56) CJD. EEG criteria were positive in 64% (n = 96) of the CJD cases and falsely positive in 9% (n = 5) of other dementias. The resulting figures for sensitivity, specificity, and positive and negative predictive values were 64%, 91%, 95%, and 49%, respectively. In the falsely positive cases, Alzheimer's disease (n = 4) and vascular dementia (n = 1) were the underlying diseases. However, only in one of these five cases both clinical and EEG data would have led to the false-positive result to diagnose probable CJD. These data prove the high diagnostic value of our objective EEG criteria in CJD.

Ann Neurol 2004;56:702–708

Sensibilidad: 63 % ; Especificidad: 98 %; VPP: 99 %; VPN: 49

Sensibilidad y especificidad diagnóstica de las pruebas en ECJ

	sensibilidad	especificidad	VPP	VPN
EEG				
España	55,6	81,8	93,1	29,4
UE	66	74	93	30
Steinhoff, 2004	64	91	95	49
14-3-3				
España	55,6	81,8	29,4	93,1
UE	94	84	97	72
RM *				
T2, Flair	63	88	-	-
Difusión	92,3	93,8	-	-

Table 3. Sensitivity of Technical Investigations by Prion Protein Type and Codon 129 Genotype (n = 108)

	PSWCs in EEG (n)	14-3-3 Protein in CSF (n)	NSE in CSF >25 ng/ml (n) Median (range)	Hyperintense Basal Ganglia in MRI (n)
PrP type and codon 129 genotype				
MM1	80% (56/70)	96% (67/70)	93% (65/70) 79.5 (10–270)	68% (13/19)
MM2	33% (1/3)	100% (3/3)	67% (2/3) 30 (17–40)	(0/2)
MV1	75% (6/8)	100% (8/8)	100% (8/8) 65 (25–213)	(2/2)
MV2	0% (0/10)	30% (3/10)	50% (5/10) 17 (11–28)	89% (8/9)
VV1	0% (0/2)	100% (1/1)	100% (1/1) 60	0% (0/1)
VV2	0% (0/15)	100% (15/15)	93% (13/14) 112 (24–175)	70% (7/10)
PrP type				
1	78% (62/80)	96% (76/79)	94% (74/79)	68% (15/22)
2	4% (1/28)	75% (21/28)	74% (20/27)	71% (15/21)

PrP = prion protein; PSWCs = periodic sharp and slow wave complexes; EEG = electroencephalogram; CSF = cerebrospinal fluid; NSE = neuron-specific enolase; MRI = magnetic resonance imaging; MM = methionine homozygosity; MV = methionine/valine heterozygosity; VV = valine homozygosity.

Zerr I, et al. Current clinical diagnosis in CJD: identification of uncommon variants. Ann Neurol 2000; 48: 323-329

Table 7. Electroencephalographic Findings (in %)

sCJD Groups (No. of Cases)	MM1 (175)	MV1 (7)	VV1 (3)	MM2-C (6)	MM2-T (6)	MV2 (26)	VV2 (42)
Typical PSWCs[a]	80 (2)	71.4 (1.9)	0	0	0	7.7 (8)	7.1 (8)
Paroxysmal Discharges[b]	9.7 (1.8)	14.3 (2)	0	16.6 (10)	0	19.2 (14)	2.4 (6)
Slowing only	10.3 (1.6)	14.3 (2.5)	100 (8)	83.4 (9.5)	100 (12)	73.1 (9.5)	90.5 (4.1)

The mean time in months of evolution of symptoms at which the electroencephalographic pattern was recorded is shown in parentheses.

[a]Periodic sharp-waves complexes.
[b]Paroxysmal discharges without periodism.

sCJD = sporadic Creutzfeldt-Jakob disease; MM2-C = MM genotype type 2 (PrP^{Sc})-cortical; MM2-T = MM genotype type 2 (PrP^{Sc})-thalamic.

Parchi P et al. Classification of sCJD based on molecular and phenotipic analysis of 300 subjects. Ann Neurol 1999; 46: 224-233

Patrón EEG similar al de la ECJ

E. Alzheimer
D C Lewy
E. Binswanger
SIDA
Abcesos cerebrales múltiples
LMP
MELAS
Encefalopatía post-anóxica

Encefalopatías metabólicas:
- Hepática
- hipoglucemia,
- Hiperhiponatremia
- Hiperamoniemia
- hiperparatiroidismo

Encefalopatías tóxicas:
- Baclofen
- Mianserina
- Litio
- metrizamida

Proteina 14-3-3

- Harrington, 1986
- Proteina de 30 kDa de la Familia 14-3-3. Neuronas (sinapsis)
- Alta sensibilidad y especificidad según contexto clínico (90 %)
- No es una prueba patognomónica (destrucción neuronal)
- Problemas de inspección visual de la +
- Falsos positivos en:
  - AVC, HSA
  - Encefalitis de diversos tipos (víral, Hashimoto, paraneoplasica, etc..)
  - Encefalopatía metabólica, hipóxica
  - ELA, Glioblastoma
  - Otras demencias rápidas (EA, DMI, DCL..)
  - Contaminación de sangre en LCR
- Falsos negativos: Fase de la enfermedad (muy pronto o muy tarde)

Table 1 Sensitivity and specificity of diagnostic techniques in sporadic CJD

	n	Sensitivity (%)	Specificity (%)
Cerebrospinal fluid			
14-3-3	1136	95	93
NSE (> 35 ng/ml)	1276	81	92
S-100 (> 4.2 ng/ml)	135	84	91
Tau (> 1400 pg/ml)	290	93	91
PrP^{Sc}	34	20	100
MRI	208	63	92
EEG	805	66	74

Data from Zerr & Poser[2].

CME

Sensitivity of 14-3-3 protein test varies in subtypes of sporadic Creutzfeldt–Jakob disease

R.J. Castellani, MD; M. Colucci, MD; Z. Xie, MD; W. Zou, MD; C. Li, MD; P. Parchi, MD; S. Capellari, MD; M. Pastore, PhD; M.H. Rahbar, PhD; S.G. Chen, PhD; and P. Gambetti, MD

Abstract—*Background:* The increase of the 14-3-3 protein in CSF is used as a diagnostic test in Creutzfeldt–Jakob disease (CJD), but the sensitivity and specificity of the 14-3-3 test are disputed. One reason for the dispute may be the recently established heterogeneity of sporadic CJD. The relationship between CSF 14-3-3 protein and sporadic CJD subtypes, distinguished by electrophoretic mobility of proteinase K-resistant prion protein (PrP^{Sc}) and genotype at codon 129 of the prion protein gene, has not been elucidated. *Methods:* The authors examined the 14-3-3 protein test in 90 patients with sporadic CJD. PrP^{Sc} type (type 1 or type 2) and the genotype at polymorphic codon 129 were determined in each patient. Mutations were excluded by prion gene sequencing. *Results:* The authors' findings indicate that the sensitivity of the 14-3-3 test is higher in patients with molecular features of the classic sporadic CJD than in patients with the nonclassic CJD subtypes. The difference appears to be related to the PrP^{Sc} type and not to the codon 129 genotype. Disease duration before 14-3-3 testing might also have an influence because it was shorter in classic sporadic CJD. *Conclusion:* The Creutzfeldt–Jakob disease clinical subtype should be considered when interpreting results of the 14-3-3 test.

NEUROLOGY 2004;63:436–442

Table 4 *Sensitivity of the 14-3-3 test according PrP^{Sc} type and sporadic CJD phenotype*

PrP^{Sc} type and phenotype	14-3-3 Test sensitivity
PrP^{Sc} type 1	94% (51/54)*
PrP^{Sc} type 2	75% (27/36)†
Classic sCJD	94% (48/51)*
Nonclassic sCJD	77% (30/39)‡

* Positive/total cases.
† Type 1 vs type 2, $p < 0.01$.
‡ Classic vs nonclassic, $p < 0.025$.

Table 3. Sensitivity of Technical Investigations by Prion Protein Type and Codon 129 Genotype (n = 108)

	PSWCs in EEG (n)	14-3-3 Protein in CSF (n)	NSE in CSF >25 ng/ml (n) Median (range)	Hyperintense Basal Ganglia in MRI (n)
PrP type and codon 129 genotype				
MM1	80% (56/70)	96% (67/70)	93% (65/70) 79.5 (10–270)	68% (13/19)
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PrP = prion protein; PSWCs = periodic sharp and slow wave complexes; EEG = electroencephalogram; CSF = cerebrospinal fluid; NSE = neuron-specific enolase; MRI = magnetic resonance imaging; MM = methionine homozygosity; MV = methionine/valine heterozygosity; VV = valine homozygosity.

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J Neurol (2003) 250 : 629–630
DOI 10.1007/s00415-003-1059-3

LETTER TO THE EDITORS

Brit Mollenhauer
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Diagnostic problems during late course in Creutzfeldt-Jakob disease

Received: 5 November 2002
Accepted: 9 December 2002

Sirs: Creutzfeldt-Jakob disease (CJD) is a rare, transmissible brain disorder affecting approximately

startle response. Three months later she could no longer walk unassisted. EEG did not show PSWCs. MRI showed mild atrophy, without high signal intensities in the basal ganglia. Because of the rapid progression of dementia and myoclonus, CJD was suspected and the patient was reported to the German CJD Surveillance Unit. A lumbar puncture was carried out and CSF was positive for proteins 14-3-3 (Table 1). The disease was classified as "probable CJD" according to the classification criteria [5] because of the neurological signs and the positive 14-3-3.

Four months after the first symptoms typical PSWCs were seen in the EEG. One year after onset she was bedridden with general increased muscle tone and akinetic mutism. She had no myoclonus. EEG no longer showed typical PSWCs. Lumbar puncture was repeated and was negative for proteins 14-3-3 (Table 1). Another lumbar puncture and MRI 21 months after onset were performed. Analysis for proteins 14-3-3 was negative and MRI (Fig. 1A–D) showed massive atrophy.

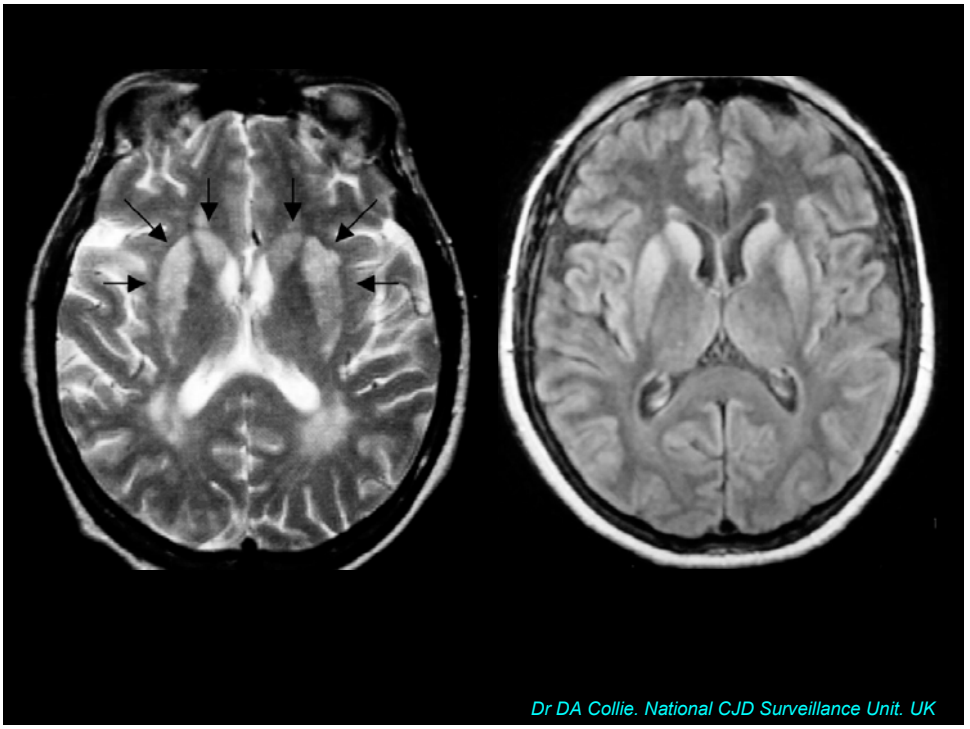
She died from pneumonia 26 months after onset of disease. Neuropathological examination verified the diagnosis of sporadic CJD. The patient had no mutation in the prion protein gene (*PRNP*) and was homozygous for methionine at codon 129. Such patients usually experience rapid progression with

