Curso de enfermedades neurodegenerativas

ENFERMEDAD DE PARKINSON Y SINUCLEINOPATÍAS

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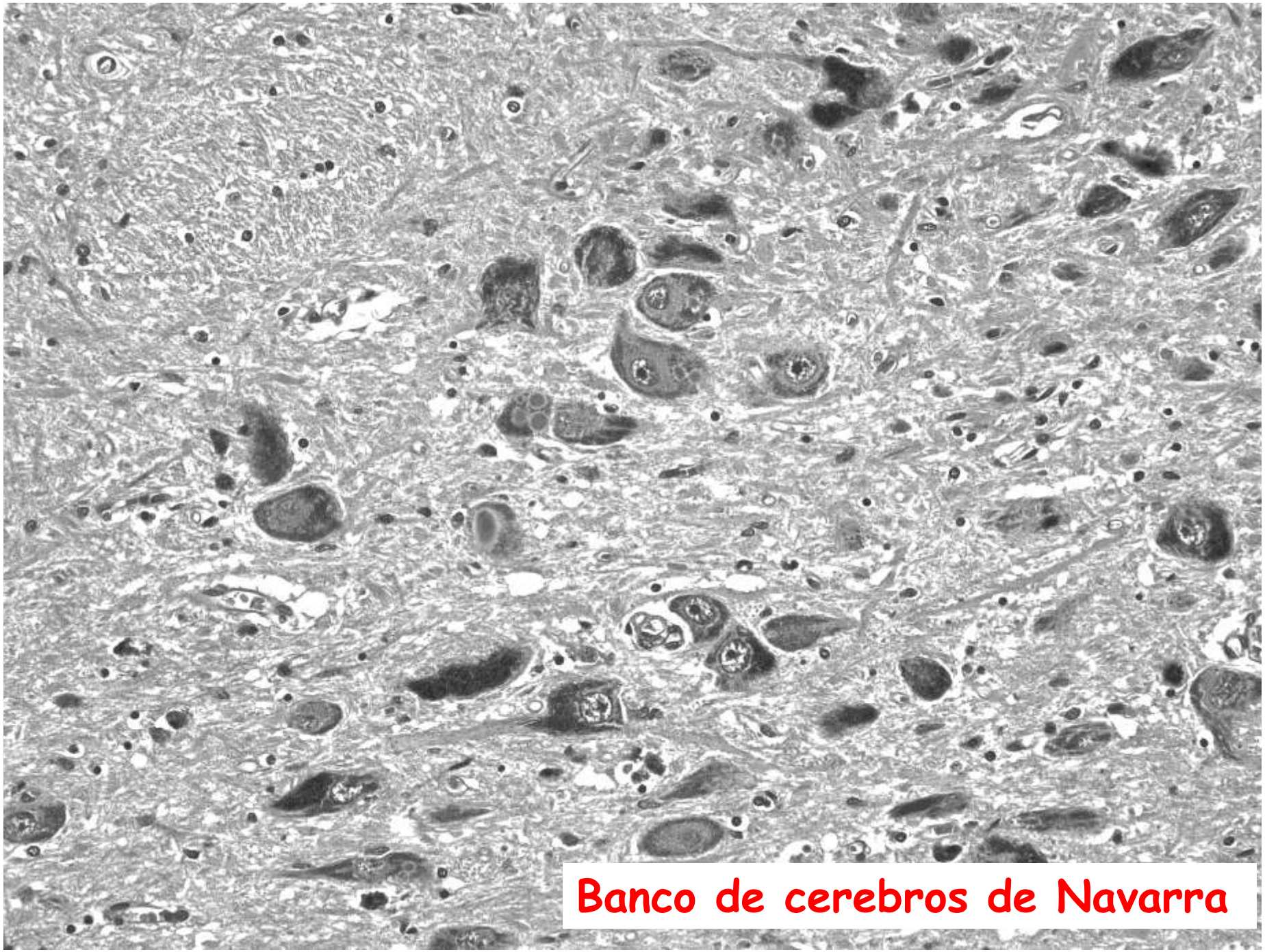
Servicio de Anatomía Patológica
Hospital Donostia

XXV Congreso de la SEAP y División Española de la International Academy of Pathology
Zaragoza, 19 de mayo de 2011

Osakidetza
DONOSTIA OSPITALEA
HOSPITAL DONOSTIA


Banco de cerebros de Navarra

Nature
1997;388(6645):839-40.

Alpha-synuclein in Lewy bodies

Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M.

- Los cuerpos de Lewy estaban formados por ubicuitina y neurofilamentos pero se desconocía si eran el componente principal de las inclusiones filamentosas.
- Describen la tinción de los CL de la EP y DCL con ASN.

Proc Natl Acad Sci USA
1998;95(11):6469-73.

Alpha-Synuclein in filamentous inclusions of LB from Parkinson's disease and dementia with LB

Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M

- Describen que la ASN es el componente principal de las inclusiones filamentosas de CL y NL.
- ASN es mejor método que la ubicuitina para detectar CL y NL

Neurosci Lett.
1998;251(3):205-8.

Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies

Spillantini MG, Crowther RA, Jakes R, Cairns NJ, Lantos PL, Goedert M.

- Describen que la ASN es el componente principal de las inclusiones filamentosas de la AMS en glía y neuronas, estableciendo un nexo de unión entre las tres entidades.

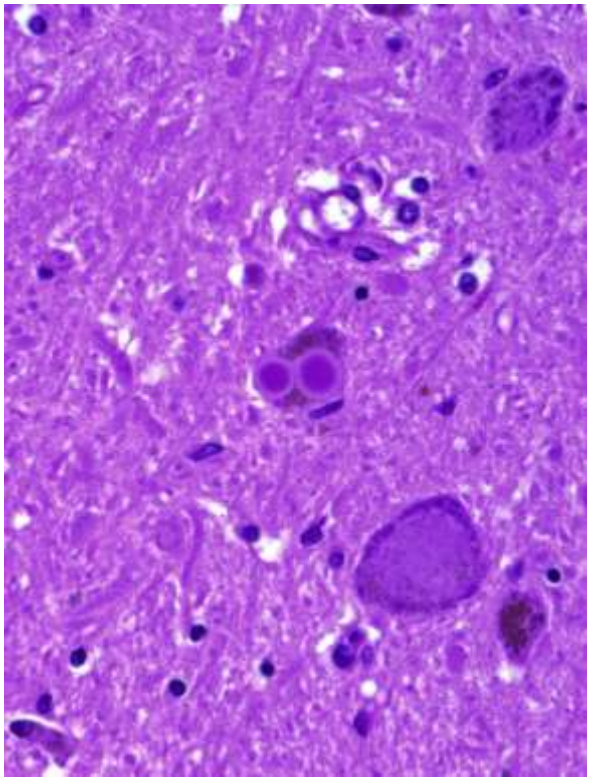
Ann N Y Acad Sci. 2000;920:16-27.

The alpha-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy.

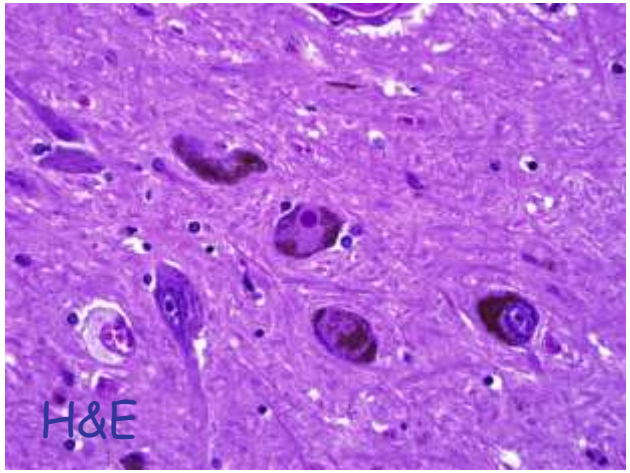
Spillantini MG, Goedert M.

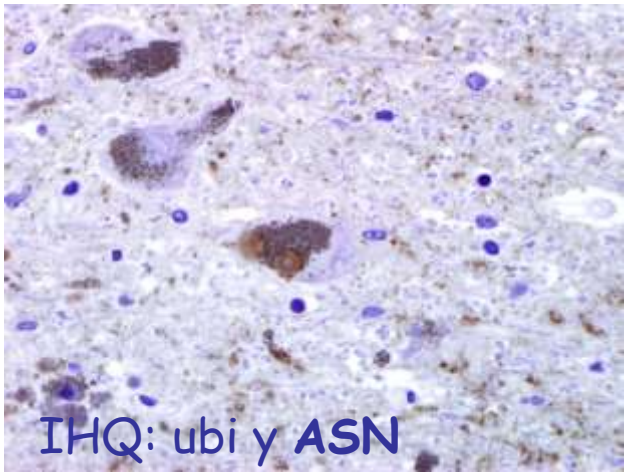
α-sinucleína

- Pertenece a la familia de las sinucleínas (prot cerebral) (α, β, γ). Secuencia común 55-62%.
- Función: ¿?. Proteína presináptica implicada en el transporte de la vesícula sináptica y en el metabolismo de la dopamina (Mov Disorders 2003, 18(6): S2-S12).
- Forma nativa no plegada y soluble → modificaciones conformacionales y postraslacionales → agregados y fibrillas insolubles → disfunción celular?
- No está claro si la formación de inclusiones es un proceso neuroprotector-adaptativo o una reacción patogénica frente a estímulos no conocidos relacionados con neurodegeneración (Mov 2003, 18(6): S2-S12, Lancet Neurol 2009; 8: 1150-1157)



