AGGIORNAMENTO IN TEMA DI BIOMARCATORI LIQUORALI NELLA DIAGNOSI DELLE MALATTIE NEURODEGENERATIVE

IL CERVELLO CHE CAMBIA 9

Dr. Federico MASSA

OSPEDALE POLICLINICO SAN MARTINO

Sommario

- ❑ *‘AD signature’ e rapporto Aβ42/Aβ40*
- ❑ *Nuovi biomarcatori nella AD: NfL e Ng*
- ❑ *Il liquor nella CJD*
- ❑ *Il liquor nelle alfa-sinucleinopatie*
- ❑ *Focus su TDP-43*

- ❑ *Perché è utile l’analisi liquorale*

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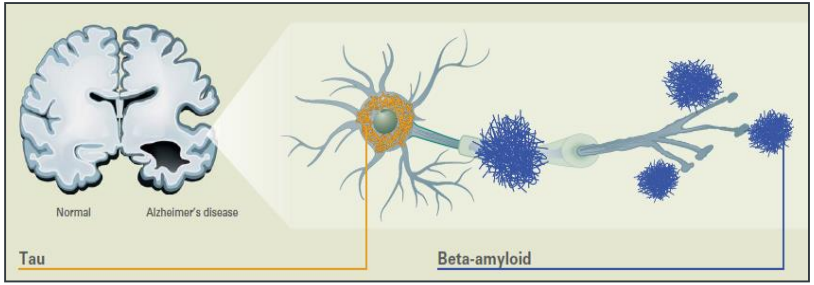
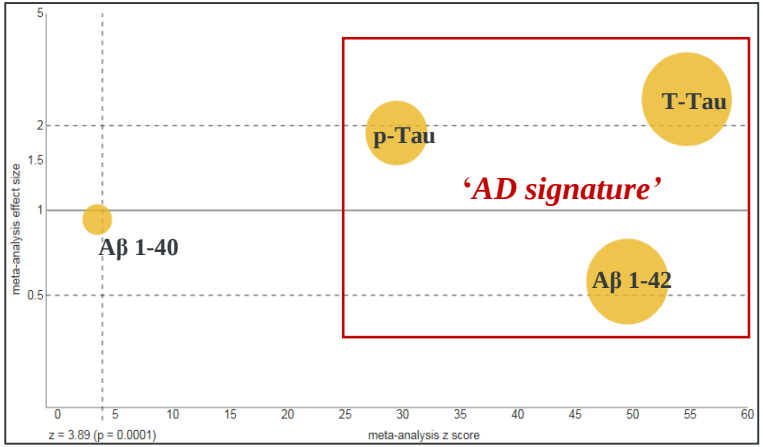
Malattia di Alzheimer (AD) – BIOMARCATORI CLASSICI



Combinazione di Aβ 1-42, p-Tau et-Tau in *MCI due to AD*
(Hansson et al. Lancet Neurol 2006)

SE 95% - SP 83-92%



AT(N) biomarker grouping

A: Aggregated Aβ or associated pathologic state
- CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
- Amyloid PET

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
- CSF phosphorylated tau
- Tau PET

(N): Neurodegeneration or neuronal injury
- Anatomic MRI
- FDG PET
- CSF total tau

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N>)	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Molinuevo et al. Alzh & Dem 2014
Jack et al. Alzh & Dem 2018