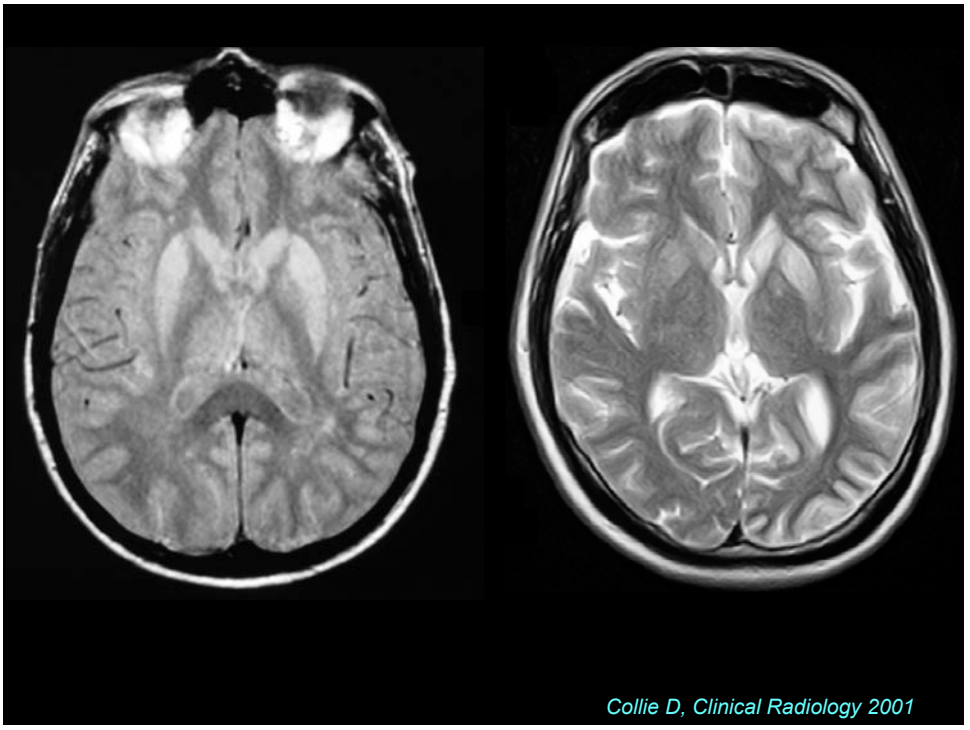
Neuroimagen: TAC / RM

- Valor inicial como técnica de exclusión
- ↑ relevancia en el diagnóstico de las EETHs
- La TAC normal en las fases iniciales
  - aparición de una atrofia cerebral progresiva,
  - hipodensidades de los lóbulos occipitales
- Hiperintensidades de señal en DP y T2 en los ganglios basales (núcleo del caudado y/o putamen)
  - menos habitual en áreas corticales cerebrales y/o cerebelosas, pálido, tálamo y excepcional en núcleo pulvinar
  - sensibilidad varia del 63-79 % con especificidad del 88-93 %
- MV2 (clínica atípica y EEG y 14-3-3 -) la RM es +

Neuroimagen en las EETHs en España

Grupo	EETHS (N= 565)	ECJ def (N= 191)
TAC Cerebral		
Practicado	75,7 (428)	74,3 (142)
Alterado (típico)	50	46,5


Dr DA Collie. National CJD Surveillance Unit. UK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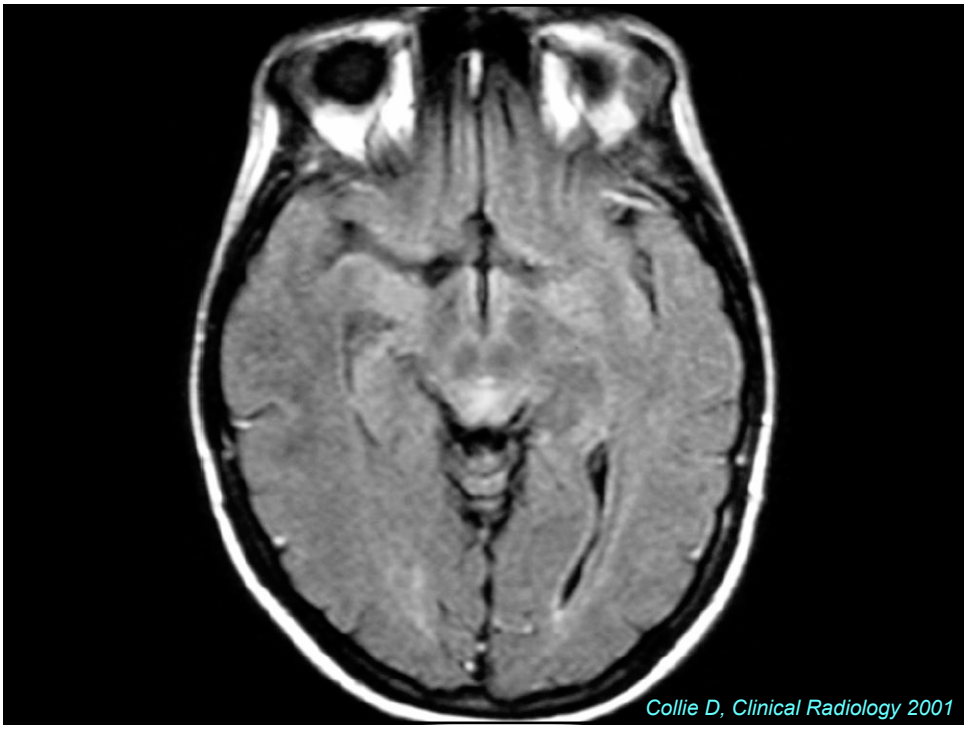
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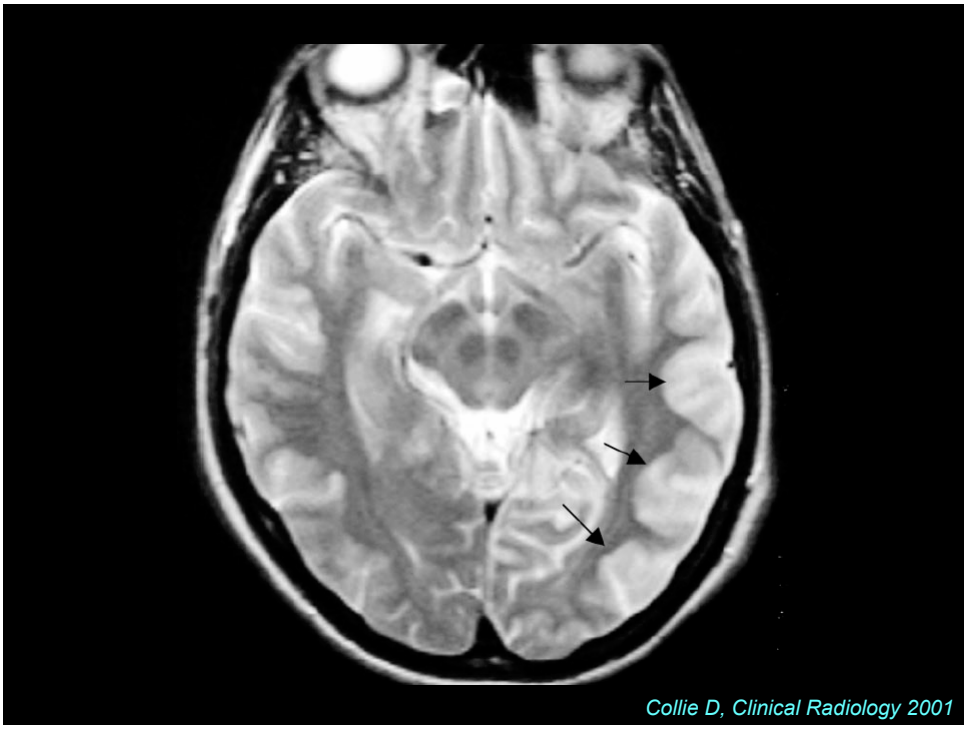
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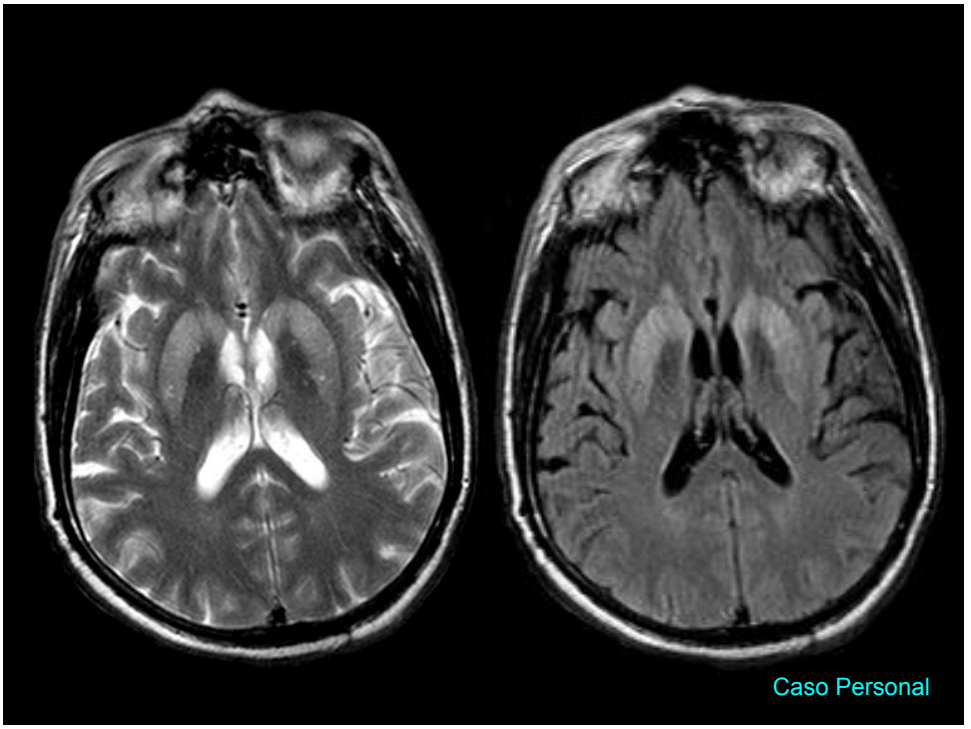
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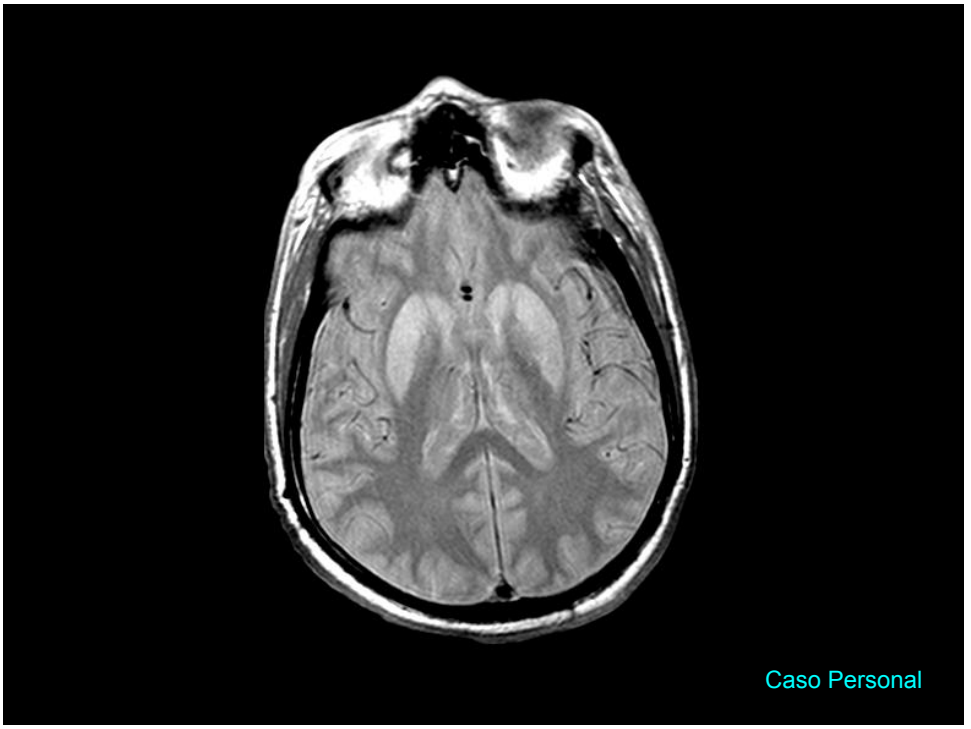
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CME