- **Detección**

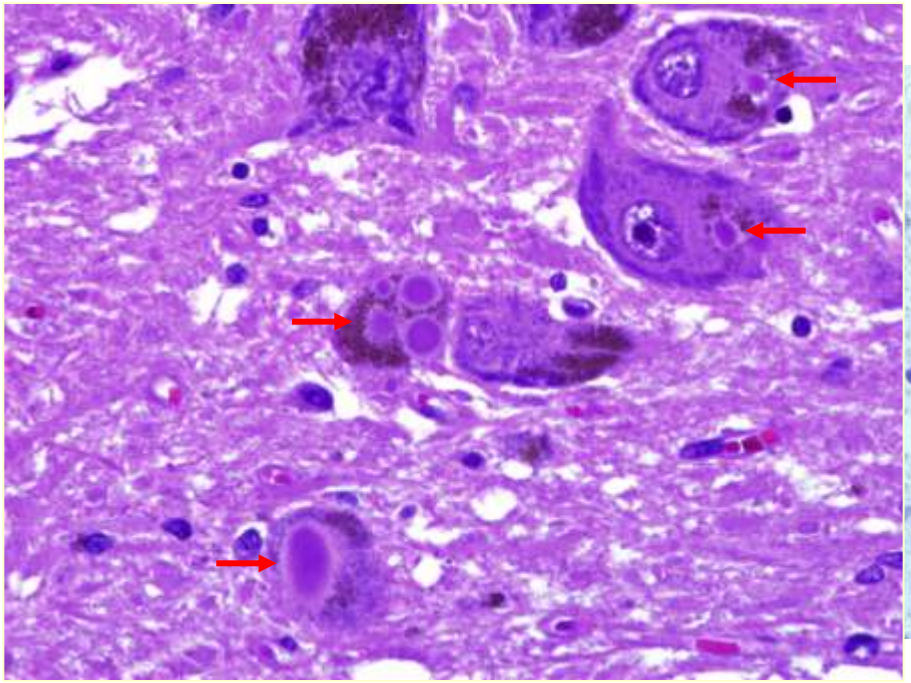


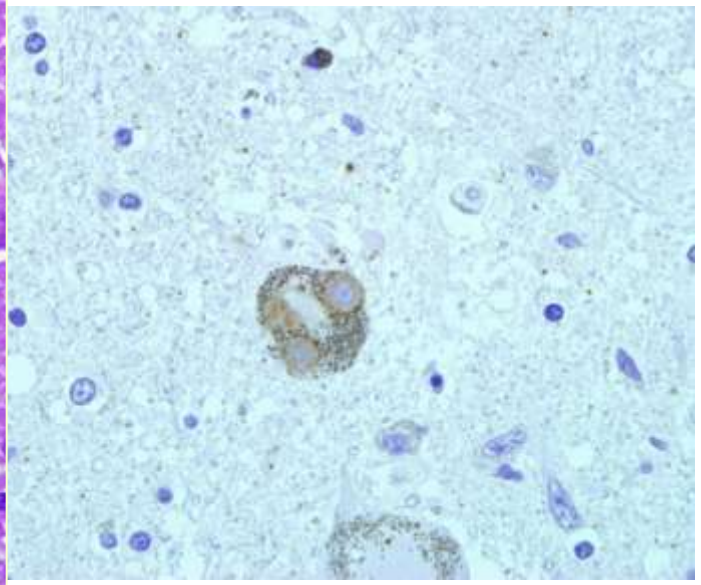


- **Depósito intracitoplasmático**
  - Neuronas
    - Soma
    - Prolongaciones celulares
  - Glía

A. **Depósito intracitoplasmático en el soma neuronal**: CUERPO DE LEWY

A.1. CUERPO DE LEWY CLASICO

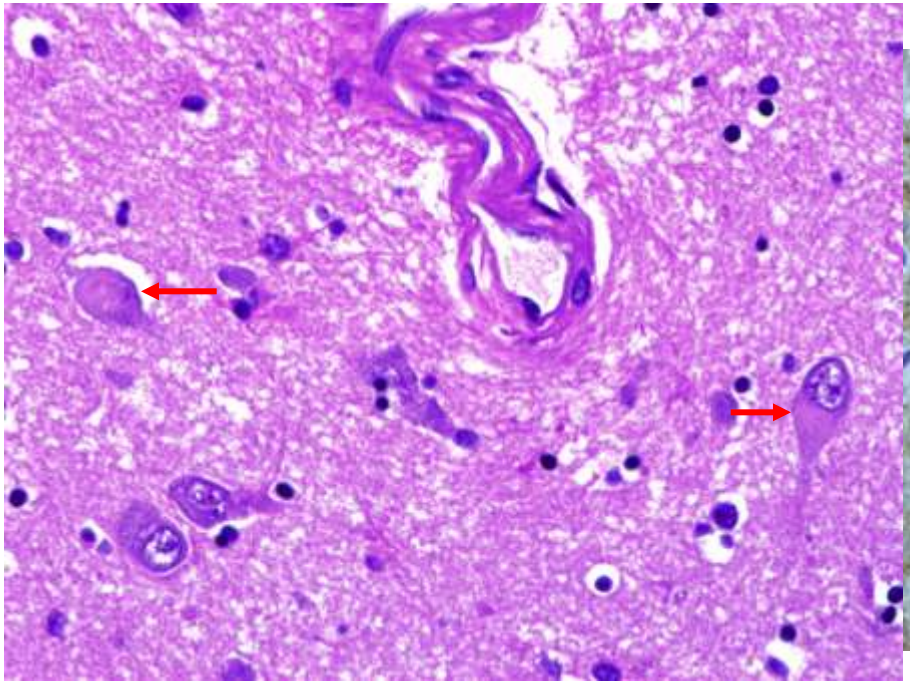


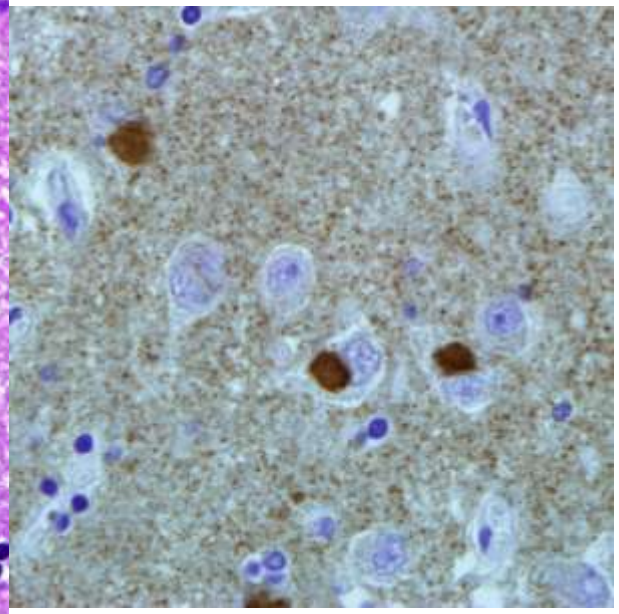


- Inclusiones redondeadas eosinófilas (8-30 µm) de centro hialino y con halo claro
- Únicas o múltiples
- El halo claro se tiñe con aSN y ubicuitina

A. **Depósito intracitoplasmático en el soma neuronal**: CUERPO DE LEWY

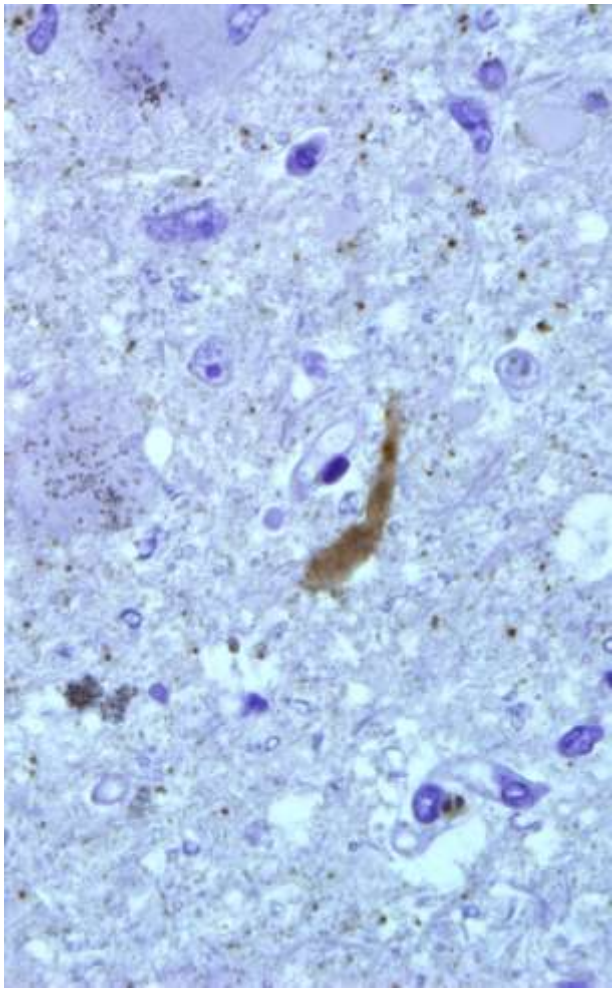
A.2: CUERPO DE LEWY TIPO CORTICAL

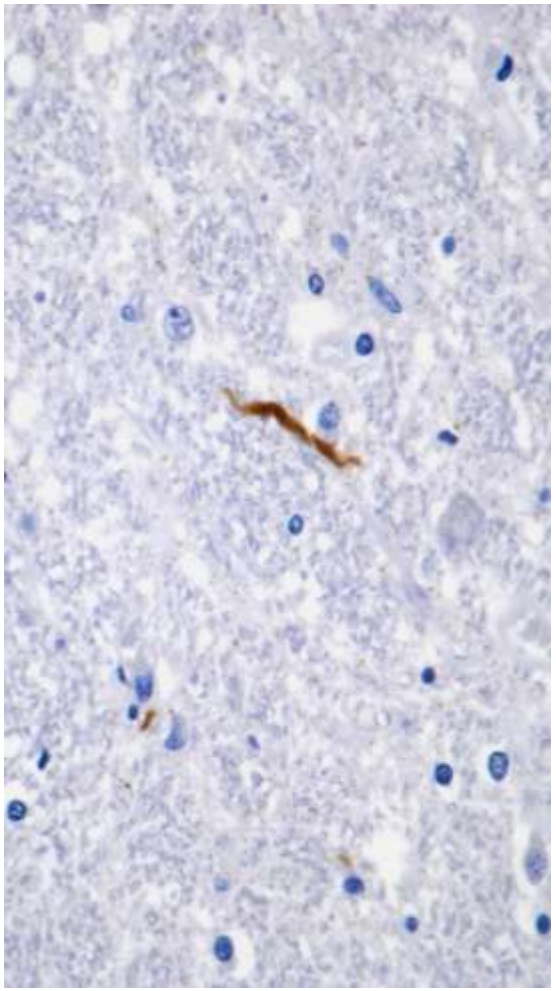


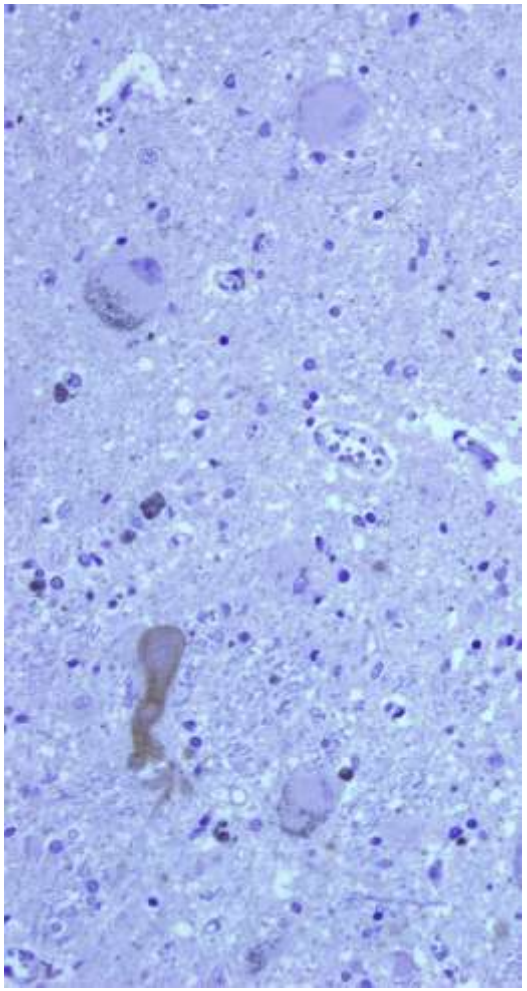


- Inclusiones hialinas eosinófilas de forma variable (redonda, ovoide, reniforme) sin halo claro
- Tinción difusa para aSN y ubicuitina
- Capas profundas (V y VI) de la corteza