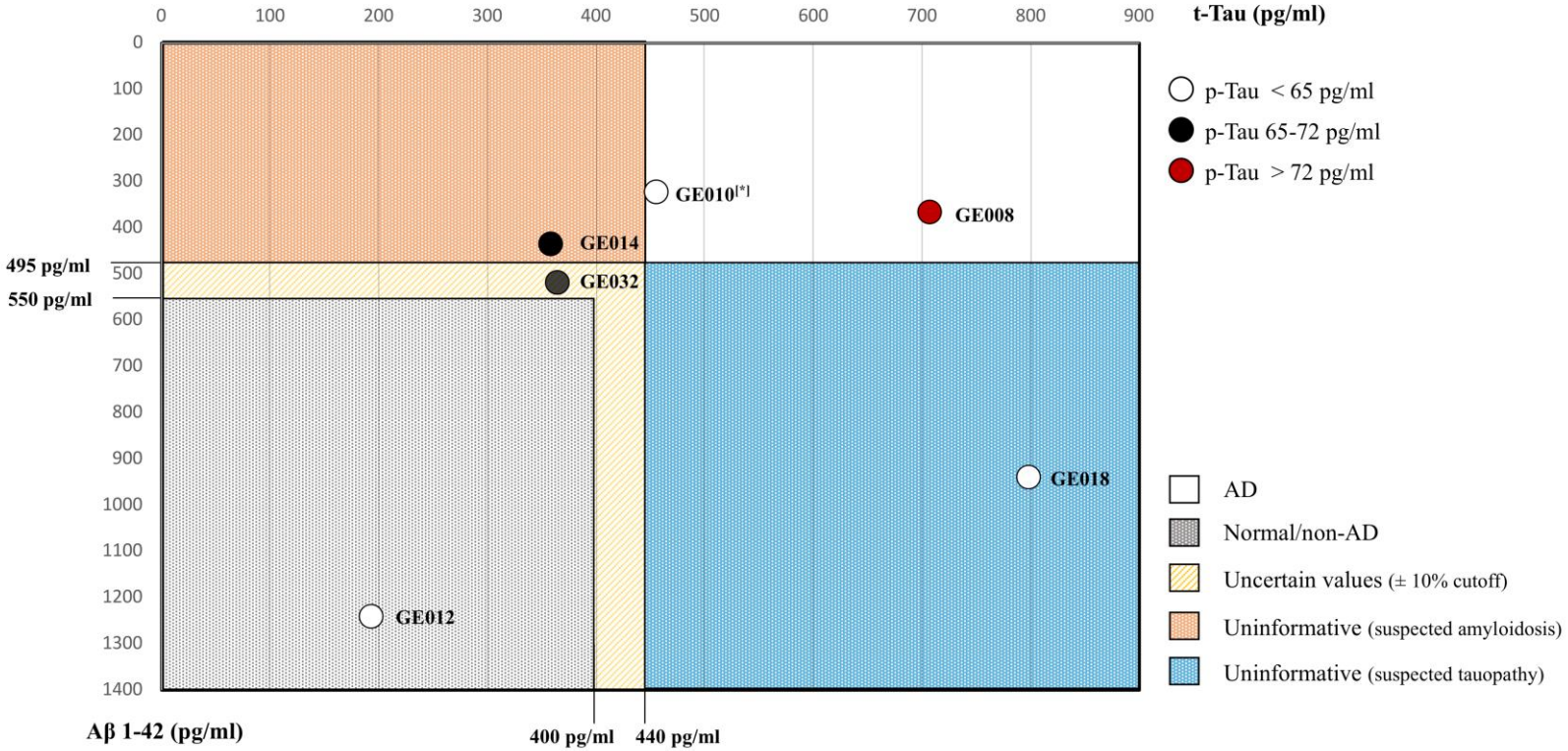
Summary of ABSI recommendations for clinical aspects for AD biomarker testing in CSF

Subject	Recommendation
Indication for LP and AD CSF biomarker analysis	All patients with memory complaints and/or those referred to memory clinics for cognitive problems should be considered for LP and AD CSF biomarker diagnosis. Thus, LP for AD CSF biomarker diagnosis should be considered in all patients with • Early-onset dementia • Minimal or mild cognitive impairment, provided the patient wants to know the result • Atypical clinical presentations or complex differential diagnosis
AD CSF biomarkers and cutoff values	• At least three biomarkers ($A\beta_{1-42}$, T-tau, and P-tau_{181P}) should be analyzed in CSF samples for accurate diagnosis of AD in combination with other data (clinical history, neuropsychological assessment, and routine neuroimaging for excluding secondary causes The $A\beta_{1-42}$:$A\beta_{1-40}$ ratio is an equally valid biomarker in centers where it has been properly validated. Currently, each laboratory should have its own validated cutoffs to ensure adequate sensitivity and specificity. Gray zones may be used to assist with the interpretation of abnormal AD CSF biomarker results. This may be defined as everything from the cutoff value + 10% (in the case of T-tau and P-tau_{181P}) or −10% (in the case of $A\beta_{1-42}$ or $A\beta_{1-42}$:$A\beta_{1-40}$ ratio).
Interpretation of the AD CSF biomarker results	An interpretation of the AD CSF biomarker results should (where possible) be given to the clinician along with the raw data. If all three (or four) classical AD CSF biomarkers are abnormal, then this can be considered "neurochemically compatible" with a diagnosis of AD based on the biomarkers. Vice versa, if all three (or four) classical AD CSF biomarkers are normal, this can be considered "neurochemically incompatible" with a diagnosis of AD.
Confounding factors	When all three (or four) classical AD CSF biomarkers are abnormal, a patient with MCI should be defined as having prodromal AD. There is no need to use different cutoffs for the AD CSF biomarkers for different age groups or depending on *APOE* status. When all three (or four) classical AD CSF biomarkers are normal, this is not compatible with AD pathology, and this is even more so for patients aged >80 years. When the results of the AD CSF biomarkers are intermediate, the disclosure must show the inconclusive interpretation (e.g., stating AD "neurochemically possible"), and the opportunity for further investigation with other biomarkers (e.g., FDG and/or amyloid PET) and the follow-up of the patient should be suggested.