Sporadic Creutzfeldt-Jakob disease

Magnetic resonance imaging and clinical findings

B. Meissner, MD; K. Köhler; K. Körtner, MD; M. Bartl, MD; U. Jastrow, MD; B. Mollenhauer, MD; A. Schröter, MD; M. Finkenstaedt, MD; O. Windl, PhD; S. Poser, MD; H.A. Kretzschmar, MD; and I. Zerr, MD

Abstract—*Objective:* To assess if clinical features, prion protein codon 129, and molecular subtype correlate with MRI basal ganglia hyperintensity in sporadic Creutzfeldt-Jakob disease (CJD). *Methods:* The authors studied 219 patients including 153 confirmed CJD cases for their neurologic symptoms and MRI findings. The MRI was assessed by a blinded investigator for the presence of high signal intensity on T2-weighted images in the basal ganglia. *Results:* Patients with basal ganglia high signal on T2-weighted images were more likely to present with rapid progressive dementia in an early stage and shorter disease duration (median 6.7 months and 8.6 months). Surprisingly, among the CJD cases, patients without signal increase of the basal ganglia were shown to have a higher frequency of extrapyramidal disturbances (82% vs 70%). More striking differences were found for symptoms such as depression and sensory disturbances, which were more frequent among cases without signal increase. MRI was more likely to be diagnostic in patients with MV2 molecular subtype. *Conclusions:* Selected clinical and pathologic features correlate with the presence of basal ganglia high signal on T2-weighted MRI in patients with definite or probable CJD.

NEUROLOGY 2004;63:450–456

Estudio prospectivo de 219 pacientes (grupo de Gottingen, 2004) remitidos a Vig Epidemiológica; con análisis ciego de la RM (T2, Flair, DP)

Table 1 *Patient characteristics and MRI findings*

Classification	MRI+, n = 105	MRI−, n = 114	Total	Hyperintense basal ganglia on T2, %	Sensitivity/specificity
Definite	58	36	94	62	Sensitivity = 63%
Probable	39	20	59	66	
Other	8*	58	66	12	Specificity = 88%

* Encephalitis (n = 2) and one each of spinocerebellar ataxia, B-cell lymphoma, Lewy body dementia, Parkinson plus syndrome, multiple sclerosis, diagnosis unknown.

MRI+ = typical hyperintense basal ganglia; MRI− = no hyperintense basal ganglia.

RM (T2,Flair, DP): sensibilidad varia del 63-79 % con especificidad del 88-93 %

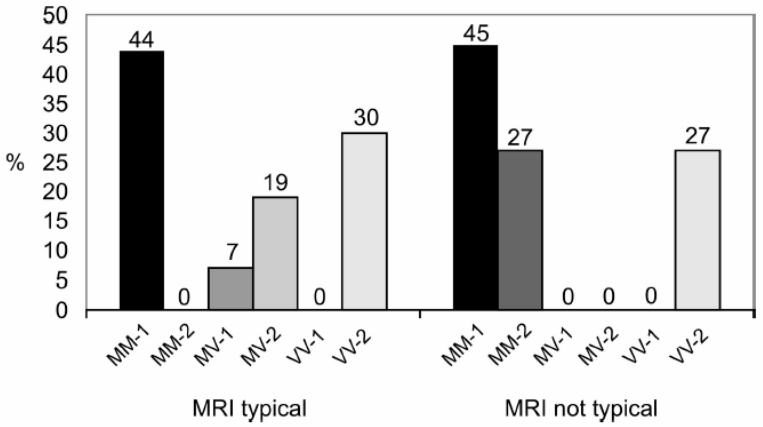


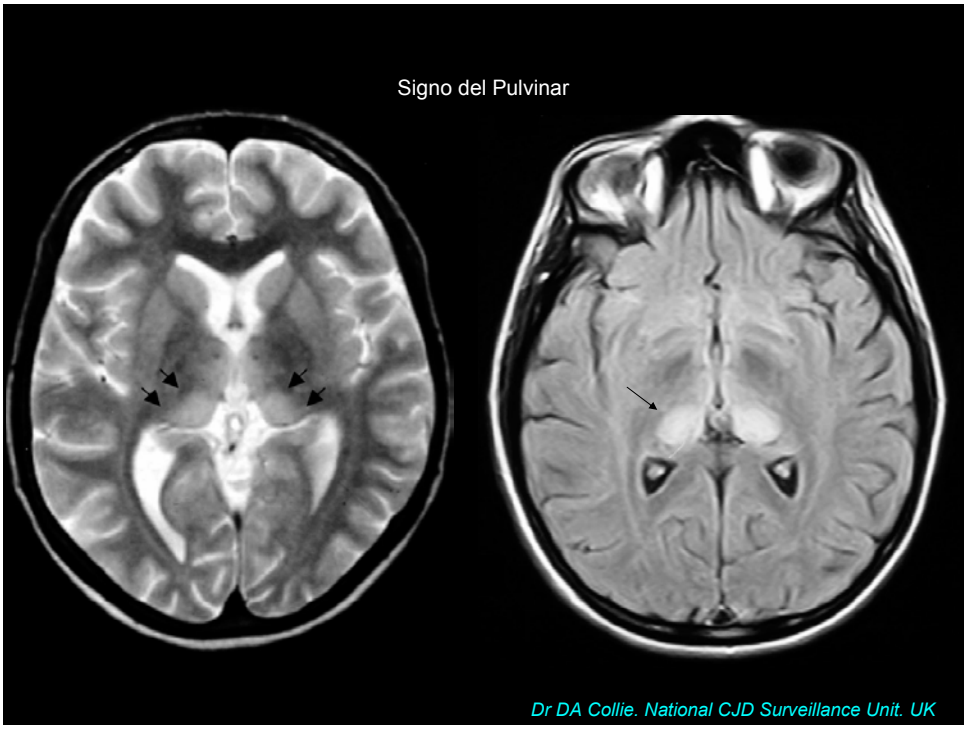
Figure 4. Molecular Creutzfeldt-Jakob disease phenotypes and MRI findings. Black represents the MM-1-phenotype. Dark gray represents the MM-2-phenotype. Medium gray represents the MV-1-phenotype. Light gray represents the MV-2-phenotype. Pale gray represents the VV-2-phenotype.

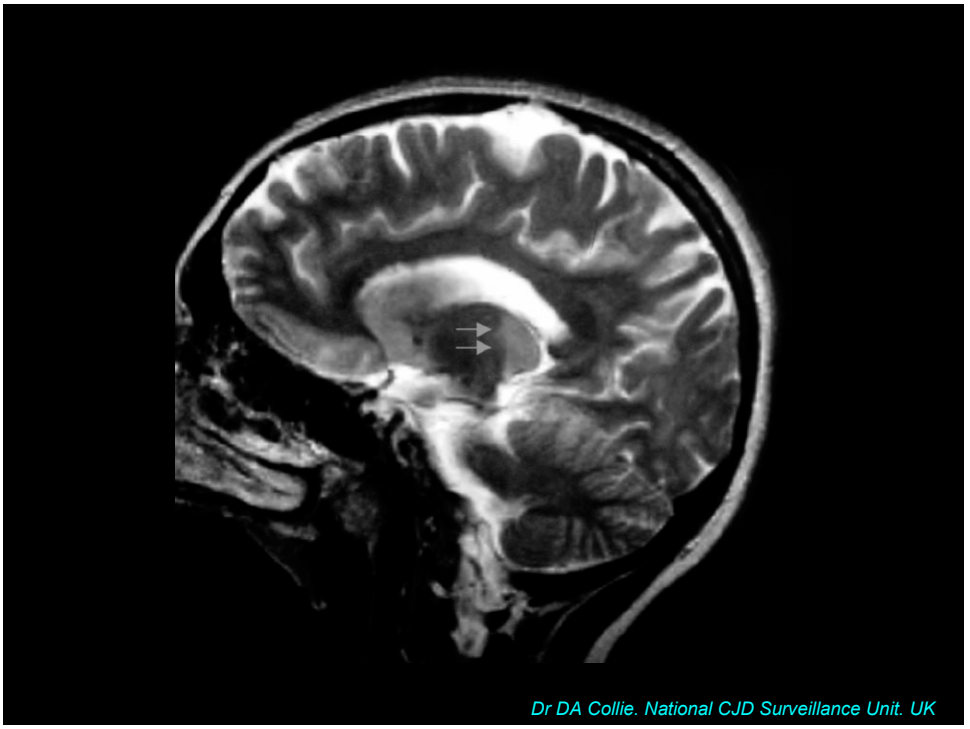
Neuroimagen en las EETHs en España

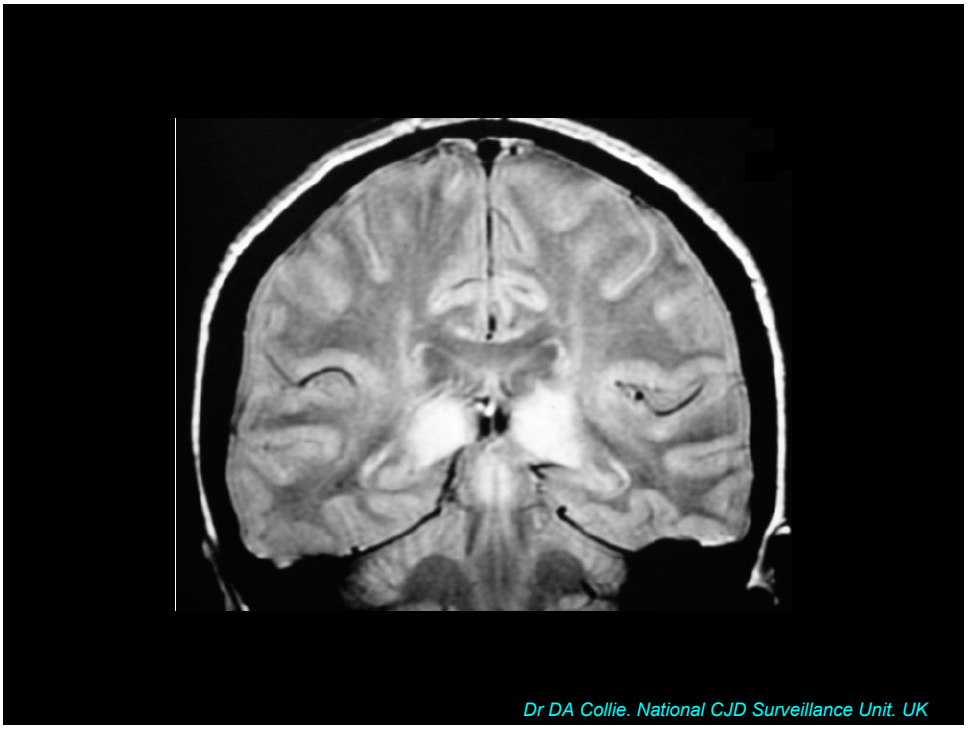
Grupo	EETHS (N= 565)	ECJ def (N= 191)
RM	**% (n)**	**% (n)**
Practicado	**62 (350)**	**66,5 (120)**
Alterada	**71,4**	**76**
inespecíficas	**43,4**	**59**
atrofia	**67,6**	**69,8**
Hiperseñal caudado	**16,8**	**20,8**
Hiperseñal tálamo	**2,29**	**3,94**
Signo pulvinar	**0**	**0**