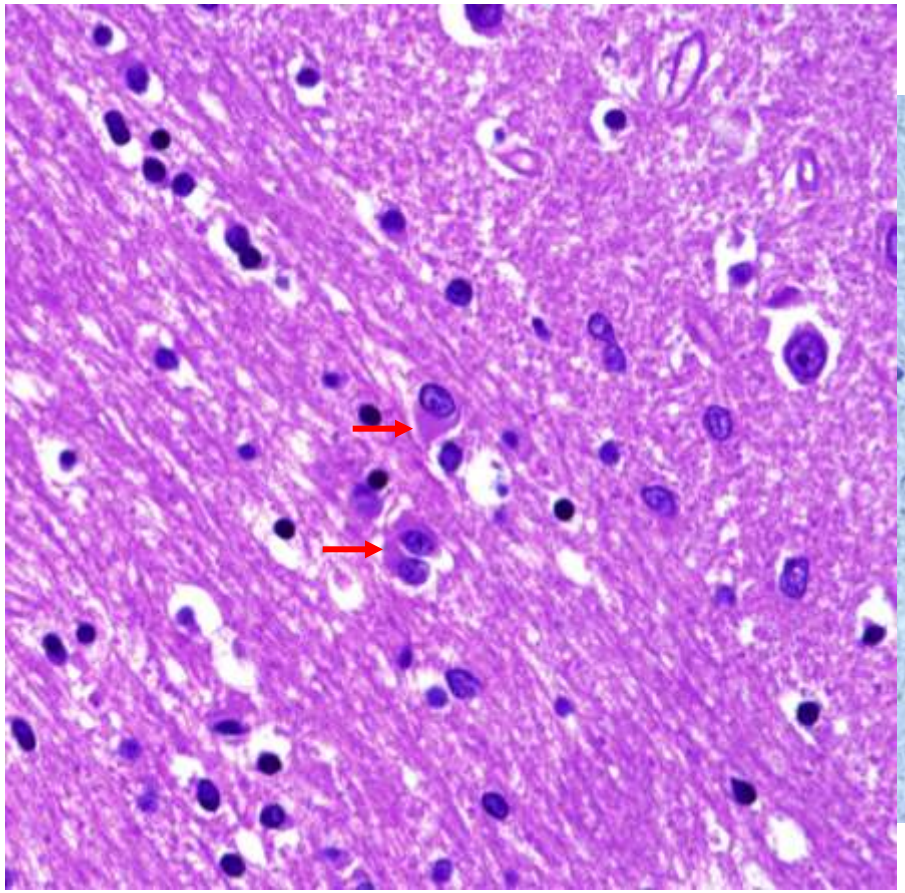
B. **Depósito intracitoplasmático en las prolongaciones celulares de neuronas:** NEURITAS DE LEWY

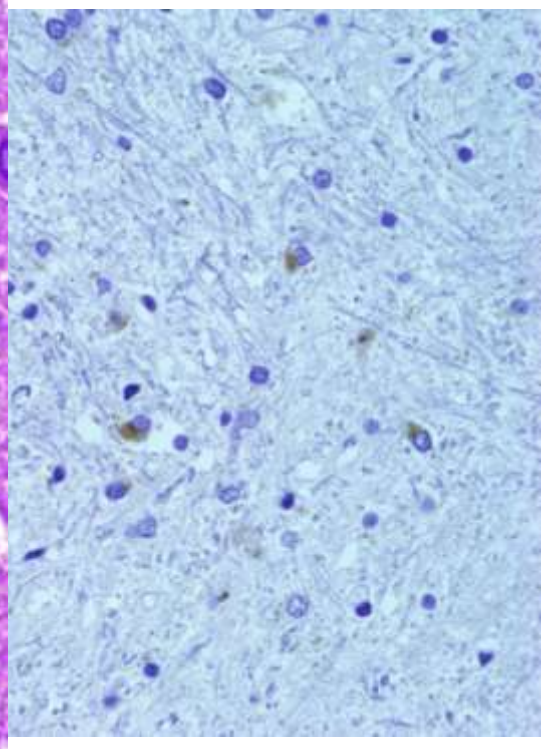






C. **Depósito intracitoplasmático en glía**
INCLUSIONES CITOPLASMATICAS GLIALES





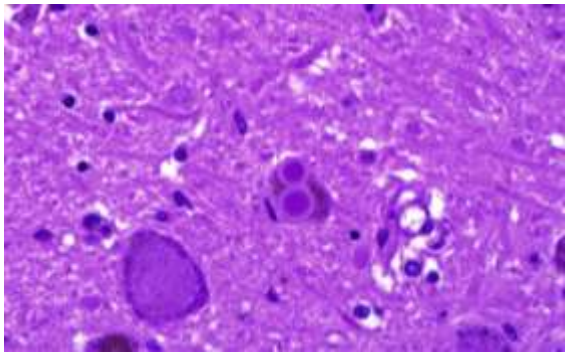
Enfermedades neurodegenerativas por agregación de a-sinucleína

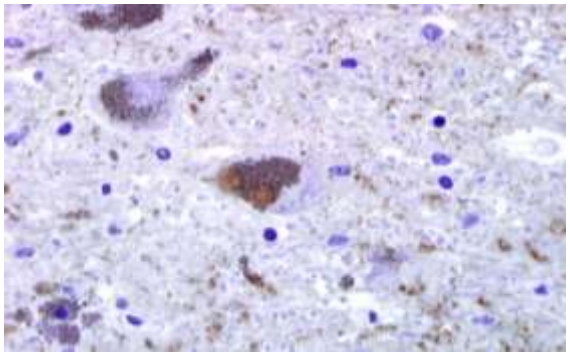
- Enfermedad de Parkinson
- Demencia por cuerpos de Lewy
- Atrofia multisistema

Enfermedad de Parkinson

- Clínica: bradiquinesia, temblor de reposo, rigidez e inestabilidad postural. Degeneración del circuito dopaminérgico nigroestriado

- Histología:
  - Pars compacta de la sustancia negra (ventrolateral).
  - Cuerpos y neuritas de Lewy





SPECIAL ARTICLE

Diagnostic Criteria for Parkinson Disease

Douglas J. Gelb, MD, PhD; Eugene Oliver, PhD; Sid Gilman, MD

The clinical diagnosis of Parkinson disease (PD) is based on the identification of some combination of the cardinal motor signs of bradykinesia, rigidity, tremor, and postural instability, but few attempts have been made to develop explicit diagnostic criteria. We propose a clinical diagnostic classification based on a comprehensive review of the literature regarding the sensitivity and specificity of the characteristic clinical features of PD. Three levels of diagnostic confidence are differentiated: Definite, Probable, and Possible. The diagnoses of Possible and Probable PD are based on clinical criteria alone. Neuropathologic confirmation is required for the diagnosis of Definite PD in patients with the clinical diagnosis of Possible or Probable PD. Criteria for histopathologic confirmation of PD are also presented. *Arch Neurol. 1999;56:33-39*

Table 3. Proposed Criteria for Histopathologic Confirmation of Parkinson Disease

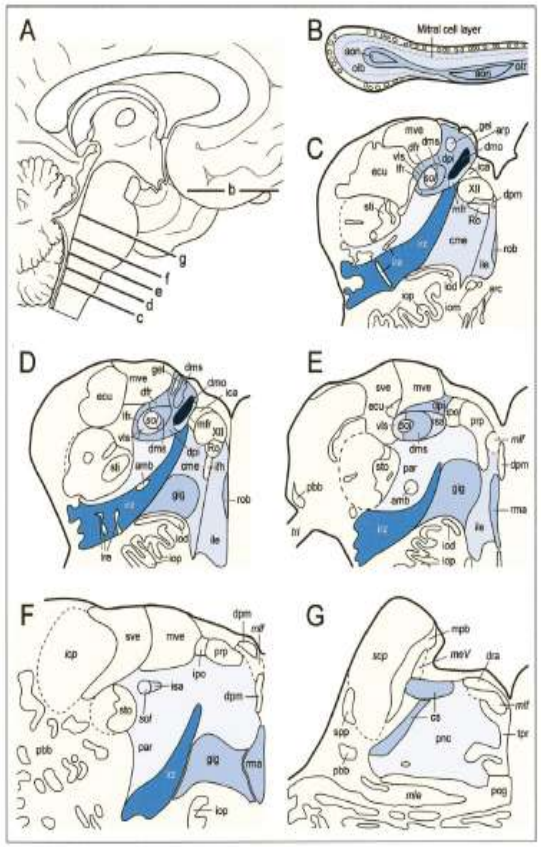
Substantial nerve cell depletion with accompanying gliosis in the substantia nigra
At least 1 Lewy body in the substantia nigra or in the locus ceruleus (note: it may be necessary to examine up to 4 nonoverlapping sections in each of these areas before concluding that Lewy bodies are absent)
No pathologic evidence for other diseases that produce parkinsonism (eg, progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degeneration) (note: in excluding other diseases that produce parkinsonism, published consensus criteria should be used when available[65])

Journal of Neuropathology and Experimental Neurology

Vol. 61, No. 5
May, 2002
pp. 413–426

Where Does Parkinson Disease Pathology Begin in the Brain?

KELLY DEL TREDICI, PHD, UDO RÜB, MD, ROB A.I. DE VOS, MD, JÜRGEN R.E. BOHL, MD, AND HEIKO BRAAK, MD



. 1. A: Median view of a medionaggital section through the human brain and brainstem for orientation. Line b indicates sition of anterior olfactory structures in (B). Lines c–g indicate the planes of the following frontal sections: line c plane of s shown in (C), line d plane of section shown in (D), etc. B: Horizontal section through the olfactory bulb (olb) and ory tract (olt), including portions of the anterior olfactory nucleus (aon). C–G: Schematized sections cut perpendicular to ert's brainstem axis showing the distribution pattern of the PD-related pathology in the lower brainstem. The frequency

Abstract. The substantia nigra is not the induction site in the brain of the neurodegenerative process underlying Parkinson disease (PD). Instead, the results of this semi-quantitative study of 30 autopsy cases with incidental Lewy body pathology indicate that PD in the brain commences with the formation of the very first immunoreactive Lewy neurites and Lewy bodies in non-catecholaminergic neurons of the dorsal glossopharyngeus-vagus complex, in projection neurons of the intermediate reticular zone, and in specific nerve cell types of the gain setting system (coeruleus-subcoeruleus complex, caudal raphe nuclei, gigantocellular reticular nucleus), olfactory bulb, olfactory tract, and/or anterior olfactory nucleus in the absence of nigral involvement. The topographical parcellation of the nuclear grays described here is based upon known architectonic analyses of the human brainstem and takes into consideration the pigmentation properties of a few highly susceptible nerve cell types involved in PD. In this sample and in all 58 age- and gender-matched controls, Lewy bodies and Lewy neurites do not occur in any of the known prosencephalic predilection sites (i.e. hippocampal formation, temporal mesocortex, pro-neocortical cingulate areas, amygdala, basal nucleus of Meynert, interstitial nucleus of the diagonal band of Broca, hypothalamic tuberomamillary nucleus).