cutoffs

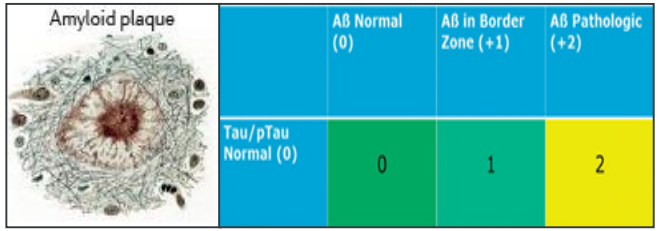
interpretazione

Molinuevo et al. Alzh & Dem 2014

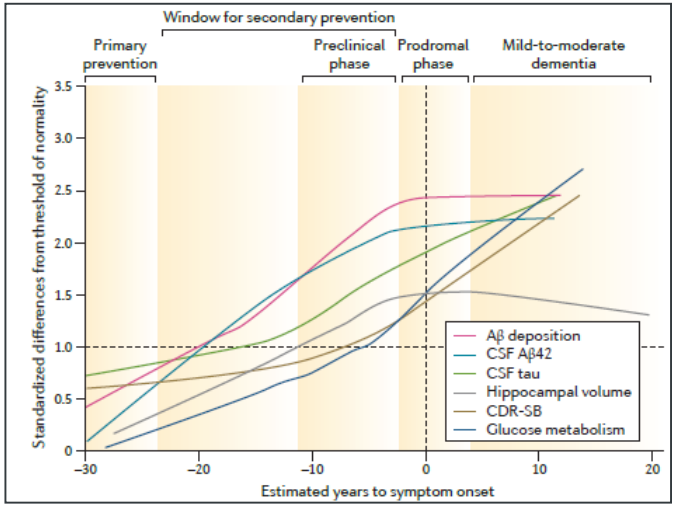


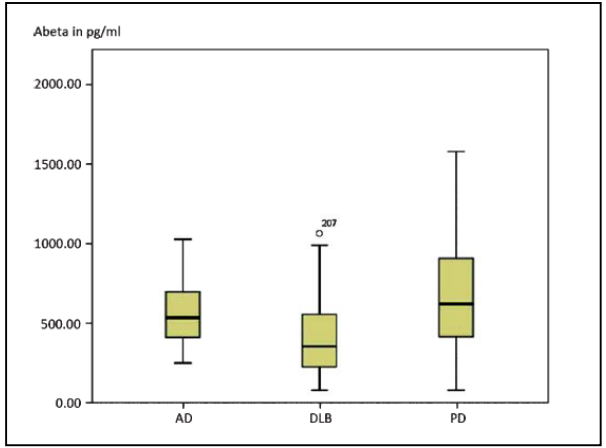
Massa et al. JAD 2019

Amyloid β 1-42



SE 78 % SP 83 % (Galasko et al, 1998)
SE 78 % SP 81 % (Hulstaert et al, 1999)
SE 69 % SP 89 % (Lewczuk et al, 2015)





Aβ 1-42 è il primo marcatore liquorale che si modifica nell'AD

REVIEW Open Access

Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease

Oskar Hansson[1,2], Sylvain Lehmann[3], Markus Otto[4], Henrik Zetterberg[5,6,7] and Piotr Lewczuk[8,9,10*]

Hansson *et al. Alzheimer's Research & Therapy* (2019) 11:34
https://doi.org/10.1186/s13195-019-0485-0