ECJv y RM

- Signo del pulvinar: hiperintensidad de señal limitada a la parte posterior del tálamo (Flair)
  - El signo diagnóstico + valioso en ECJv
  - sensibilidad del 79 % y una especificidad cercana al 100 %
  - en ocasiones la única prueba diagnóstica alterada
  - incluido dentro de los criterios diagnósticos ECJv
- Descrito en ECJe, aunque la hiperintensidad de señal del núcleo pulvinar < que la de otros núcleos de la base
- Este signo puede aparecer en otras enfermedades pero con un perfil clínico muy diferente




Dr DA Collie. National CJD Surveillance Unit. UK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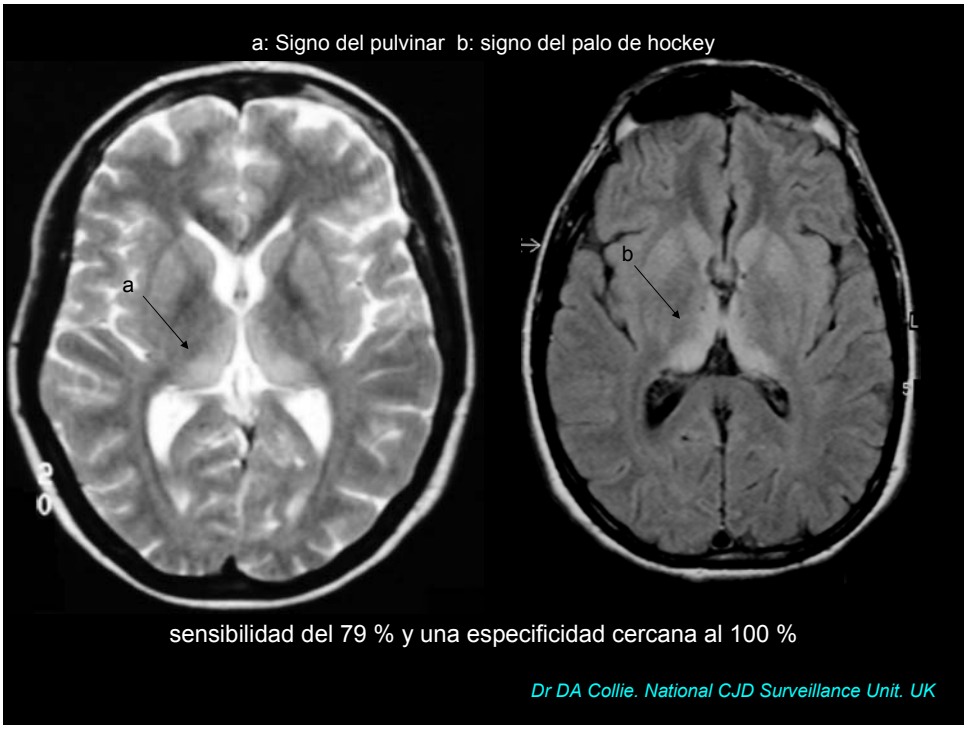
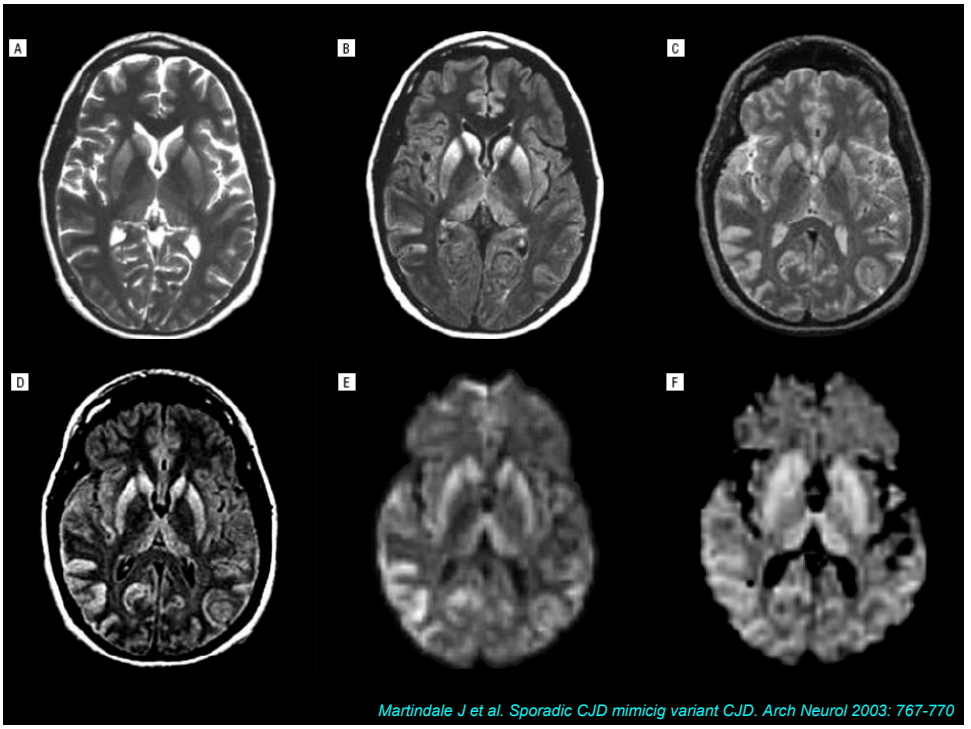

a: Signo del pulvinar b: signo del palo de hockey
a
b
sensibilidad del 79 % y una especificidad cercana al 100 %
Dr DA Collie. National CJD Surveillance Unit. UK


A
B
C
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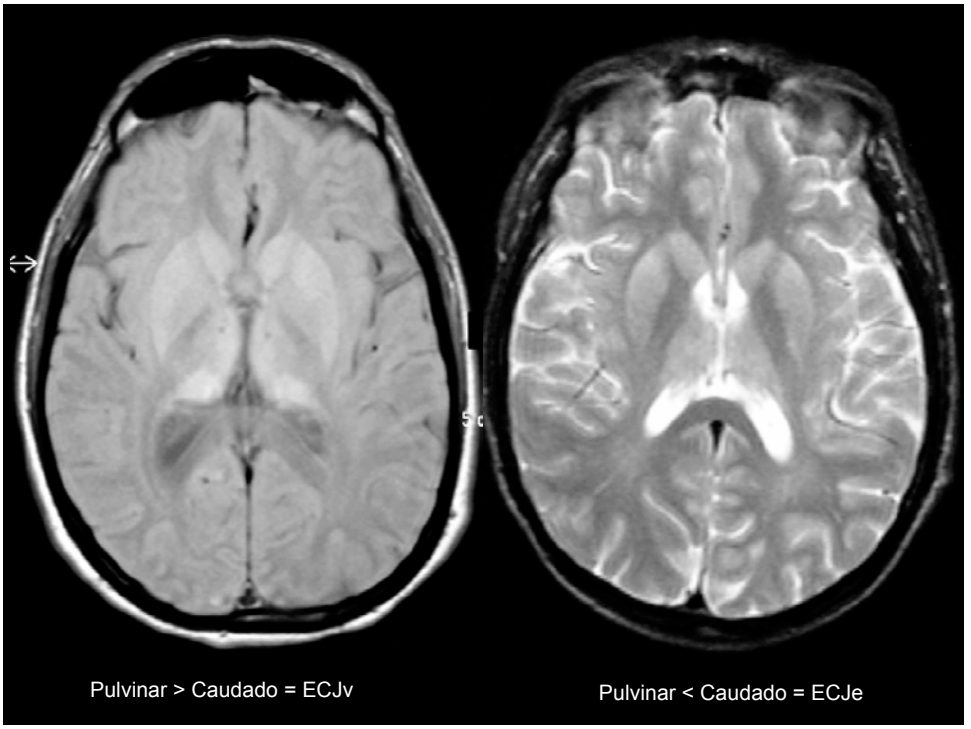
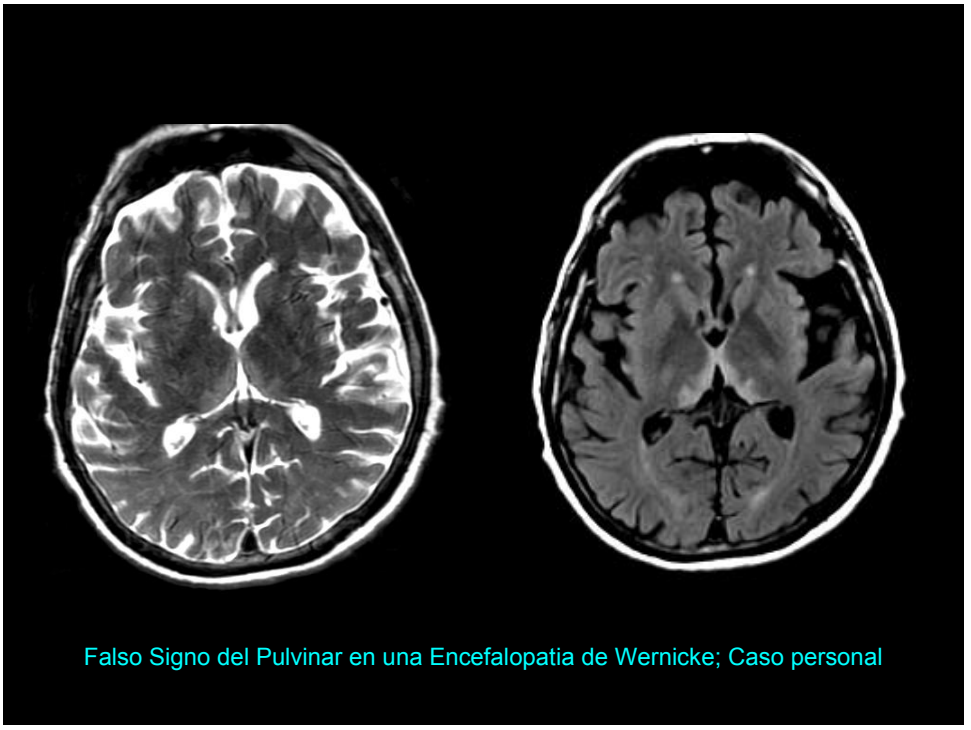
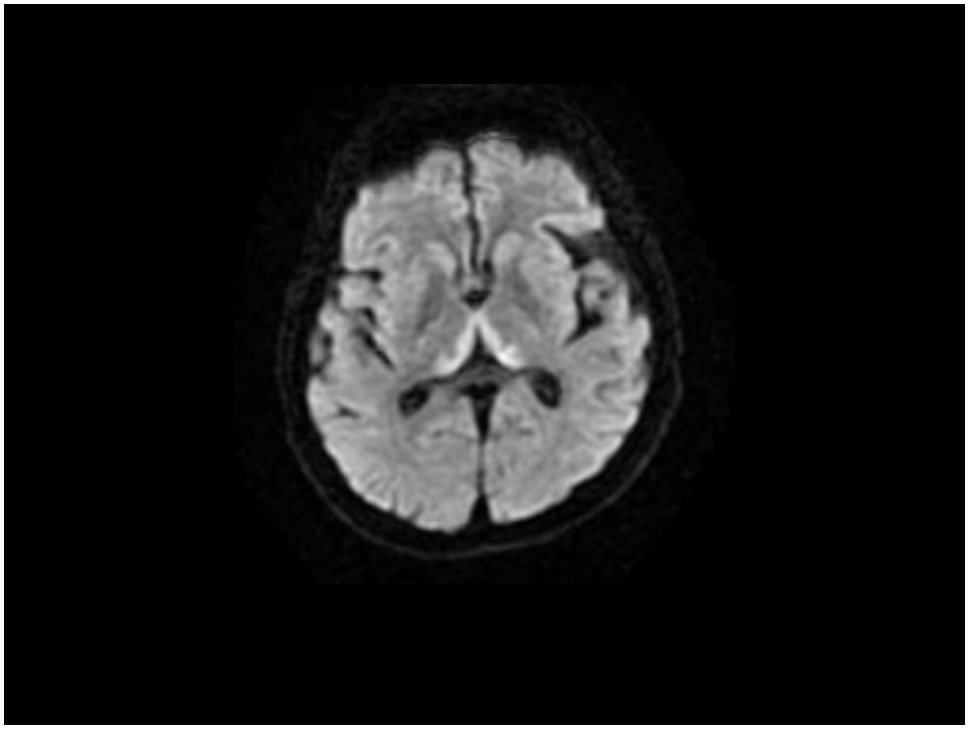
E
F
Martindale J et al. Sporadic CJD mimicig variant CJD. Arch Neurol 2003: 767-770