-Existen áreas extranigrales afectadas antes de la afectación de la nigra? Relevancia de la patología extranigral.

-Existencia de LB en grupos neuronales específicos (núcleo motor IX/X, locus ceruleus-complejo subceruleus) de forma precoz.

-Los LB/LN no son cambios asociados al envejecimiento.

ELSEVIER

Neurobiology of Aging 24 (2003) 197–211

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Staging of brain pathology related to sporadic Parkinson's disease

Heiko Braak[a,*], Kelly Del Tredici[a], Udo Rüb[a], Rob A.I. de Vos[b], Ernst N.H. Jansen Steur[b], Eva Braak[a,†]

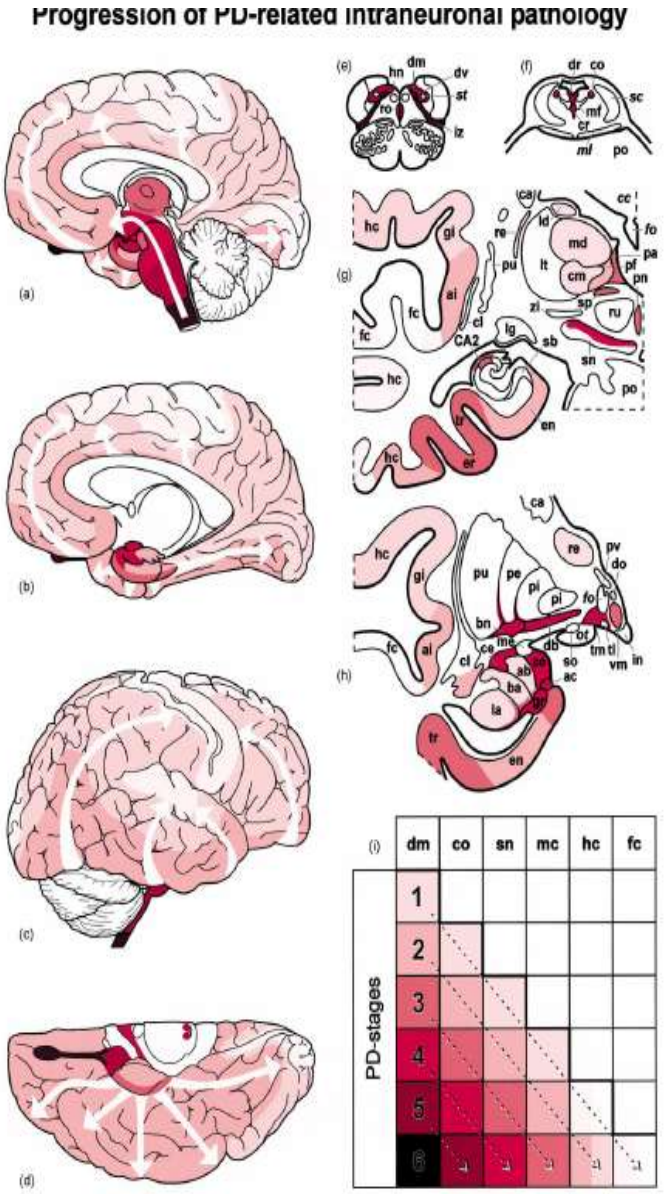
[a] Department of Clinical Neuroanatomy, J.W. Goethe University, Theodor Stern Kai 7, D-60590 Frankfurt/Main, Germany
[b] Department of Neurology MST Hospital Group and Laboratorium Pathologie Oost Nederland, Burg. Edo Bergsmalaan, 7512 AD Enschede, The Netherlands

Received 30 January 2002; received in revised form 23 April 2002; accepted 30 April 2002

-EP esporádica afecta a muchas circuitos neuronales resultado de cambios que se producen en unas pocas poblaciones neuronales susceptibles.

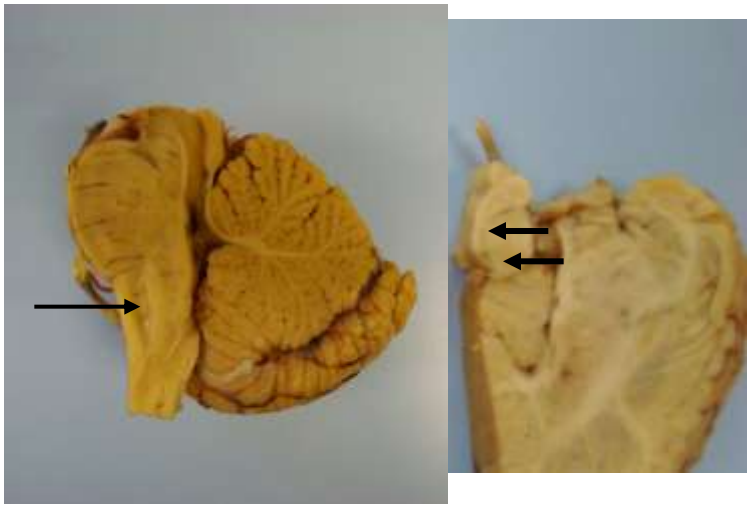
-Comienza en núcleos motor dorsal del IX/X y núcleo olfatorio anterior, afectándose posteriormente otras áreas.

-PROGRESION ASCENDENTE.



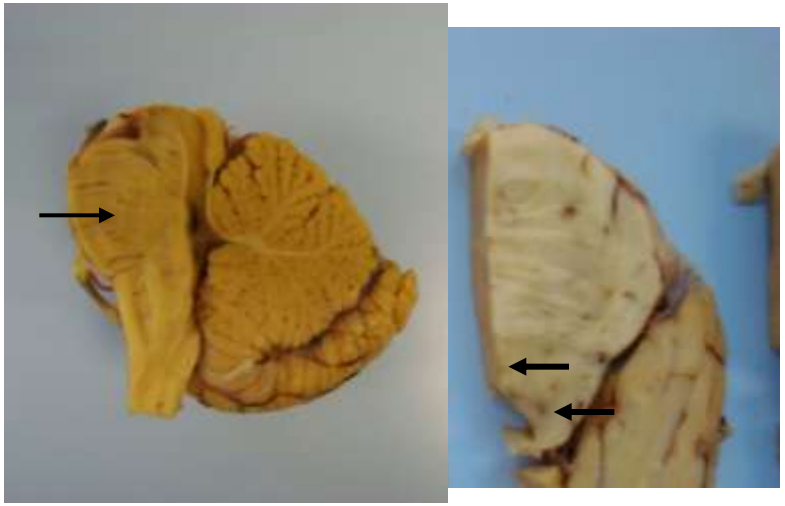
ESTADIO 1
bulbo raquídeo

- Lesiones en el núcleo dorsal motor IX y X y/o en la zona reticular intermedia.
- Bulbo olfatorio
- Sistema autonómico (Cell Tissue Res 2004; 318:121-134).



ESTADIO 2
bulbo raquídeo y tegmento pontino

- Estadio 1 + lesiones en el núcleo caudal del rafe, núcleo reticular giganto celular y complejo ceruleus/subceruleus.

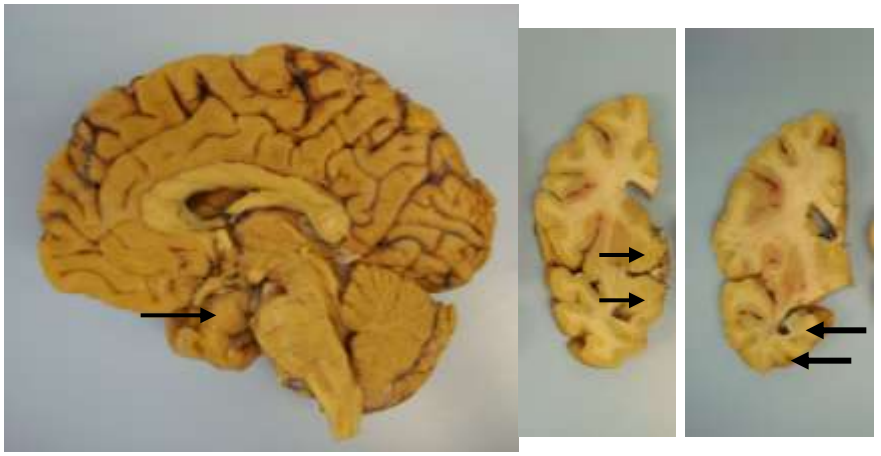


ESTADIO 3
mesencéfalo

- Estadio 2 + lesiones en mesencéfalo (pars compacta de la sustancia negra).

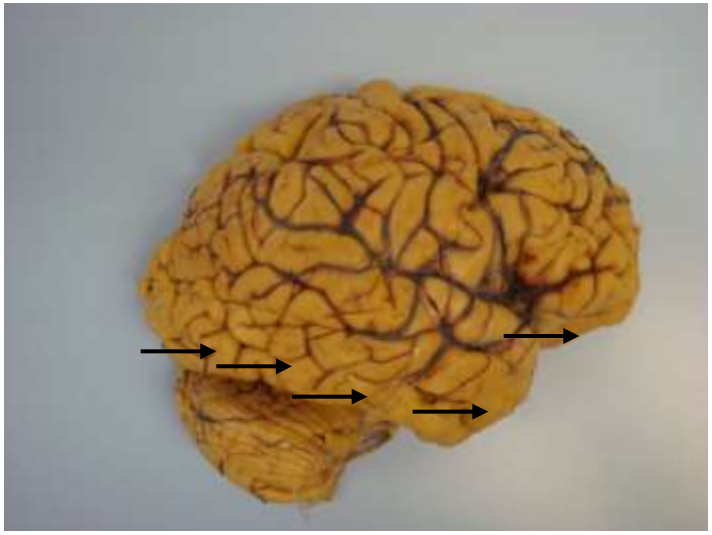
ESTADIO 4
prosencéfalo basal
mesocortex

- Estadio 3 + lesiones en prosencéfalo (amígdala, núcleo basal de Meynert).
- Afectación cortical limitada a corteza temporal medial (región transtentorrinal) y alocortex (región CA2-plexo).