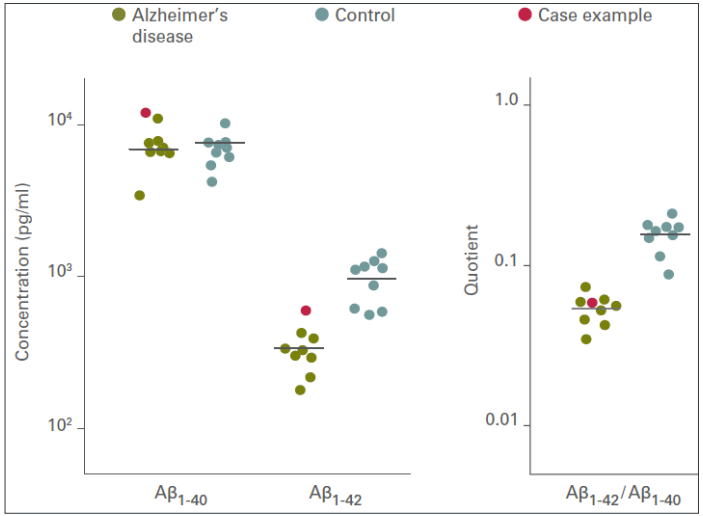
The working group therefore makes the following recommendations:

The $A\beta_{42/40}$ ratio should always be analysed, irrespective of the results of other AD biomarkers, and without paying attention to whether $A\beta_{42}$ is normal or pathologic. This is driven by the fact that the $A\beta_{42/40}$ ratio can equally change the CSF interpretation from 'normal to pathologic' as from 'pathologic to normal'. Analysing the $A\beta_{42/40}$ ratio only in cases with abnormal $A\beta_{42}$ (leaving cases with normal $A\beta_{42}$ without further consideration, i.e. as truly not having amyloidosis) would neglect the former scenario. On the other hand, performing $A\beta_{42/40}$ ratio analysis only in cases with normal $A\beta_{42}$ (with subjects with abnormal $A\beta_{42}$ considered as truly having amyloidosis) would neglect the latter case.

$A\beta_{42}$ versus the $A\beta_{42/40}$ ratio

Comparison of the diagnostic accuracy in the context of use of differential diagnostics when discriminating AD from other neurodegenerative disorders

In summary, the accumulation of evidence clearly points to the usefulness of the CSF $A\beta_{42/40}$ ratio for the diagnosis of AD in patients with dementia. The CSF $A\beta_{42/40}$ ratio is also better than CSF $A\beta_{42}$ alone at distinguishing AD dementia from non-AD dementias, not only from controls.



OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia

U.O.C. – U26 Clinica Neurologica
(Direttore Giovanni Luigi Mancardi)

Laboratorio di Diagnostica Liquorale
U26L2

BIOMARKERS LIQUORALI PER MALATTIA DI ALZHEIMER

Data 24/07/2018

Nome [redacted]

Reparto Clinica Neurologica (U26D3)

Proteina Amiloide Beta (Aβ 1-42): 347.8 pg/ml	v.n. > 600 pg/ml
Proteina Amiloide Beta (Aβ 1-40): 2843 pg/ml	
Rapporto Amiloide Beta 1-42/1-40 (Aβ 1-42/1-40): 0.12	v.n > 0.1
Proteina Tau totale (h-Tau):. 257 pg/ml	v.n. < 400 pg/ml
Proteina Tau Fosforilata (P-Tau 181): 27.9 pg/ml	v.n. < 40 pg/ml

INTERPRETAZIONE: Il quadro neurochimico liquorale non è compatibile con AD.

→ **DLB**

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U.O.C. – U26 Clinica Neurologica
(Direttore FF Angelo Schenone)

Laboratorio di Diagnostica Liquorale
U26L2

BIOMARKERS LIQUORALI PER MALATTIA DI ALZHEIMER

Data 04/01/2019

Nome [redacted]

Reparto DSA Clinica Neurologica – U26A

Proteina Amiloide Beta (Aβ 1-42): 956.8 pg/ml	v.n. > 600 pg/ml
Proteina Amiloide Beta (Aβ 1-40): 11332.5 pg/ml	
Rapporto Amiloide Beta 1-42/1-40 (Aβ 1-42/1-40): 0.084	v.n > 0.1
Proteina Tau totale (h-Tau): 604.1 pg/ml	v.n. < 400 pg/ml
Proteina Tau Fosforilata (P-Tau 181): 46.9 pg/ml	v.n. < 40 pg/ml

INTERPRETAZIONE: Il quadro neurochimico, con la correzione del valore di Aβ 1-42 su Aβ 1-40, è compatibile con AD.