Pulvinar > Caudado = ECJv
Pulvinar < Caudado = ECJe


Falso Signo del Pulvinar en una Encefalopatia de Wernicke; Caso personal



SHORT REPORT

The ''pulvinar sign'' in a case of paraneoplastic limbic encephalitis associated with non-Hodgkin's lymphoma

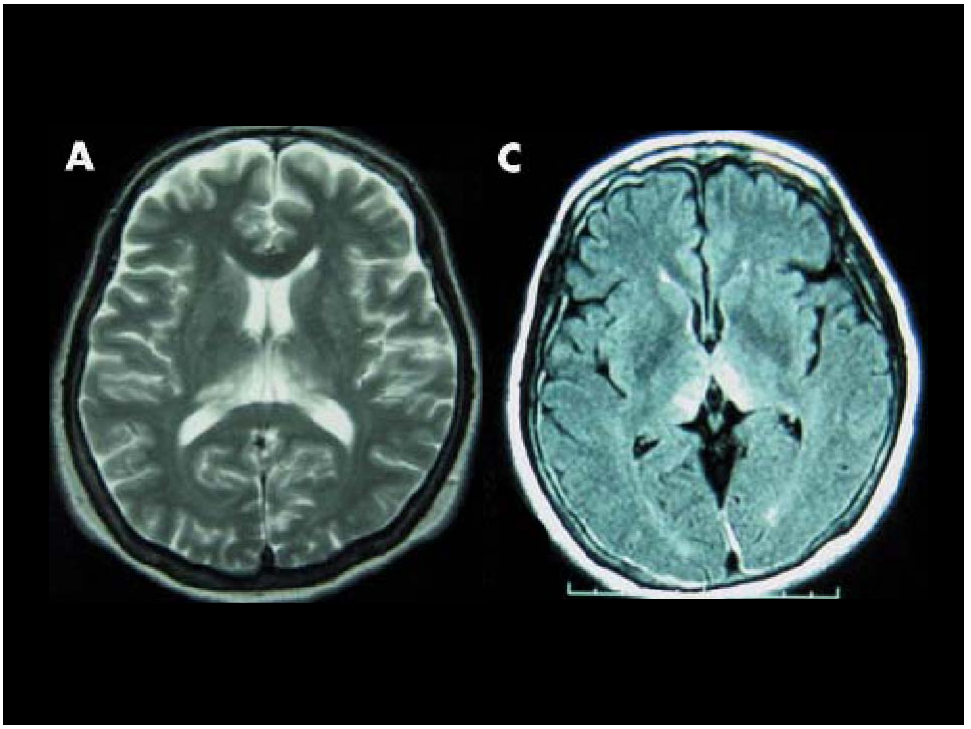
M Mihara, S Sugase, K Konaka, F Sugai, T Sato, Y Yamamoto, S Hirota, K Sakai, S Sakoda

J Neurol Neurosurg Psychiatry 2005;**76**:882–884. doi: 10.1136/jnnp.2004.049783

This paper reports a 59 year old woman with paraneoplastic limbic encephalitis associated with diffuse large B cell lymphoma. Her brain magnetic resonance imaging scan showed bilateral posterior thalamic hyperintensities, similar to the ''pulvinar sign''. Her symptoms included progressive psychiatric disturbance and resembled the initial symptoms of variant Creutzfeldt–Jakob disease (vCJD). Clinicians should consider this treatable disorder in the differential diagnosis of vCJD.

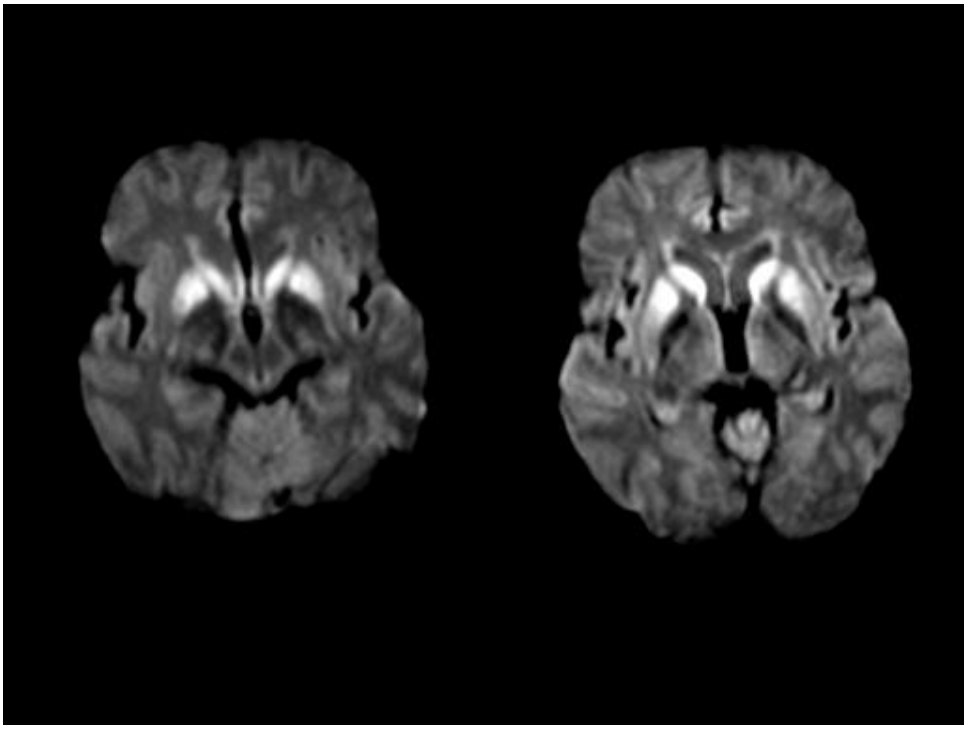
Table 1 Neuropsychological examination results of the patient

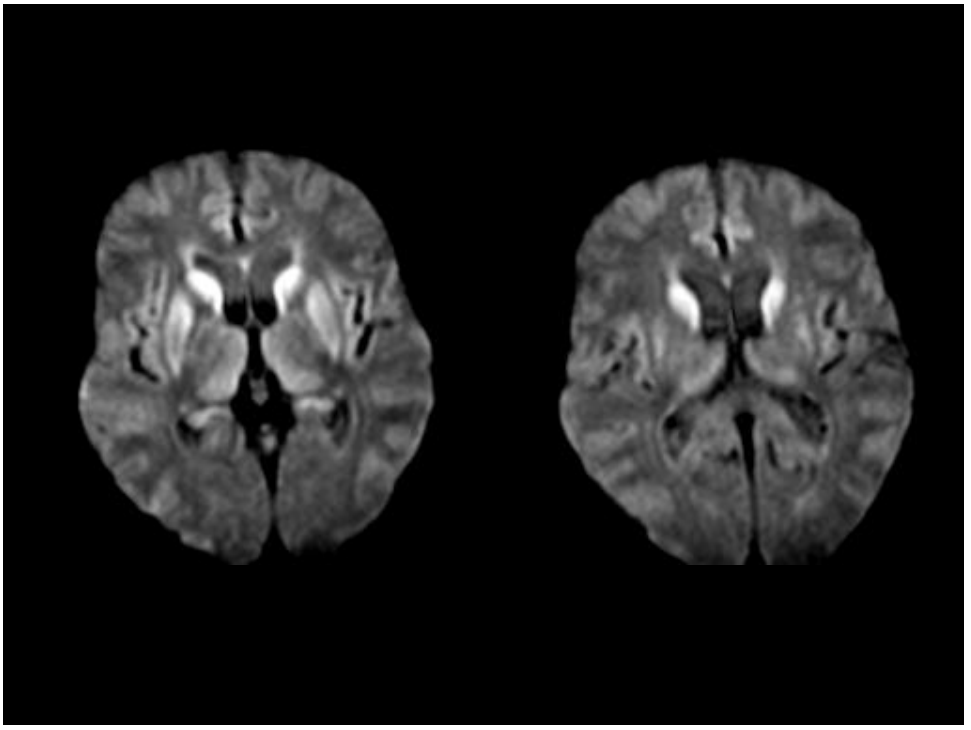
Test battery (normal)	Result
Mini Mental State Examination (>23)	24/30
Digit span (F >5 B >3)	Forward: F 6; backward: B 4
Frontal Assessment Battery (>16)	13/18
Wechsler Adult Intelligence Scale-Revised (>80)	VIQ 83; PIQ 89; IQ 86
Wisconsin Card Sorting Test (CA >4.2 PE <4.0)	Achieved categories: CA 1 Perseverative error: PE 11 Non-perseverative error 5
Verbal fluency (letter >7.6 category >13.6)	Letter 5/minute Category 5.3/minute



RM-DWI

- Recientemente imágenes + en las secuencias de difusión (DWI)
- Shiga y cols en una serie de 36 ECJe y análisis ciego de la RM:
  - sensibilidad del 92 % y especificidad del 94 % (> la 14-3-3)
- Precocidad: es + antes que la RM convencional (T2)
  - con tan solo 3 semanas de evolución en un paciente y con una media de 11 semanas
- series mas amplias y controladas para conocer la verdadera utilidad diagnostica de la DWI





Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt–Jakob disease

Y. Shiga, MD, PhD; K. Miyazawa, MD; S. Sato, MD, PhD; R. Fukushima, MD; S. Shibuya, MD, PhD; Y. Sato, MD, PhD; H. Konno, MD, PhD; K. Doh-ura, MD, PhD; S. Mugikura, MD, PhD; H. Tamura, MD, PhD; S. Higano, MD, PhD; S. Takahashi, MD, PhD; and Y. Itoyama, MD, PhD

Abstract—*Objective:* To evaluate the usefulness of diffusion-weighted MRI (DWI) for the early diagnosis of Creutzfeldt–Jakob disease (CJD). *Methods:* Thirty-six consecutive patients (age 56 to 82 years) were enrolled, and 26 were examined by DWI. Nine were definite based on the World Health Organization criteria, and 27 were probable. The percentages of DWI abnormalities, periodic sharp wave complexes (PSWCs) on the EEG, detection of CSF 14-3-3 protein, and increase of CSF neuron-specific enolase (>25 ng/mL) on the first examination were compared. For DWI, 32 patients (age 31 to 84 years) who showed progressive dementia or impaired consciousness served as disease controls. *Results:* The percentage of DWI abnormalities was 92.3%, of PSWCs 50.0%, of 14-3-3 protein detection 84.0%, and of NSE increase 73.3%. Two of the 32 control subjects were falsely positive on DWI. The sensitivity of DWI was 92.3% (95% CI 74.8 to 99.5%) and specificity 93.8% (95% CI 79.2 to 99.2%). In 17 patients who did not show PSWCs on the first EEG, abnormal DWI findings were still clearly detected. Four patients who were negative for 14-3-3 protein also showed DWI abnormalities. DWI abnormalities