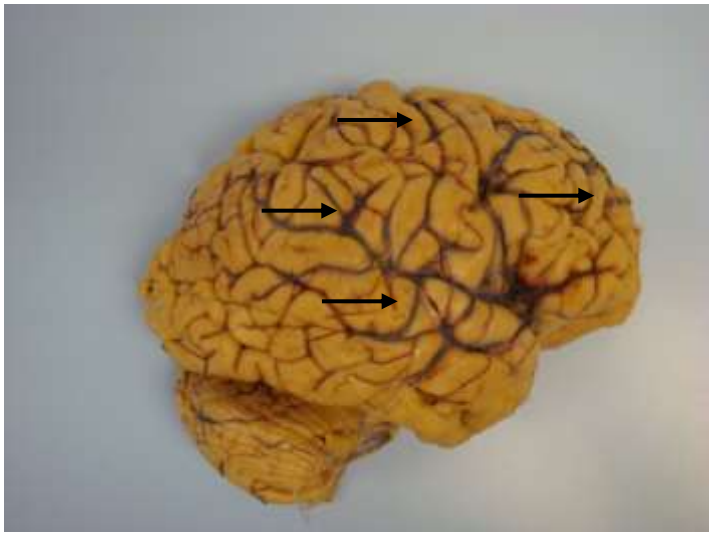
ESTADIO 5
neocortex

- Estadio 4 + lesiones en áreas de asociación mayores del neocortex y corteza prefrontal.



ESTADIO 6
neocortex

- Estadio 5 + lesiones en corteza sensorial primarias del neocortex y áreas premotoras corteza prefrontal.



No correlación del sistema de estadiaje…

Neuropathology 2005; 25, 304–314

Original Article

Widespread and abundant α-synuclein pathology in a neurologically unimpaired subject

Laura Parkkinen,[1] Tuula Pirttilä,[1,2] Markku Tervahauta[3] and Irina Alafuzoff[1,4]

[1]Department of Neuroscience and Neurology, Kuopio University, Departments of [2]Neurology and [4]Pathology, Kuopio University Hospital, Kuopio and [3]Leppävirta Health Care Center, Leppävirta, Finland

Ann Neurol 2005;57:82–91

α-Synuclein Pathology Does Not Predict Extrapyramidal Symptoms or Dementia

Laura Parkkinen, MSc,[1] Tarja Kauppinen, MLT,[1] Tuula Pirttilä, MD, PhD,[1,2] Jaana M. Autere, MD, PhD,[1,2] and Irina Alafuzoff, MD, PhD[1,3,4]

Acta Neuropathol (2008) 116:1–16
DOI 10.1007/s00401-008-0406-y

REVIEW

A critical reappraisal of current staging of Lewy-related pathology in human brain

Kurt A. Jellinger

- 6.3-43% de casos se desvían del sistema de estadiaje caudo-rostral propuesto por Braak, especialmente en jóvenes.
  - Estadío 4 y 5 sin afectación de bulbo
  - Síntomas en estadío 2 y 3.
- El estadiaje no es útil para los casos que tienen una clínica predominante de demencia. La demencia no se correlaciona con estadíos avanzados de LB

Movement Disorders
Vol. 24, No. 13, 2009, pp. 1998–2019

Neuropathology of Parkinson's Disease with the R1441G Mutation in *LRRK2*

José-Félix Martí-Massó,[1,2]* Javier Ruiz-Martínez,[1,2]
Maria J. Bolaño,[1] Irune Ruiz,[3] Ana Gorostidi,[4]
Fermin Moreno,[1] Isidre Ferrer,[2,5]
and Adolfo López de Munain[1,2]

Abstract: **We report the neuropathological findings in a patient with Parkinson's disease (PD) associated with Basque R1441G-*LRRK2*/dardarin mutation. The patient was a man with disease onset at 68 years of age, with unilateral rest tremor; the Parkinsonism was well controlled with medication for 15 years. He died at the age of 86, after 18 years of evolution. The neuropathological examination disclosed mild neuronal loss in the substantia nigra pars compacta without α-synuclein, tau, *LRRK2*, or ubiquitin cytoplasmic inclusions. Lewy bodies and Lewy neurites were absent. This is the first neuropathological study of PD associated with brain with the R1441G mutation in *LRRK2*.** © 2009 Movement Disorder Society

J Neuropathol Exp Neurol

Vol. 65, No. 7
July 2006
pp. 685–697

ORIGINAL ARTICLE

Alzheimer Disease With Amygdala Lewy Bodies: A Distinct Form of α-Synucleinopathy

Hirotake Uchikado, MD, PhD, Wen-Lang Lin, MD, PhD, Michael W. DeLucia, and Dennis W. Dickson, MD

- Forma amigdalar: casos en los que los CL predominan o sólo se localizan en la amígdala.
- La mayoría de los casos están relacionados con Alzheimer o con Síndrome de Down.
- Entidad diferente dentro de las a-sinucleinopatías.

Patterns and stages of α-synucleinopathy

Relevance in a population-based cohort

Conclusion: α-Synucleinopathy (AS) is common in older people, and frequently associated with Alzheimer disease–type pathology. Although half of brains corresponded to the Braak hypothesis, and 29% to amygdala-predominant AS, there were a high proportion of cases which did not fit a staging system. An unexpectedly high proportion with a cortical form of Lewy body disease was identified. *Neurology*® 2008;70:1042-1048

Forma cortical: Casos con intenso depósito de ASN en corteza y pocos CL en tronco

Acta Neuropathol (2008) 115:445–451
DOI 10.1007/s00401-007-0313-7

ORIGINAL PAPER

Reduced striatal tyrosine hydroxylase in incidental Lewy body disease

Thomas Gerald Beach · Charles H. Adler · Lucia I. Sue · Jeffrey B. Peirce · Jyothi Bachalakuri · Jessica E. Dalsing-Hernandez · Lih Fen Lue · John N. Caviness · Donald J. Connor · Marwan N. Sabbagh · Douglas G. Walker

- El descenso de TH (marcador dopaminérgico) en el estriado en pacientes con iLB vs controles sugiere que se trata de un precursor de EP.

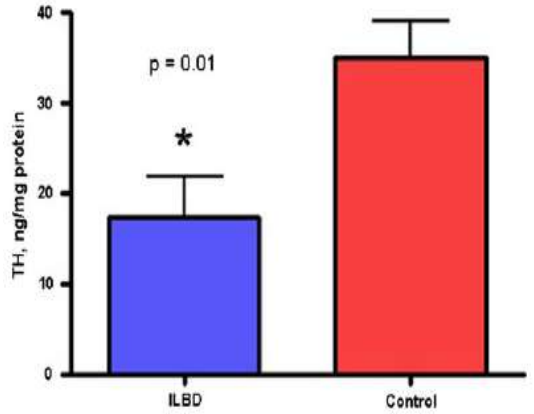


Fig. 2 Graph showing the concentrations of tyrosine hydroxylase (TH), as measured by ELISA, in the striatum of ILBD and control cases. The concentrations of TH were depleted in ILBD cases to 49.8% of control levels ($P = 0.01$)

Acta Neuropathol (2008) 115:437–444
DOI 10.1007/s00401-008-0345-7

ORIGINAL PAPER

Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease

Dennis W. Dickson · Hiroshige Fujishiro · Anthony DelleDonne · Joshua Menke · Zeshan Ahmed · Kevin J. Klos · Keith A. Josephs · Roberta Frigerio · Melinda Burnett · Joseph E. Parisi · J. Eric Ahlskog

- Patrón de distribución semejante al del EP pero sin pérdida neuronal.
- Estadío preclínico por estudios de tirosina hidroxilasa (↓). Niveles de TH mayores que en EP pero menores que en grupo control.

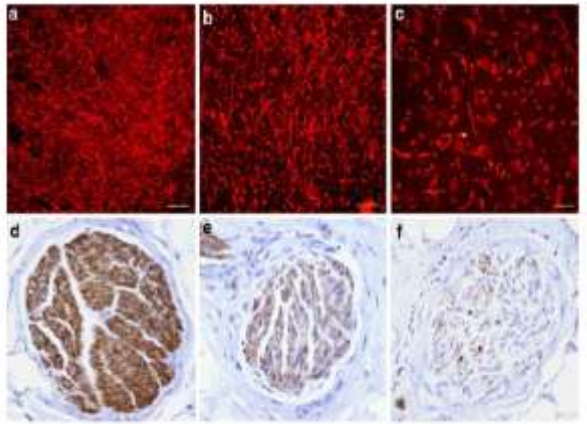
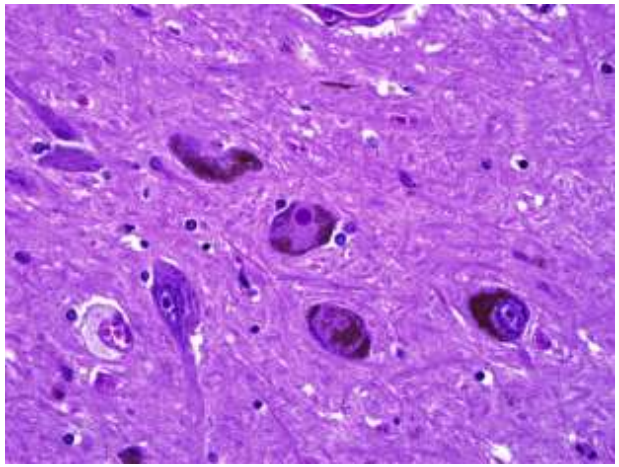


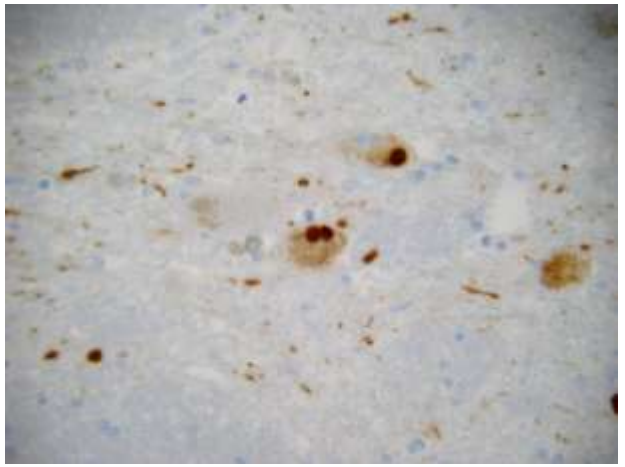
Fig. 1 Tyrosine hydroxylase immunofluorescence in putamen in normal (a), iLBD (b) and PD (c). TH immunohistochemistry in epicardial nerve fibers in normal (d), iLBD (e) and PD (f)

Demencia por cuerpos de Lewy

- Clínica: deterioro cognitivo que interfiere con la vida habitual, fluctuación, alucinaciones visuales recurrentes y parkinsonismo.