→ **AD**

REVIEW Open Access

Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease

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Hansson *et al. Alzheimer's Research & Therapy* (2019) 11:34
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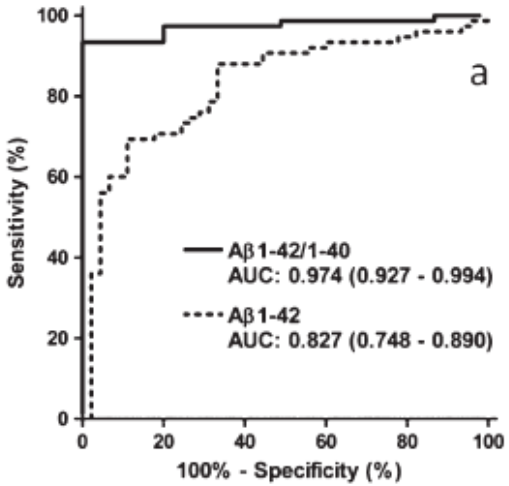
Comparison of the diagnostic accuracy for predicting the development of ADD in patients with MCI

Together these reports provide evidence that clearly demonstrates the added value of the CSF $A\beta_{42/40}$ ratio in accurately predicting progression to ADD.

Effects of pre-analytical handling on $A\beta_{42}$ and the $A\beta_{42/40}$ ratio

the CSF $A\beta_{42/40}$ ratio could therefore contribute toward pre-analytical standardization, allowing for the use of CSF AD biomarkers in routine clinical practice.



Aβ 1-42 (cut off 691 pg/ml) SE 69% SP 89%
Aβ 1-42/1-40 (cut off 0.06) SE 93% SP 100%

76.7% vs 95.8% di pazienti correttamente classificati

Lewczuk et al. J Alz Dis 2015

REVIEW Open Access

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Oskar Hansson[1,2], Sylvain Lehmann[3], Markus Otto[4], Henrik Zetterberg[5,6,7] and Piotr Lewczuk[8,9,10*]

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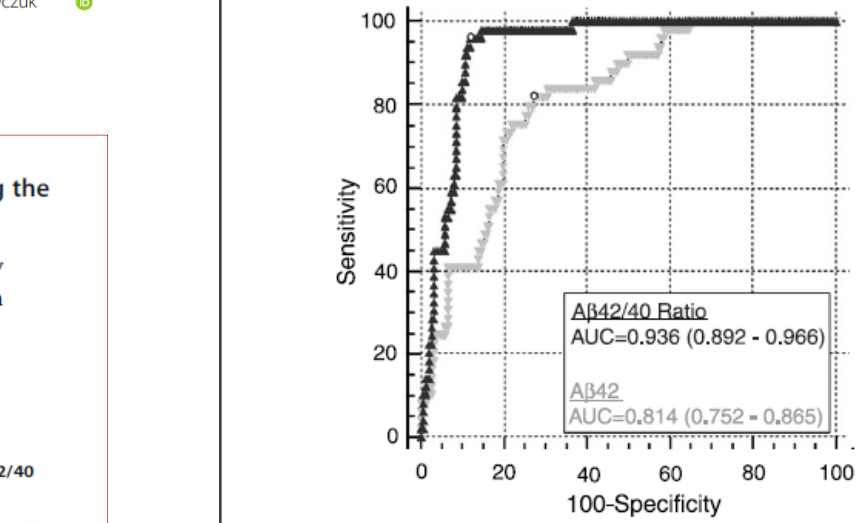