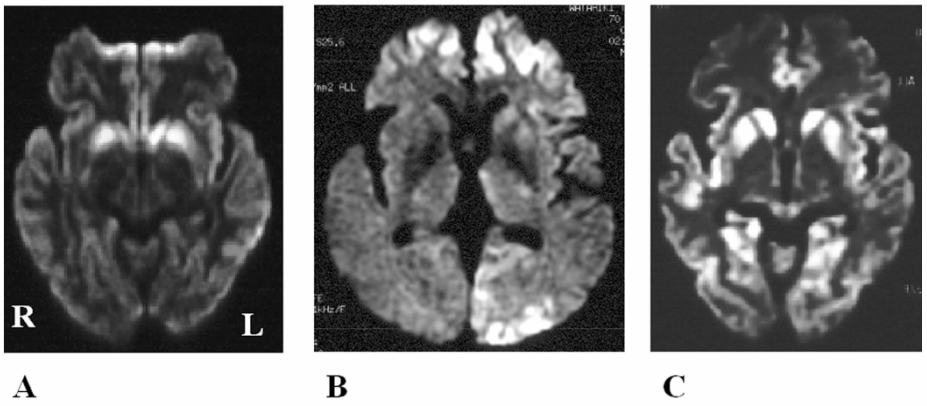
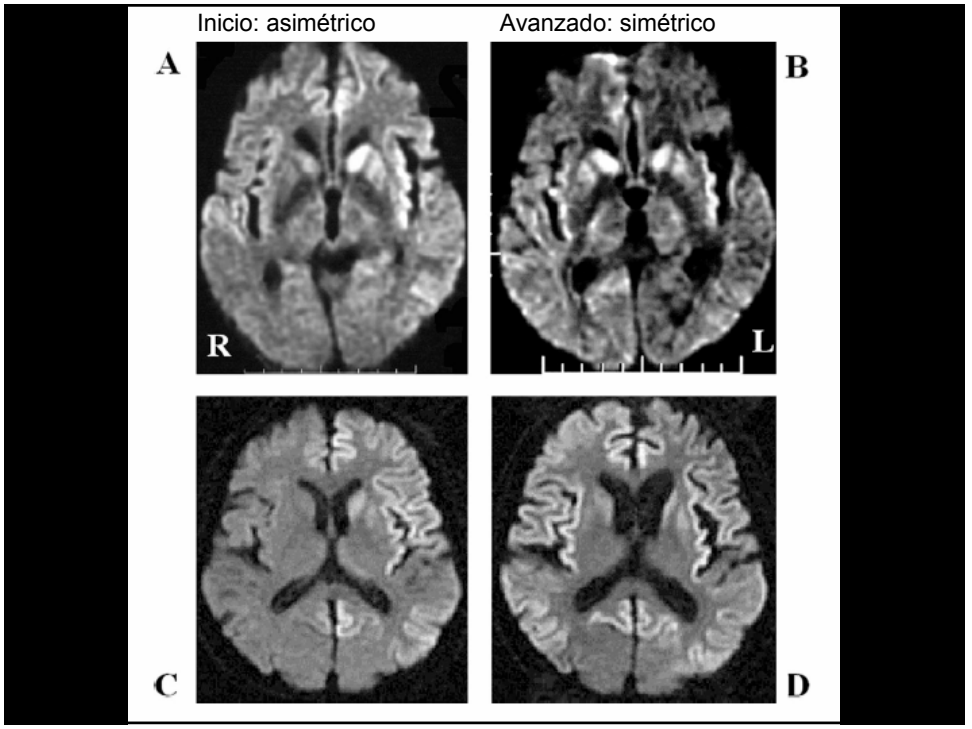
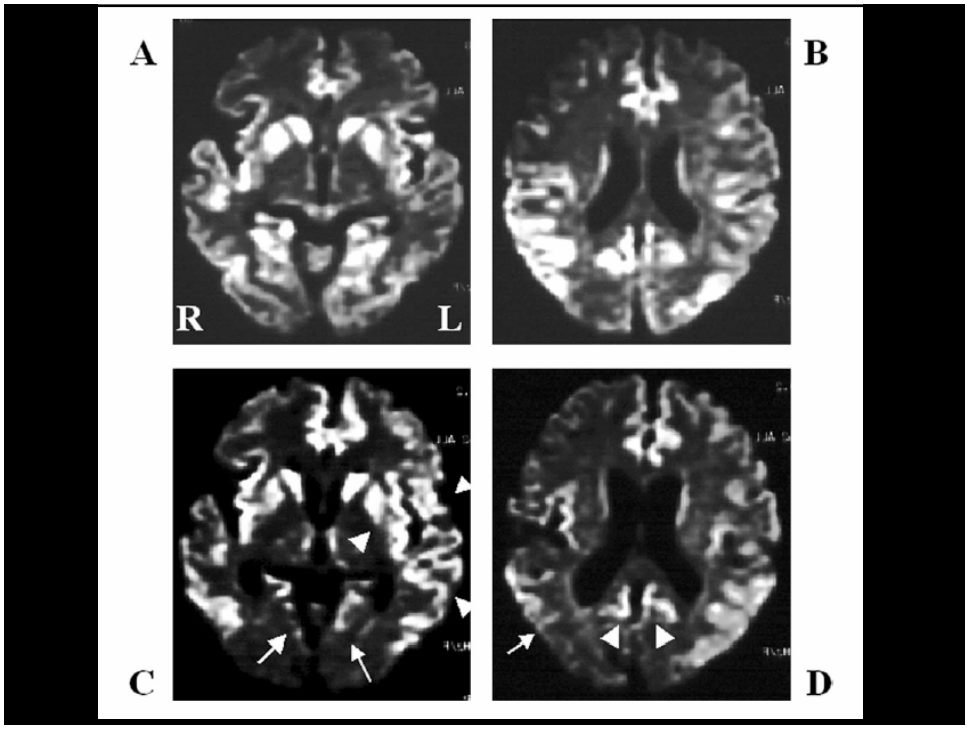


Figure 1. MRI changes seen in Creutzfeldt–Jakob disease. Three patterns of high-intensity lesions were seen: striatal lesion (A), cerebral cortical lesion (B), and a combination of both lesions (C).

N = 36

12 % en ganglios basales (caudado y/o putamen)
42 % imágenes lineales en el córtex cerebral
46 % simultáneamente en ambos lugares
12,5 % en el tálamo y ninguna en el cerebelo


Inicio: asimétrico
Avanzado: simétrico
A
B
R
L
C
D


A
B
R
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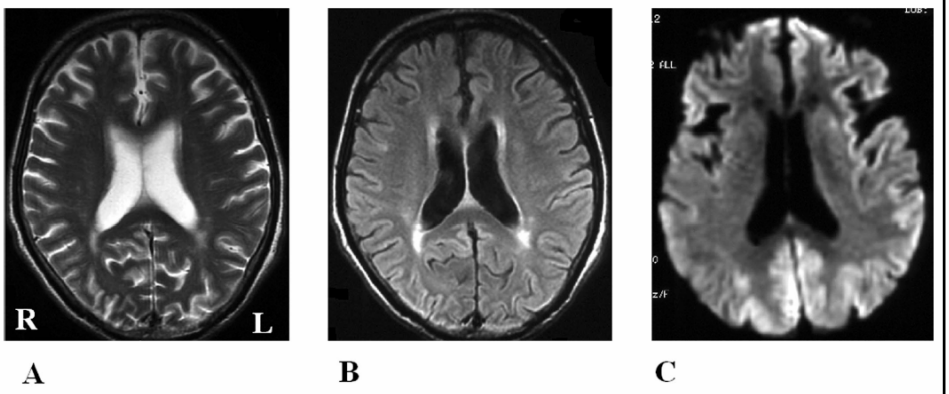
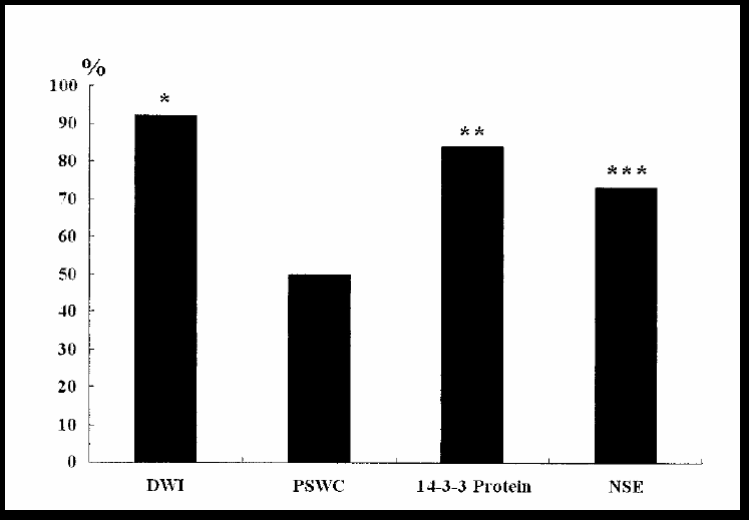


Figure 4. Comparison of conspicuity of Creutzfeldt–Jakob disease–related changes of the same patient on different MRI sequences. T2-weighted imaging (A) and fluid-attenuated inversion recovery imaging (B) show normal findings, and diffusion-weighted MRI (C) demonstrates high-intensity lesions in the cerebral cortex.

Precocidad: es + antes que la RM convencional (T2) con tan solo 3 semanas de evolución en un paciente y con una media de 11 semanas



DWI: sensibilidad del 92 % y especificidad del 94 % (> la 14-3-3)

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DOI 10.1007/s00415-003-0983-6

ORIGINAL COMMUNICATION

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Accuracy of diffusion-weighted MR imaging in the diagnosis of sporadic Creutzfeldt-Jakob disease

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Abstract The definitive diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) is based on brain autopsy. The 14-3-3 analysis in the CSF is considered a highly sensitive and specific procedure. Sensitivity, specificity and accuracy of EEG, the 14-3-3 assay and MR imaging

Table Summary of the clinical findings and results of the technical examinations

Case n°	Neurological features	EEG	14-3-3	T2/FLAIR	DWI	Classification	Final diagnosis
1	M, V	–	+	SV	–	probable sCJD	Paraneoplastic encephalomyelitis (aut)
2	V, P	+	+	SV	+	probable sCJD	sCJD (aut)
3	M, V, P	+	–	SV	–	possible sCJD	Alzheimer dementia (aut)
4	M, V	–	+	SV	–	probable sCJD	Binswanger disease (aut)
5	V, P	–	+	SV	–	probable sCJD	subacute metabolic encephalopathy
6	M, V, P	–	–	SV	–	possible sCJD	neuroborreliosis
7	M, V, P	–	+	SV, BG	+	probable sCJD	sCJD (aut)
8	M, V, P	+	+	SV, BG?	+	probable sCJD	sCJD (aut)
9	V, P	–	+	SV, BG?	+	probable sCJD	sCJD (aut)
10	M, V, P	–	–	SV	–	possible sCJD	subacute metabolic encephalopathy
11	M, V	+	+	SV	+	probable sCJD	sCJD (aut)
12	V, P	–	+	SV	–	probable sCJD	Frontotemporal dementia (aut)

M myoclonus; *V* visual or cerebellar disturbance; *P* pyramidal/extrapyramidal dysfunction; *SV* small vessel disease; *BG* basal ganglia involvement as can be
BG? questionable basal ganglia involvement as can be seen in sCJD; *aut* autopsy proven

Table Summary of the clinical findings and results of the technical examinations

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1	M, V	–	+	SV	–	probable sCJD	Paraneoplastic encephalomyelitis (aut)
2	V, P	+	+	SV	+	probable sCJD	sCJD (aut)
3	M, V, P	+	–	SV	–	possible sCJD	Alzheimer dementia (aut)
4	M, V	–	+	SV	–	probable sCJD	Binswanger disease (aut)
5	V, P	–	+	SV	–	probable sCJD	subacute metabolic encephalopathy
6	M, V, P	–	–	SV	–	possible sCJD	neuroborreliosis
7	M, V, P	–	+	SV, BG	+	probable sCJD	sCJD (aut)
8	M, V, P	+	+	SV, BG?	+	probable sCJD	sCJD (aut)
9	V, P	–	+	SV, BG?	+	probable sCJD	sCJD (aut)
10	M, V, P	–	–	SV	–	possible sCJD	subacute metabolic encephalopathy
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M myoclonus; *V* visual or cerebellar disturbance; *P* pyramidal/extrapyramidal dysfunction; *SV* small vessel disease; *BG* basal ganglia involvement as can be seen in sCJD; *BG?* questionable basal ganglia involvement as can be seen in sCJD; *aut* autopsy proven

Patrón RM similar al de la ECJ

T2, Flair:
E. Alzheimer, DCL, DMI
E. Huntington
Parkinson-plus
SIDA
PESS, Encefalitis japonesa
CADASIL, Infarto bitalámico,
E. Mitocondriales
Glioma bitalámico
Mieloma
EM, Enf. de Beçhet
E. de depósito (Wilson, GM2)
Encefalopatías metabólicas
(hipoglucemia, hipoxia)

Difusión:
Encefalitis herpética y fúngica,
Intoxicación por CO
E. Alcohólica
E. de Wernicke

Sg pulvinar
Enf. por arañazo de gato
E. Alpers
Hipertensión Intracraneal
idiopática
Encefalomielitis post infecciosa
Encefalitis paraneoplásica
E. de Wernicke

MRI of Creutzfeldt–Jakob Disease: Imaging Features and Recommended MRI Protocol

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Creutzfeldt–Jakob Disease (CJD) is a rare, progressive and invariably fatal neurodegenerative disease characterized by specific histopathological features. Of the four subtypes of CJD described, the commonest is sporadic CJD (sCJD). More recently, a new clinically distinct form of the disease affecting younger patients, known as variant CJD (vCJD), has been identified, and this has been causally linked to the bovine spongiform encephalopathy (BSE) agent in cattle. Characteristic appearances on magnetic resonance imaging (MRI) have been identified in several forms of CJD; sCJD may be associated with high signal changes in the putamen and caudate head and vCJD is usually associated with hyperintensity of the pulvinar (posterior nuclei) of the thalamus. These appearances and other imaging features are described in this article. Using appropriate clinical and radiological criteria and tailored imaging protocols, MRI plays an important part in the *in vivo* diagnosis of this disease.
Collie, D. A. *et al*. (2001). *Clinical Radiology* **56**, 726–739.