- Histología:
  - Cuerpos y neuritas de Lewy.
  - Lesiones similares a las de EP pero mayor extensión a corteza.





report of the DLB consortium

Neurology 1996; 47: 1113-1124

- Estudios neuropatológicos 15-25% de pacientes con demencia tenían LB en el tronco y cerebro. 2ª causa de demencia después de EA
- Establecer criterios diagnósticos clínicos
- Establecer criterios para la valoración y caracterización de los hallazgos histológicos en la autopsia.

  - LB en tronco y corteza son esenciales en el Dx (asociados pero no esenciales LN, ONF, placas, pérdida neuronal…).
  - Tinción: H&E ubicuitina (tau…). Recomendaban un marcador más sensible y específico
  - Muestreo cerebral (BA8/9, BA21, BA40; BA24, BA28; TE)
  - Valoración de LB en las diferentes áreas
  - DLB estadío troncoencefálico, límbico y neocortical (Kosaka, Clin Neuropathol. 1984; 3:185-192)

Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

NEUROLOGY 2005;65:1863–1872

Abstract—The dementia with Lewy bodies (DLB) Consortium has revised criteria for the clinical and pathologic diagnosis of DLB incorporating new information about the core clinical features and suggesting improved methods to assess them. REM sleep behavior disorder, severe neuroleptic sensitivity, and reduced striatal dopamine transporter activity on functional neuroimaging are given greater diagnostic weighting as features suggestive of a DLB diagnosis. The 1-year rule distinguishing between DLB and Parkinson disease with dementia may be difficult to apply in clinical settings and in such cases the term most appropriate to each individual patient should be used. Generic terms such as Lewy body (LB) disease are often helpful. The authors propose a new scheme for the pathologic assessment of LBs and Lewy neurites (LN) using alpha-synuclein immunohistochemistry and semiquantitative grading of lesion density, with the pattern of regional involvement being more important than total LB count. The new criteria take into account both Lewy-related and Alzheimer disease (AD)-type pathology to allocate a probability that these are associated with the clinical DLB syndrome. Finally, the authors suggest patient management guidelines including the need for accurate diagnosis, a target symptom approach, and use of appropriate outcome measures. There is limited evidence about specific interventions but available data suggest only a partial response of motor symptoms to levodopa: severe sensitivity to typical and atypical antipsychotics in ~50%, and improvements in attention, visual hallucinations, and sleep disorders with cholinesterase inhibitors.

- Revisan criterios diagnósticos clínicos
- Establecen criterios para la valoración y caracterización de los hallazgos histológicos en la autopsia.
  - LB y **LN** en tronco y corteza son esenciales en el Dx.
  - Tinción: **α-sinucleína**
  - Muestreo cerebral (BA8/9, BA21, BA40; BA24, BA28; TE)
  - Valoración de LB y LN en las diferentes áreas
  - DLB estadío troncoencefálico, límbico y neocortical (Kosaka, Clin Neuropathol. 1984; 3:185-192)
  - **Relacionan los cambios de EA en la clínica del paciente**

Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

NEUROLOGY 2005;65:1863–1872

- The following scoring system for LB is recommended (figure):

  0 = None

  1 = Mild (sparse LBs or LNs)

  2 = Moderate (more than one LB in a low power field and sparse LNs)

  3 = Severe (four or more LBs and scattered LNs in a low power field)

  4 = Very severe (numerous LBs and numerous LNs)

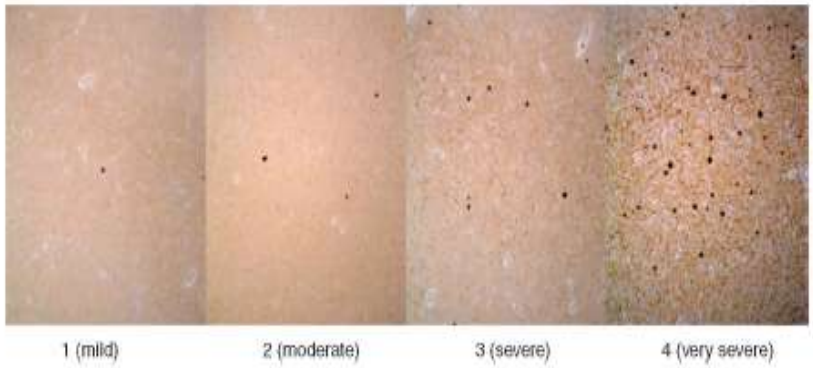


Figure. Stag
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LNs; Stage 3
LNs in low p
merous LBs
of Dr. E. Jaros. 5 μm thick sections, pretreated with pressure cooker for 1 minute in EDTA pH
castra mouse monoclonal alpha-synuclein antibody (clone KM51), 1:30 dilution, DAB final rea

Table 2 *Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

Brain regions are as defined anatomically in the original Consensus report.[1]

IX = 9th cranial nerve nucleus; X = 10th cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert.

***Table 3** Assessment of the likelihood that the pathologic findings are associated with a DLB clinical syndrome*

	Alzheimer type pathology		
	NIA-Reagan Low (Braak stage 0–II)	NIA-Reagan Intermediate (Braak stage III–IV)	NIA-Reagan High (Braak stage V–VI)
Lewy body type pathology			
Brainstem-predominant	Low	Low	Low
Limbic (transitional)	High	Intermediate	Low
Diffuse neocortical	High	High	Intermediate

DLB = dementia with Lewy bodies; NIA = National Institute on Aging.

***Table 2** Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
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Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

Brain regions are as defined anatomically in the original Consensus report.[1]

IX = 9th cranial nerve nucleus; X = 10th cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert.

Acta Neuropathol (2009) 117:635–652
DOI 10.1007/s00401-009-0523-2

ORIGINAL PAPER

Staging/typing of Lewy body related α-synuclein pathology: a study of the BrainNet Europe Consortium

Irina Alafuzoff · Paul G. Ince · Thomas Arzberger · Safa Al-Sarraj · Jeanne Bell · Istvan Bodi · Nenad Bogdanovic · Orso Bugiani · Isidro Ferrer · Ellen Gelpi · Stephen Gentleman · Giorgio Giaccone · James W. Ironside · Nikolaos Kavantzas · Andrew King · Penelope Korkolopoulou · Gábor G. Kovács · David Meyronet · Camelia Monoranu · Piero Parchi · Laura Parkkinen · Efstratios Patsouris · Wolfgang Roggendorf · Annemieke Rozemuller · Christine Stadelmann-Nessler · Nathalie Streichenberger · Dietmar R. Thal · Hans Kretzschmar

BRAINNET EUROPE

BNE-protocolo:

EP: - concordancia 65% (36%)

- Braak: cada estadio requiere de la afectación de nuevas áreas y de mayor grado de afectación del estadio anterior.

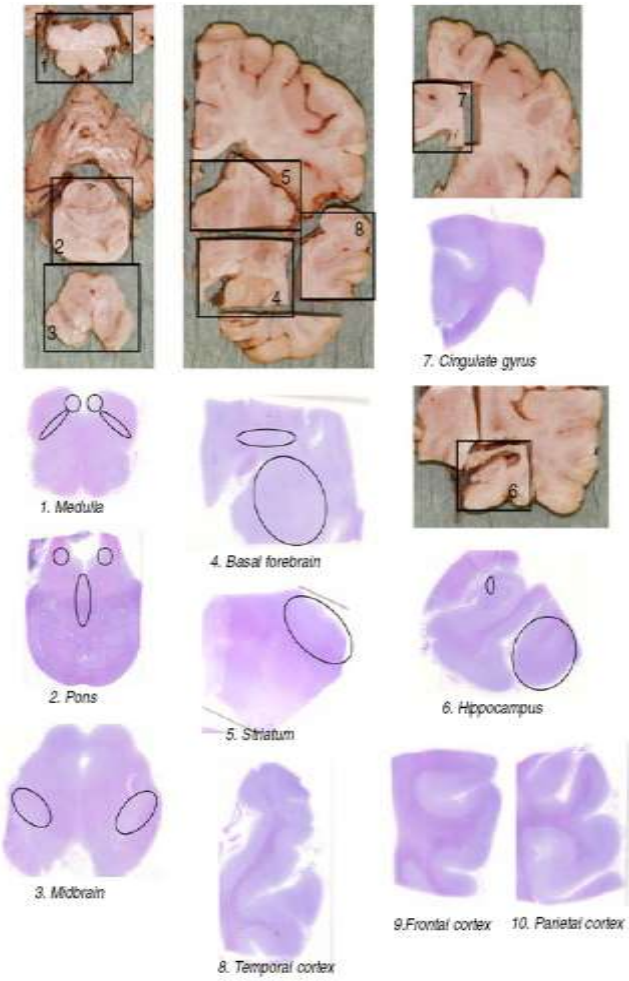
DCL: - concordancia 80% (73%)

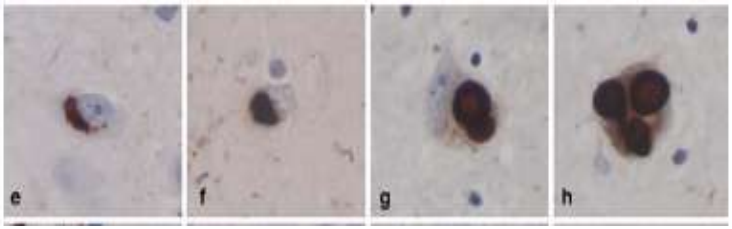
- McKeith: no existe clara diferenciación entre las 3 categorías

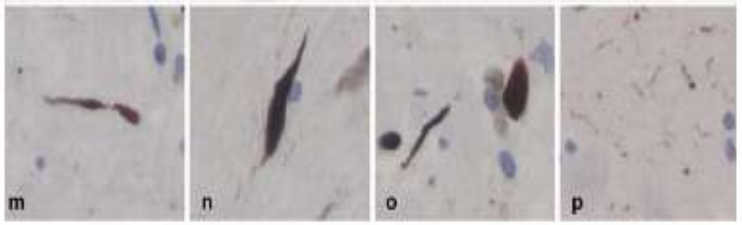
Objetivo aumentar el grado de concordancia entre observadores

- Estudian 13 regiones en 9 bloques
- Presencia o ausencia de reactividad para asn
- Lesión requerida (NL y/o CL)
- Afectación predominante de la amígdala.