Concordanza con AmyPET+

Lewczuk et al. J Alz Dis 2017

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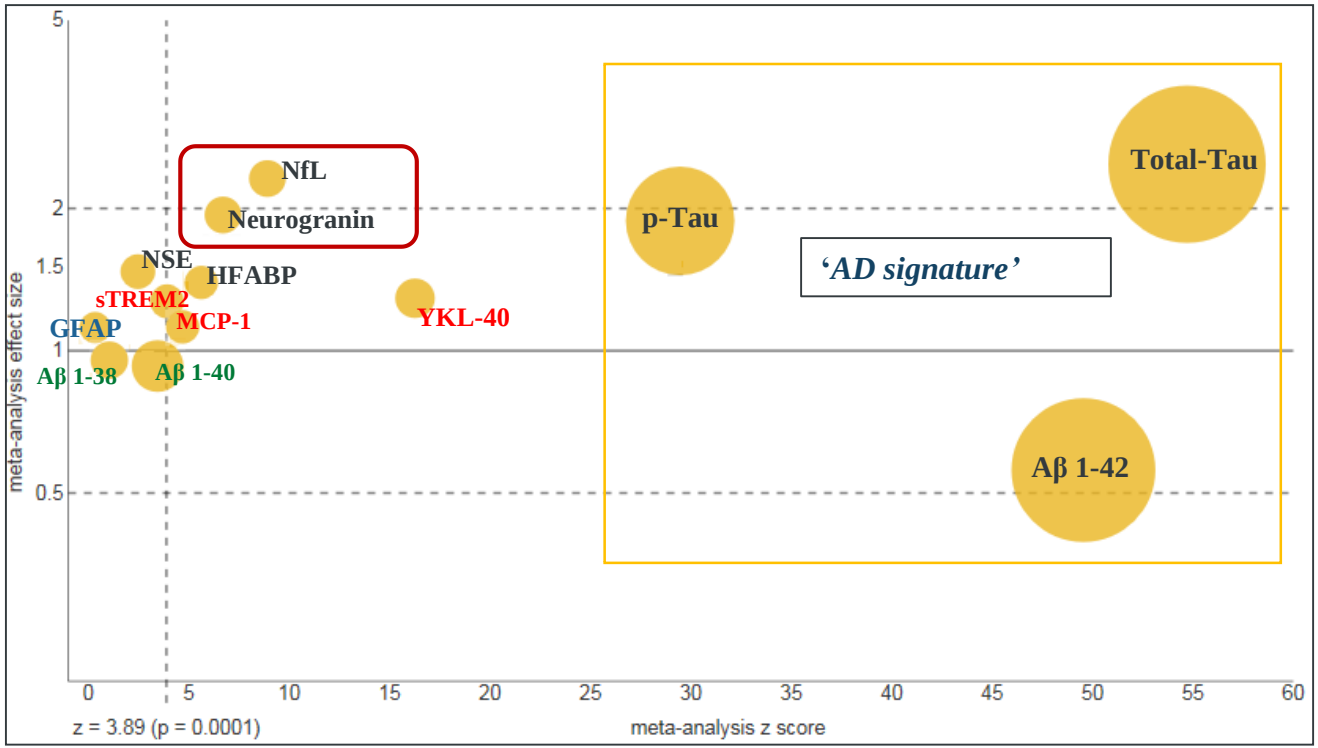
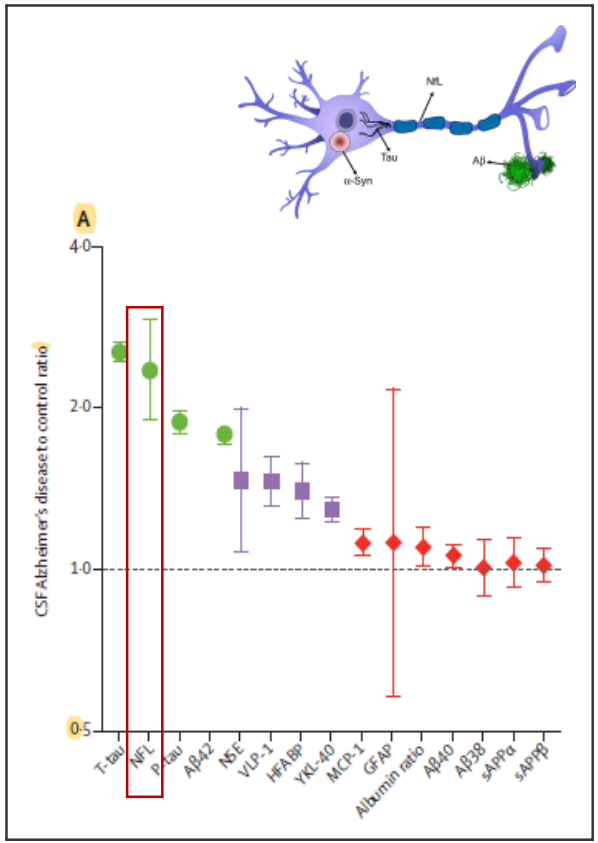