Key words: MRI, Creutzfeldt–Jakob disease, variant CJD, sporadic CJD, pulvinar, thalamus, basal ganglia.

Table 4 – Recommended guidelines for imaging technique for assessment of patients with suspected variant CJD

MRI system	High field MRI 1.0T–1.5T
Patient preparation	The majority of patients can be scanned without general anaesthetic If very marked movement artefact, general anaesthetic recommended
Minimum sequences	T2 and proton density axial images Slice thickness 3–5 mm (3 mm preferred) FLAIR axial (3–5 mm) +/− FLAIR sagittal (3–5 mm) to include thalamus, caudate and putamen
Preferred additional sequences*	Diffusion-weighted imaging (DWI) axial (isotropic) if available T1-weighted volume acquisition whole brain
Image plane†	Axial images parallel to anterior commissure–posterior commissure line preferred to allow comparison of signal intensity of grey matter nuclei on same slice
Sequence and imaging variables	Vary widely depending on MRI system and generation. Sequence parameters should be selected to provide appropriate weighting, with clear distinction between grey matter in the basal ganglia and cortex, and the adjacent white matter. The highest resolution obtainable in acceptable time should be selected. Ideal parameters include: matrix 190/256 or greater, FOV 18 × 30, no interslice gap, slice thickness 5 mm (3 mm preferred). The radiologist should review the images on the monitor; hard copy window level and width should be selected to obtain good contrast between grey and white matter, without 'washout' of CSF detail
Archive	Original films (as contrast is lost on copy film) can be sent to the National CJD Surveillance Unit. Original digital data may be requested for further analysis
Quantitative analysis	Hard copy images showing ROI signal intensity over the pulvinar of the thalamus, anterior half of the putamen and caudate head, and frontal cortex are also of value [39]

*To date the proton density axial image has proved the most important widely available sequence for diagnosing vCJD. Sensitivity of sequences to signal changes in CJD: DWI > FLAIR > PD > T2 > T1

†Coronal imaging tends to obscure the contrast between the pulvinar and the other grey matter of the brain.

‡If the putamen is used as the control area in quantitative analysis the anterior half of the nucleus should be used, due to partial volume artefact posteriorly.

Collie D, Clinical Radiology 2001

Criterios Diagnósticos

- Master y cols en 1979 y Catala los modifica en 1979
- Grupo EETHs de la Unión Europea en 1994,1998, 2003
- OMS 1998
- 95 % de casos de ECJ probables se confirman con AP
- quizás se incorpore la RM a estos criterios de la ECJe
- la posible clasificación con subtipos clínico-moleculares
  - puede modificar estos criterios para cada una de las entidades
  - pudiendo cambiar la utilidad de las diferentes pruebas diagnósticas en cada una de ellas (MV2 y RM)
- posible aparición de nuevos fenotipos de EETHs
  - (ECJv heterocigota ?)

Criterios Diagnósticos de ECJ

Tipo de ECJ	Master [35]	Catalá [10]	Unión Europea [36] (1994 / 1998)
Definitivo	Confirmación NP demencia progresiva y al menos 1 hallazgo clínico	Confirmación NP IH, W-B, o SAF	Confirmación NP, IH, W-B o SAF
Probable	Demencia progresiva y al menos 1 hallazgo clínico (sin confirmación NP)	Demencia progresiva, EEG típico y al menos 2 hallazgos clínicos	Demencia progresiva, EEG típico y al menos 2 hallazgos clínicos o 14-3-3 + (1998)
Posible	Demencia progresiva + mioclonías y duración < 3 a.	Demencia progresiva, 3 hallazgos clínicos, EEG ausente o no típico	Demencia progresiva, 2 hallazgos clínicos, EEG negativo y duración < 2 a.
Hallazgos clínicos	Mioclonías, Sg. Piramidales Sg cerebelosos Sg extrapiramidales EEG típico	Mioclonías Sg. Cerebelosos Sg piramidal o extrapiramidal Sg visuales Mutismo acinético	Mioclonías Sg visual o cerebelosos Sg piramidal o extrapiramidal Mutismo acinético

DIAGNOSTIC CRITERIA FOR HUMAN TSEs - SURVEILLANCE CRITERIA

1. SPORADIC TSE

1.1 DEFINITE

Neuropathologically/immunocytochemically confirmed

1.2 PROBABLE

1.2.1 I + 2 of II + III

1.2.2 Possible + positive 14-3-3

1.3 POSSIBLE

I + 2 of II + duration < 2 years

I Rapidly progressive dementia

II
- A Myoclonus
- B Visual or cerebellar problems
- C Pyramidal or extrapyramidal features
- D Akinetic mutism

III Typical EEG

DIAGNOSTIC CRITERIA FOR HUMAN TSEs - SURVEILLANCE CRITERIA

2. ACCIDENTALLY TRANSMITTED TSE

2.1 DEFINITE

Definite TSE with a recognised iatrogenic risk factor (see box)

2.2 PROBABLE

2.2.1 Progressive predominant cerebellar syndrome in human pituitary hormone recipients

2.2.2 Probable TSE with recognised iatrogenic risk factor (see box)

RELEVANT EXPOSURE RISKS FOR THE CLASSIFICATION AS IATROGENIC CJD

The relevance of any exposure to disease causation must take into account the timing of exposure in relation to disease onset

- Treatment with human pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft.
- Corneal graft in which the corneal donor has been classified as definite or probable human prion disease.
- Exposure to neurosurgical instruments previously used in a case of definite or probable human prion disease.

This list is provisional as previously unrecognised mechanisms of human prion disease may occur

DIAGNOSTIC CRITERIA FOR HUMAN TSEs - SURVEILLANCE CRITERIA

3. GENETIC TSE

3.1 DEFINITE

3.1.1 Definite TSE + definite or probable TSE in 1st degree relative

3.1.2 Definite TSE with a pathogenic PRNP mutation (see box)

3.2 PROBABLE

3.2.1 Progressive neuropsychiatric disorder + definite or probable TSE in 1st degree relative

3.2.2 Progressive neuropsychiatric disorder + pathogenic PRNP mutation (see box)

- **PRNP MUTATIONS ASSOCIATED WITH GSS NEUROPATHOLOGICAL PHENOTYPE**
  P102L, P105L, A117V, G131V, F198S, D202N, Q212P, Q217R, M232T, 192 bpi
- **PRNP MUTATIONS ASSOCIATED WITH CJD NEUROPATHOLOGICAL PHENOTYPE**
  D178N-129V, V180I, V180I+M232R, T183A, T188A, E196K, E200K, V203I, R208H, V210I, E211Q, M232R, 96 bpi, 120 bpi, 144 bpi, 168 bpi, 48 bp*deletion*
- **PRNP MUTATIONS ASSOCIATED WITH FFI NEUROPATHOLOGICAL PHENOTYPE** - D178N-129M
- **PRNP MUTATION ASSOCIATED WITH VASCULAR PRP AMYLOID** - Y145s
- **PRNP MUTATIONS ASSOCIATED WITH PROVEN BUT UNCLASSIFIED PRION DISEASE**
  H187R, 216 bpi, ##(?)
- **MUTATIONS ASSOCIATED WITH NEUROPSYCHIATRIC DISORDER BUT NOT PROVEN PRION DISEASE**
  I138M, G142S, Q160S, T188K, M232R, 24 bpi, 48 bpi, 48 bpi + nucleotide substitution in other octapeptides
- **PRNP MUTATIONS WITHOUT CLINICAL AND NEUROPATHOLOGICAL DATA**
  T188R, P238S
- **PRNP POLYMORPHISMS WITH ESTABLISHED INFLUENCE ON PHENOTYPE**
  M129V
- **PRNP POLYMORPHISMS WITH SUGGESTED INFLUENCE ON PHENOTYPE**
  N171S, E219K, 24 bp deletion
- **PRNP POLYMORPHISMS WITHOUT ESTABLISHED INFLUENCE ON PHENOTYPE**
  P68P, A117A, G124G, V161V, N173N, H177H, T188T, D202D, Q212Q, R228R, S230S

DIAGNOSTIC CRITERIA FOR HUMAN TSEs - SURVEILLANCE CRITERIA

4. vCJD

4.1 DEFINITE

1A **and** neuropathological confirmation of vCJD[e]

4.2 PROBABLE

4.2.1 I **and** 4/5 of II **and** IIIA **and** IIIB

4.2.2 I **and** IV A[d]

4.3 POSSIBLE

I **and** 4/5 of II **and** IIIA

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness > 6 months
	C	Routine investigations do not suggest an alternative diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of TSE
II	A	Early psychiatric symptoms[a]
	B	Persistent painful sensory symptoms[b]
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sporadic CJD[c] (or no EEG performed)
	B	Bilateral pulvinar high signal on MRI scan
IV	A	Positive tonsil biopsy[d]

a depression, anxiety, apathy, withdrawal, delusions
b this includes both frank pain and/or dysaesthesia
c generalised triphasic periodic complexes at approximately one per second
d tonsil biopsy is **not** recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.
e spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum.

Diagnóstico Diferencial

- En la mayoría de series (suficiente perspectiva temporal) se reduce a otras demencias degenerativas o encefalopatías
- E. de Alzheimer, Demencia de Cuerpos de Lewy y Multi-Infarto
- En las encefalopatías aparecen formas de muy diversas etiologías
  - víricas, paraneoplásicas, inmunomediadas, Hashimoto, metabólicas…
  - diagnóstico alternativo + rápido, pruebas diagnósticas específicas
- las diversas EETHs pueden ser confundidas entre ellas
  - hereditaria y esporádica
  - yatrógena con la esporádica
  - En UK el diagnóstico alternativo + importante de la ECJv es la ECJe
- los falsos + del EEG y la RM
  - las claras diferencias en su perfil clínico con la ECJ
- Casos Aislados problemáticos (ECJ probable)

Diagnóstico Diferencial de la ECJ

País Periodo Nª Total Casos	UK [2] (1990-1994) N = 144	Alemania [39] (1993-1997) N= 413	España (1992-2003) N = 565	Bélgica [40] (1998-2003) N = 250
Nº No Casos	41 (29 %)	104 (25,2 %)	70 (12,5 %)	141 (56 %)
EA	17	28	6	45
DCL	2	14	2	16
DMI	9	-	5	18
Otras demencias	-	-	6	-
Parkinson-plus	3	-	4	-
Tumores	1 (metástasis carcinoma)	-	4 (3 linfoma)	-
Encefalopatías vírica paraneoplásica hashimoto Wernicke Otras	11 1 1 1 1 = 1	- - - - - -	4 1 - 1 1 = 1	62 6 5 3 - 1

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ORIGINAL COMMUNICATION

Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients

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Abstract Our objective was to describe the clinical signs of 'possible' Creutzfeldt-Jakob disease (CJD) and to investigate whether current diagnostic criteria can accurately differentiate between different forms of dementia. We stud-