- **Bulbo raquídeo**
  - **Núcleo motor dorsal X**
  - **Zona intermedia reticular**
- **Protuberancia**
  - **Locus ceruleus**
  - **Núcleo dorsal del rafe**
- **Sustancia negra (pars compacta)**
- **Prosencéfalo basal**
  - **Núcleo basal de Meynert**
  - **Amígdala**
- Estriado con corteza insular
- **Hipocampo**
  - **CA2**
  - **Corteza temporooccipital**
- **Giro cingular**
- **Corteza temporal sup/media**
- **Corteza frontal (9)**
- **Corteza parietal (39/40)**







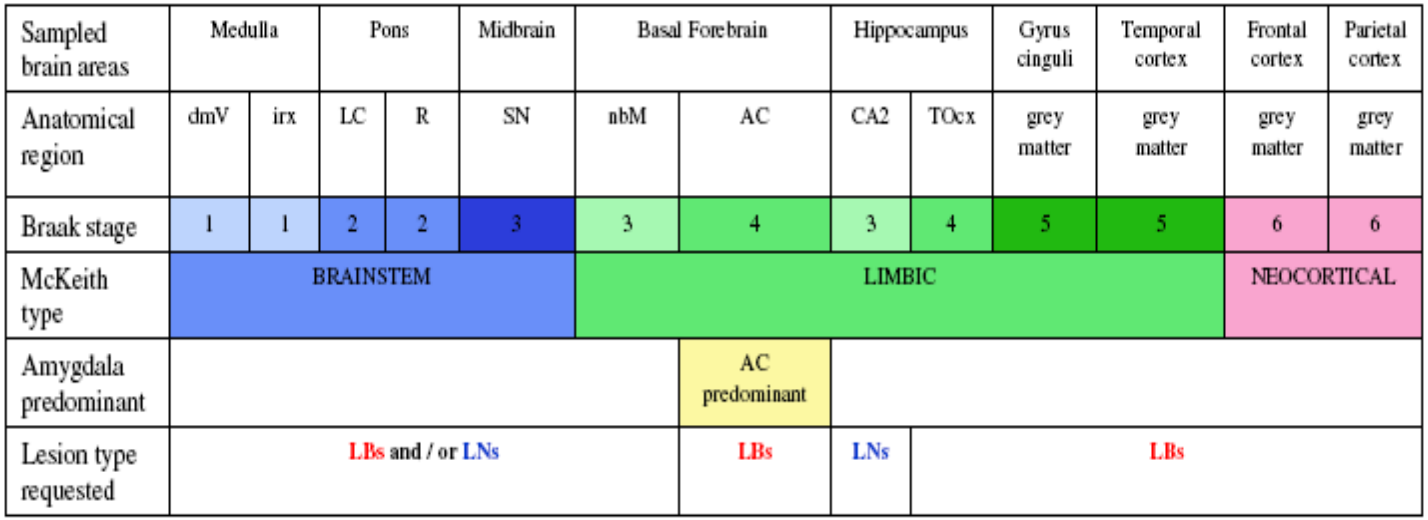


Fig. 5 BrainNet Europe protocol, i.e. assignment of the Braak stage and McKeith type of α-synuclein (αS) immunoreactive (IR) Lewy body (LB) disease related pathology as proposed by BrainNet Europe consortium. *dmV* Dorsal motor nucleus of vagus, *irx* intermediate reticular zone, *LC* locus coeruleus, *R* raphe, *SN* substantia nigra, *nbM* nucleus basalis of Meynert, *AC* amygdala, *CA2* cornu Ammonis of hippocampus, region 2 *TOcx* temporo-occipital cortex. *LN* Lewy neurites. Two to three regions represent each Braak stage. For a Braak stage only one of the required regions needs to be affected with the required (LB or LN) αS-IR pathology. Note, if a case does not fulfil sequentially all Braak stages, it is designated as an IF case, i.e. staging criteria incompletely fulfilled. For the McKeith brainstem type, one of the obligatory brainstem regions (medulla, pons, midbrain) has to be affected with LB and or LN. Only one of the two regions in Limbic or Neocortical type needs to be affected with the required (LB or LN) pathology to merit classification to this category. In Amygdala predominant type, the αS-IR LBs are either noted only in the AC or they are seen in excess in AC when compared to the brainstem regions. If occasional αS-IR LNs are seen in AC or in cortical regions without LBs, the case is assigned as a "+" case, i.e. a Braak stage 3+ or a McKeith brainstem +, when the case displays LBs and/or LNs up till midbrain but in addition LNs are seen in neocortical areas

Concordancia para EP del 83%, para DCL del 84%

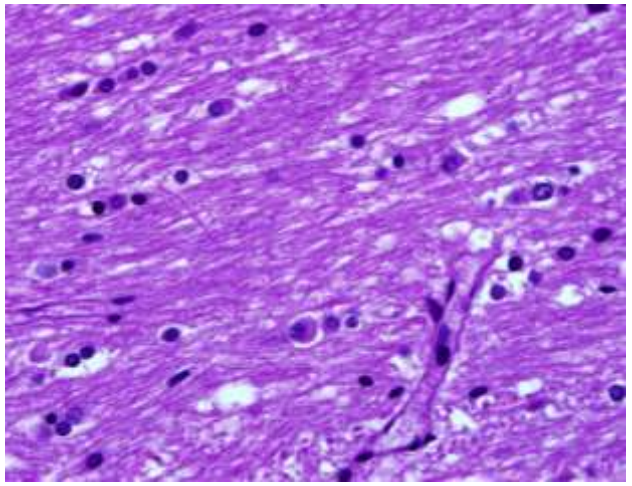
Atrofia multisistema

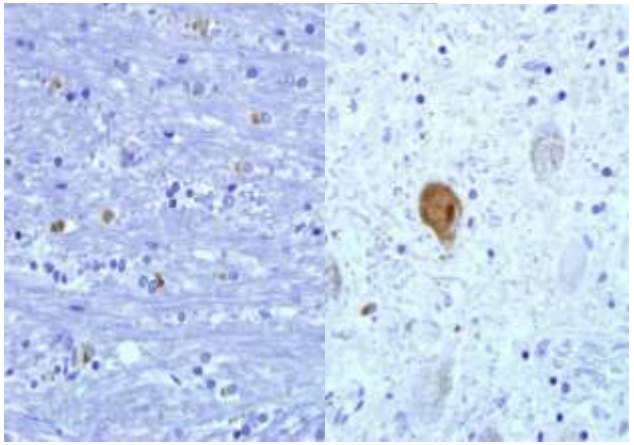
- Comienzo adulto, esporádico, progresiva.
- Clínica: diferentes grados de parkinsonismo, ataxia cerebelosa, fallo autonómico y alteración corticoespinal.

  AMS-P/AMS-C
- Histología:

  - Degeneración estrionígrica y/o olivopontocerebelosa

  - Inclusiones oligodendrogliales de a-sinucleína (inclusiones de Papp-Lantos)



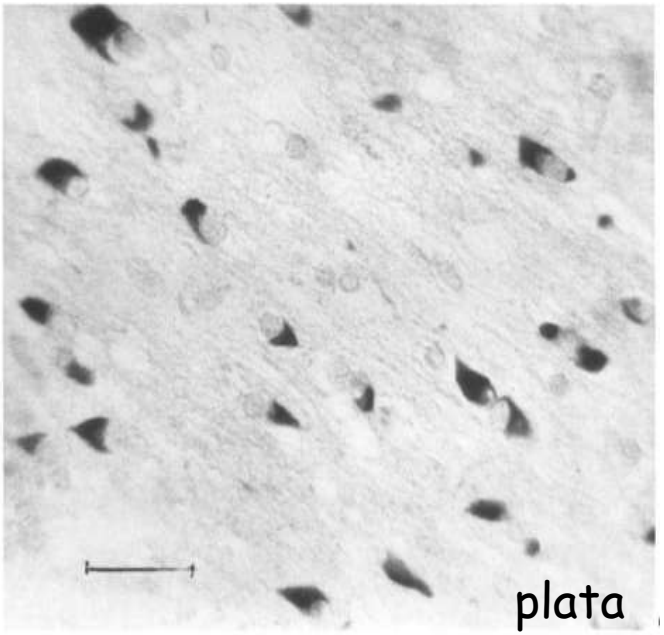


Journal of the Neurological Sciences, 1989, 94: 79–100
Elsevier

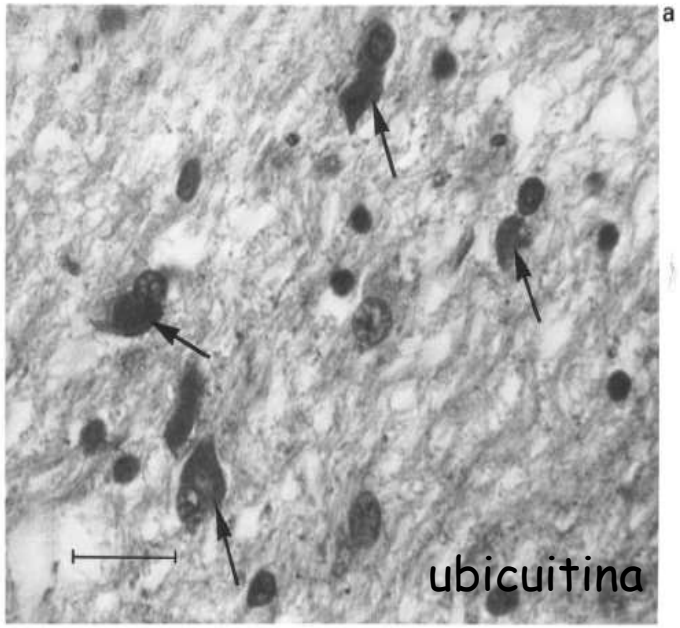
JNS 03247

Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome)*

Matyas I. Papp[1], Jacob E. Kahn[2] and Peter L. Lantos[2]

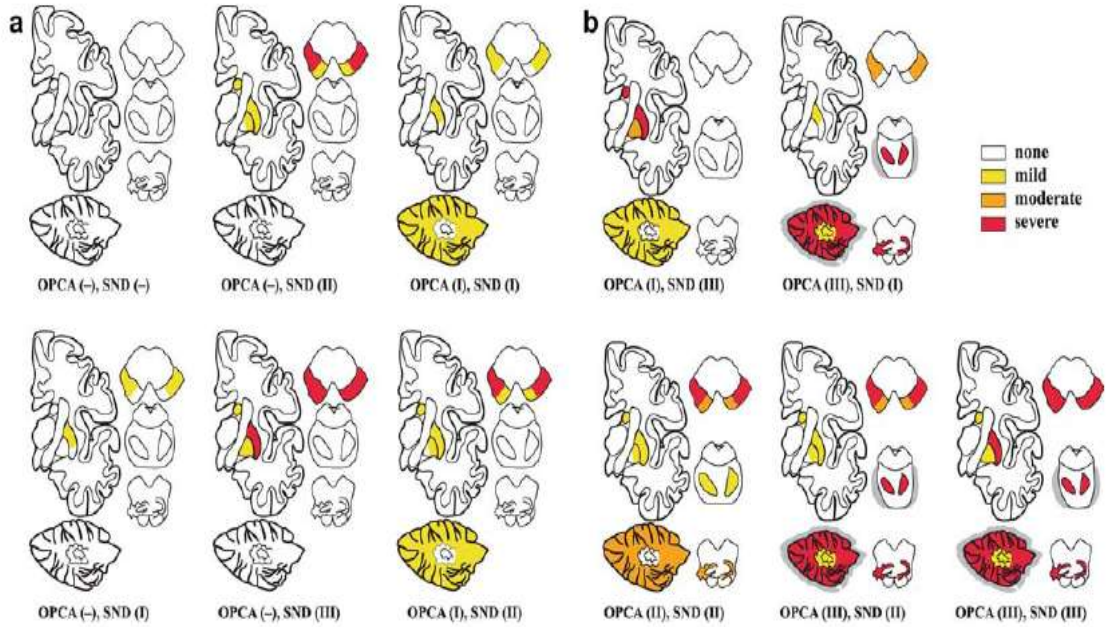


- Inclusiones citoplásmaticas gliales, mediante tinciones de plata, IHQ y ME en el SNC.
- Localizadas en la sustancia blanca junto con aumento de OD y desmielinización.
- La presencia de inclusiones en 11 pacientes y no en controles indican que es un hallazgo característico de AMS y que los 3 síndromes son diferentes manifestaciones de la misma enf.



Movement Disorders
Vol. 20, Suppl. 12, 2005, pp. S29–S36

Grading of Neuropathology in Multiple System Atrophy: Proposal for a Novel Scale



Sistema de clasificación que valora la degeneración estrionígrica y la atrofia olivopontocerebelosa

- 4 grados (0, I, II, III)
- pérdida neuronal, astrogliosis e inclusiones citoplasmáticas gliales
- estriado, pálido, SN, puente, cerebelo, oliva inferior.

Se necesitan estudios prospectivos para validad la utilidad clínica de esta clasificación

Neuropathology and Applied Neurobiology (2007), **33**, 615–620 doi: 10.1111/j.1365-2990.2007.00907.x

Proposed neuropathological criteria for the *post mortem* diagnosis of multiple system atrophy

J. Q. Trojanowski* and T. Revesz† for the Neuropathology Working Group on MSA[1]

MSA Workshop recognized the glial cytoplasmic inclusions (GCIs) composed of filamentous alpha-synuclein as a defining morphological feature of MSA, and it recommends that widespread GCIs should be a criterion for the definite neuropathological diagnosis of MSA. The deliberations and recommendations of the Working Group on Diagnostic Neuropathology Criteria for MSA are summarized in this report.

system and neocortex of AD patients, GCIs are rarely if ever observed in normal individuals lacking the clinical manifestations of a movement disorder. Thus, the detection of GCIs in the central nervous system (CNS), especially when GCIs are abundant and widespread, is diagnostic of MSA. Pathological observations of widespread GCIs in both 'minimal change' MSA, in which atrophy and nerve cell loss is restricted, and also in MSA with supposedly short disease duration, further underpin the diagnostic significance of GCIs [18,19]. For these

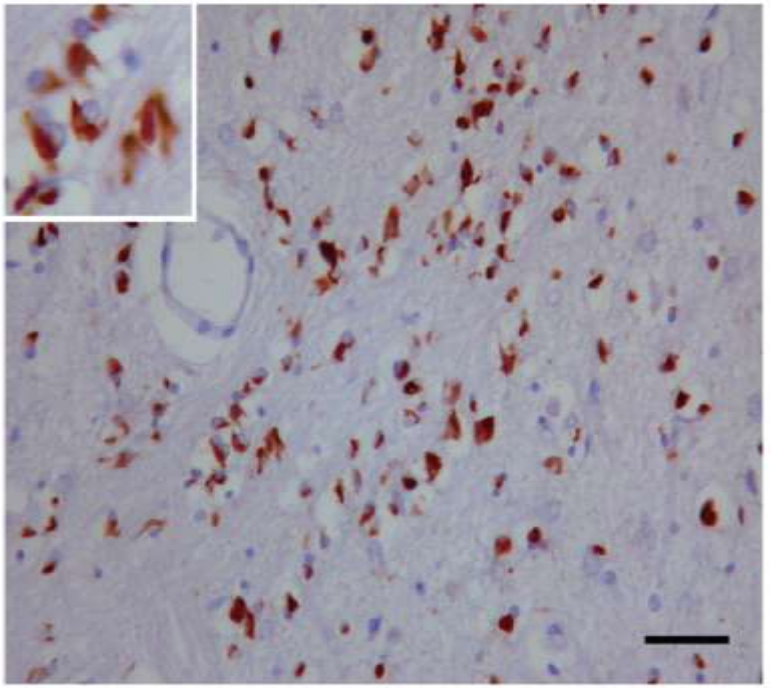


Figure 1. Numerous glial cytoplasmic inclusions in the striatum in a case of multiple system atrophy (alpha-synuclein immunohistochemistry; bar representing 40 μm in the main figure and 20 μm in the insert).

Las GCI no se observan en pacientes asintomáticos →las inclusiones son diagnósticas

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Updated criteria for the neuropathological diagnosis of MSA

The diagnostic signature lesion of MSA is the GCI. These filamentous alpha-synuclein inclusions are found in oligodendrocytes where they can have a flame-like, triangular or sickle-shaped appearance. GCIs can be observed throughout the white matter and they are also abundant in the basal ganglia, substantia nigra, pontine nuclei, medulla and cerebellum. Filamentous alpha-synuclein-positive inclusions are also present in the nuclei, cytoplasm and processes of neurones of some of the grey nuclei, such as the pontine nuclei, although they are not usually abundant. However, consistent with the views *post mortem* brain. This notwithstanding, the Neuropathology Working Group on MSA acknowledged that compared with other neurodegenerative diseases, the neuropathology that defines MSA is so unique, distinct and uncommon in individuals lacking clinical evidence of a CNS disease that the presence of abundant alpha-synuclein-positive GCIs alone in the *post mortem* brain is sufficient to make a definite diagnosis of MSA in the absence of a clinical history of MSA. However, the Neuropathology Working Group on MSA emphasizes the need to exclude other brain disorders that could account for a clinical parkinsonian syndrome in order to establish a neuropathological diagnosis of definite MSA, and that there should be a plausible correlation between the neuropathology and the findings in patients with clinical MSA. Informed by these principles, the Neuropathology Working Group on MSA recommends the following neuropathological criteria for MSA:

A definite neuropathological diagnosis of MSA is established when there is evidence of widespread and abundant CNS alpha-synuclein-positive GCIs in association with neurodegenerative changes in striatonigral or olivopontocerebellar structures.

Diagnóstico definitivo: GCI sinucleína positivas con degeneración estrionígrica u olivopontocerebelosa

Acta Neuropathol (2008) 116:269–275
DOI 10.1007/s00401-008-0398-7

ORIGINAL PAPER

Glial cytoplasmic inclusions in neurologically normal elderly: prodromal multiple system atrophy?

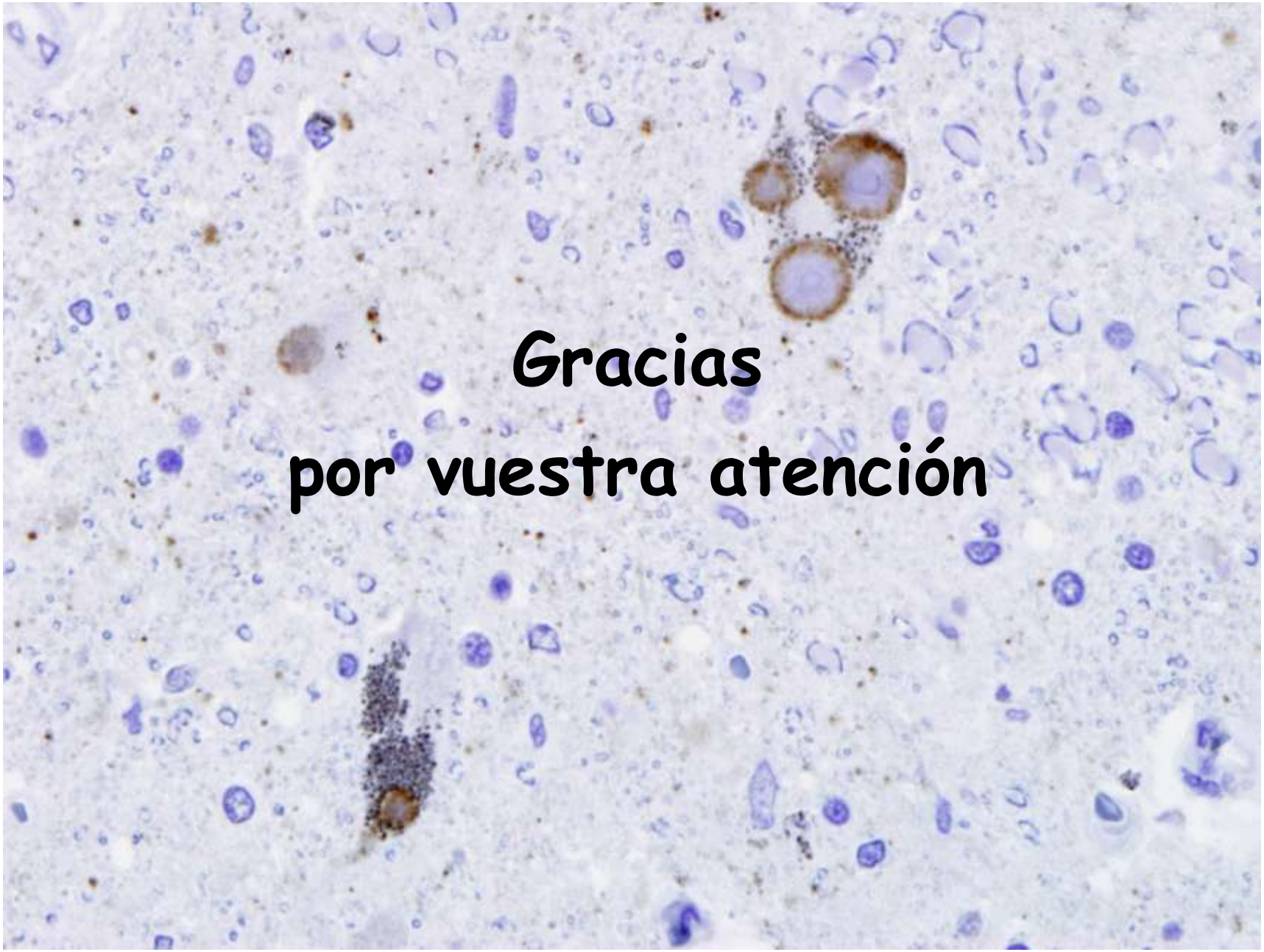
Hiroshige Fujishiro · Tae-Beom Ahn · Roberta Frigerio · Anthony DelleDonne · Keith A. Josephs · Joseph E. Parisi · J. Eric Ahlskog · Dennis W. Dickson

IHQ con ASN

1/241 y 1/125 pacientes sin evidencia de enfermedad neurológica

Both cases showed widespread GCI in the central nervous system, as well as a few neuronal cytoplasmic inclusions, but no neuronal loss or gliosis in vulnerable brain regions, including the substantia nigra, putamen, inferior olive and pontine base.

. Further studies are needed to determine if GCI in neurologically normal elderly represents prodromal MSA or a rare non-progressive age-related α-synucleinopathy.


Gracias
por vuestra atención