In patients with rapidly progressive dementia and focal neurological signs, CJD should be considered. When faced with the triad: dementia, myoclonus, and initial memory problems AD should be considered if the disease duration is longer

Table 2 Clinical signs and symptoms at disease onset in the different 'possible' CJD populations distinguished on the basis of their definite diagnoses

Initial signs/ symptoms	CJD (N = 52, %)	AD (N = 45, %)	DLB (N = 16, %)	VD (N = 18, %)
Dementia	58	89	86	89
Myoclonus	10	2	0	11
Cerebellar signs	27	11	13	17
Extra-pyramidal signs	19	4	44	0
Pyramidal signs	11	2	0	0
Visual problems	8	2	0	0
Psychiatric problems	44	36	38	17
Sensory problems	10	0	0	0

	CJD (N = 52, %)	AD (N = 45, %)	DLB (N = 16, %)	VD (N = 18, %)
PSWCs in EEG	52	7 (3 pac)	6 (1 pac)	6 (1 pac)
Protein 14-3-3 in CSF	100	4 (2 pac)	19 (2 pac)	6 (1 pac)
Tau > 1300 pg/ml	87	0	6	6
Tau: average ± SD (pg/ml)	12634±7568	631±407	1234±914	547±369
Aβ average ± SD (pg/ml)	304±207	215±115	211±126	230±169
Brain imaging typical for CJD	37	4	0	0

ECJ probable: Demencia + Mioclonías + EEG o 14-3-3 + = 8 pacientes
(EA: 4 ; DCL: 3; DMI: 1)

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LETTER TO THE EDITORS

Susanne Reinwald
Ingo M. Westner
Nikolaj Niedermaier

Rapidly progressive Alzheimer's disease mimicking Creutzfeldt-Jakob disease

Received: 12 December 2003
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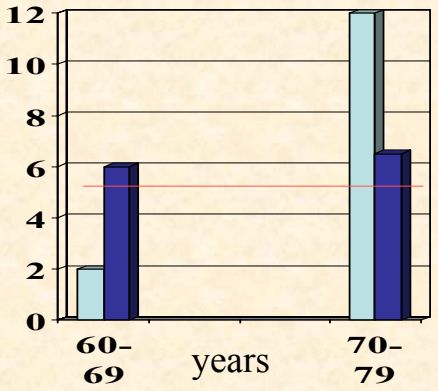
Sirs: A 69 year old man was referred with a 14 day history of progressive dizziness, vertigo and diplopia, also complaining about gait difficulties with a drift towards the left. A slight loss of intellectual and motor functions were normal, but reflexes were slightly stronger on the left side. Examination of coordination showed bilateral dysmetric finger-to-nose tests and mild ataxia in the heel, knee, shin test.

Initial and late MRI of the brain were unremarkable, showing only a few subcortical vascular lesions. Diffuse generalized theta activity and intermittent periodic triphasic discharges were seen in the EEG. The CSF was normal. The serological tests for neurotropic viruses were negative. Tau-protein was increased (4014 pg/nl; normal: up to 200 pg/nl) protein 14–3–3 could be detected. Laboratory tests revealed increased creatine kinase (184 U/l; norm: up to 80 U/l), the rest of the routine studies, including continent, his gait disturbance and ataxia worsened and intermittent visus reduction occurred. His speech became impoverished, and within only a few days there was increasing dysarthria. After approximately one week, he was completely care dependent and sat on hands and knees in his bed jactitating with the upper part of the body. The clinical symptoms with rapid progressive dementia and neurological deficits in combination with the detection of protein 14-3-3 and increased tau-protein in the CSF, as well as the EEG abnormalities with intermittent periodic discharges suggested the diagnosis of Creutzfeldt-Jakob disease (CJD). 40 days after the first symptoms had been noticed and 26 days after admission the patient



Demencia vs ECJe
60-79 años
Razón de tasas=1000

Asumiendo: Demencia vs Demencia de evolución rápida
Razón de tasas =100? 200? (1%?, 0,5%)
Implicaciones: Demencia de evolución rápida vs ECJe
Razón de tasas RR =10? 5?
(10 o 5 casos de DER por cada ECJe)

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CASE REPORT

J.E. Donahue • P.A. Hanna • S. Hariharan

Autopsy-proven Creutzfeldt-Jakob disease in a patient with a negative 14-3-3 assay and nonspecific EEG and MRI

Received: 11 May 2003 / Accepted in revised form: 3 October 2003

Abstract Detection of 14-3-3 protein in cerebrospinal fluid (CSF), in combination with findings on electroencephalography (EEG) and magnetic resonance imaging (MRI), is a highly sensitive and specific diagnostic test for sporadic Creutzfeldt-Jakob disease (CJD) in patients premortem. We

Introduction

Creutzfeldt-Jakob disease (CJD) is a devastating, degenerative neurologic disorder caused by an accumulation of abnormal

Perspectiva Futura Diagnóstico EETHs

- El diagnóstico clínico no plantea problemas
  - (> 80 % un cuadro clínico fácilmente reconocible)
- Dificultades al inicio
  - la rapidez en la instauración
  - la negatividad de las exploraciones complementarias + comunes (¿DWI de la RM?)
- Evolución con 14-3-3 y RM ↓ dificultades
  - casos aislados (EA, DCL, DMI con pruebas +)
- Problemas diagnósticos
  - en los casos atípicos (persistencia de signos focales)
  - con evolución más prolongada
  - EEG, LCR negativo o RM normal
  - no se han realizado análisis genéticos.

Perspectiva Futura Diagnóstico EETHs

- Problema diagnóstico EETHs menos habituales
  - genéticas con fenotipos diferentes a la ECJ clásica (IFF)
  - la variante de la ECJ
  - Clínica diferente y pruebas - (EEG, LCR o RM)
  - confusión con otras enfermedades neuro-degenerativas
- Problema diagnóstico (epidemiología y salud publica)
  - detección precoz (portadores humanos o animales) para evitar la transmisión de la enfermedad
  - test sensibles, específicos y fáciles de aplicar (sangre / orina) ?
  - Dificultad inicio camino terapéutico viable EETHs

Similitud clínica entre ECJv y ECJe en < 50 años

Table 1. Synopsis of Clinical Data of sCJD Patients ≤50 and >50 Years and Patients with vCJD

	Sporadic CJD		Variant CJD[12,34]	Statistical Analysis ≤50 vs >50 (*P*)
	≤50	>50		
	Test results, % (n)			
EEG (PSWC)	24 (12/51)	66 (212/354)	0 (0)	0.001[a]
14-3-3 in CSF	92 (45/49)	94 (281/294)	57 (13/23)	0.829
MRI	40 (18/45) (basal ganglia hyperintensities)	63 (75/157)	70 (22/31) (pulvinar sign)	0.01[a]
	Duration of illness, months (median [range]) *Mean (standard deviation)*			
Total	16 (2–76)	6 (1–39)		<0.001[a]
	16.125 (±13.506)	*8.503 (±7.218)*		
MM	13.5 (2–76)	5 (1–39)	14 (8–38)	<0.001[a]
	15.038 (±15.038)	*7.645 (±6.950)*		
MV	17.5 (4–44)	12 (2–35)		0.23
	16.5 (±14.775)	*12.48 (±7.534)*		
VV	14.5 (6–49)	8 (2–40)		<0.001[a]
	17.750 (±10.686)	*8.344 (±6.741)*		

Boesenberg C, Ann Neurol 2005; 58: 533-543

LETTERS

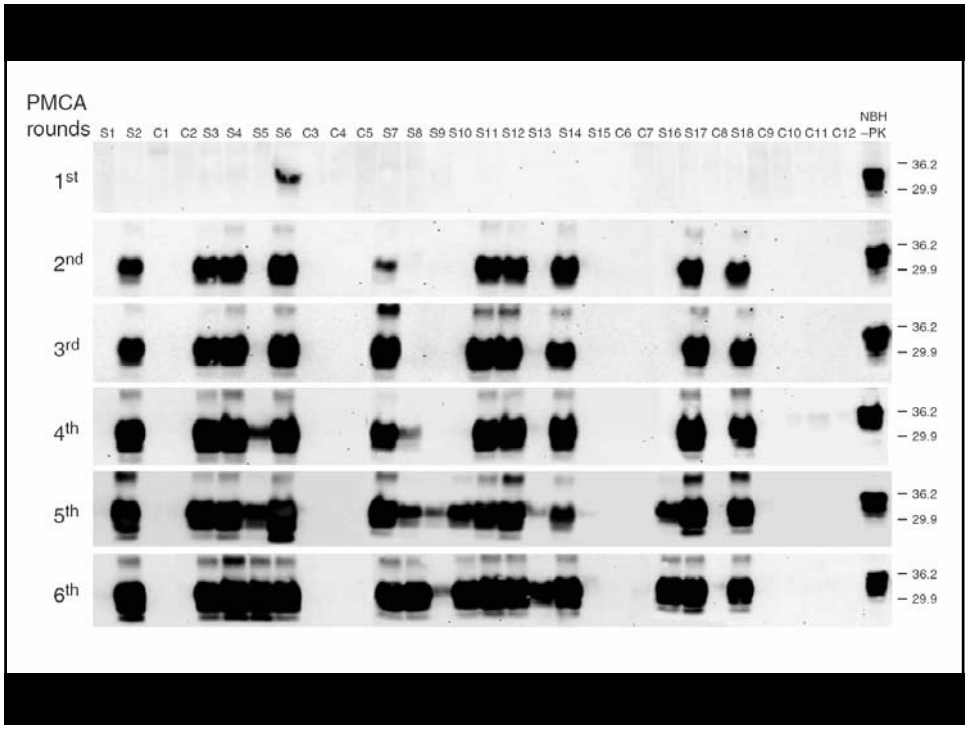
nature medicine

Detection of prions in blood

Joaquín Castilla[1], Paula Saá[1,2] & Claudio Soto[1]

Prion diseases are caused by an unconventional infectious agent termed prion, composed mainly of the misfolded prion protein (PrP^{Sc})[1]. The development of highly sensitive assays for biochemical detection of PrP^{Sc} in blood is a top priority for minimizing the spread of the disease[2]. Here we show that the protein misfolding cyclic amplification (PMCA) technology[3] can be automated and optimized for high-efficiency amplification of PrP^{Sc}. We show that 140 PMCA cycles leads to a 6,600-fold increase in sensitivity over standard detection methods. Two successive rounds of PMCA cycles resulted in a 10 million–fold

tube[3]. This method, termed protein misfolding cyclic amplification (PMCA), is based on conversion of large amounts of PrP^{C} triggered by undetectable quantities of PrP^{Sc} (refs. 3,13). In a cyclic manner and conceptually analogous to PCR cycling, PrP^{Sc} is incubated with excess PrP^{C} to enlarge the PrP^{Sc} aggregates, which are then sonicated to generate multiple smaller units for the continued formation of new PrP^{Sc} (ref. 3). We and others have previously reported that PMCA enables an increase of sensitivity for PrP^{Sc} detection between 10- and 60-fold[3,14–17] and the technology was applied to replicate the misfolded protein from diverse species[18]. The newly generated protein



Conclusiones

- Elevado grado de fiabilidad diagnóstica mayoría EETHs
  - Criterios Diagnósticos validos (95 % confirmación)
- EEG técnica accesible, pero con menor sensibilidad que LCR y RM
  - EEG y LCR + = VPP 98 % (ECJ muy probable)
  - EEG y LCR - = VPN 79 % (ECJ muy poco probable)
- La RM técnica prometedora (DWI)
  - sensibilidad y especificidad elevadas, pero sobre todo precocidad
  - ¿inclusión en los criterios diagnósticos ECJe ? (tras series epidemiológicas)
- Diagnóstico Diferencial:
  - EA, DCL, DMI
  - ECJ v con ECJe / ECJh con ECJe
- posibilidad no descartable de nuevos fenotipos de EETHs
  - ECJv en MV o VV
  - ¿ clínica diferente a la ECJv + semejante a la ECJe o hereditaria ?
  - o bien pasar desapercibido con otras demencias mas comunes
- Test diagnósticos futuros (¿PMCI?)