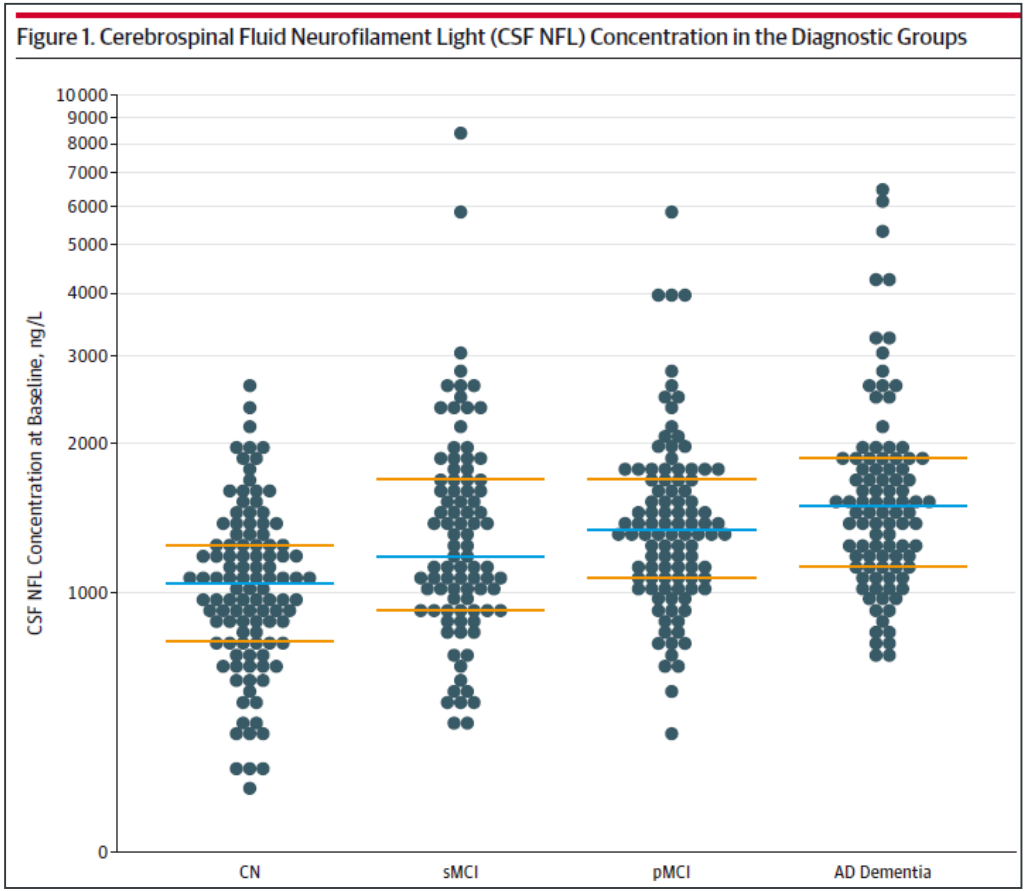


Olsson et al. Lancet Neurol 2016

Neurofilament Light chain (NfL)





Olsson et al. Lancet Neurol 2016

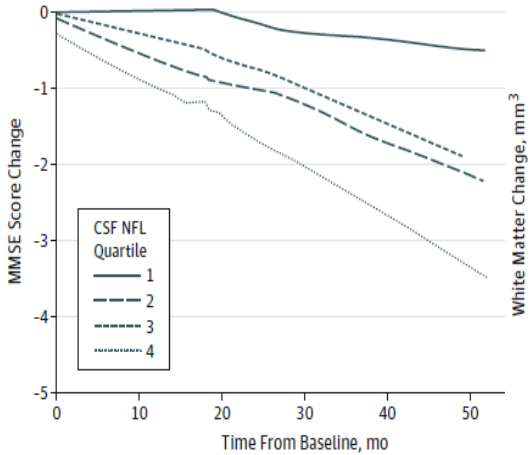
Zetterberg et al. Jama Neurol 2016

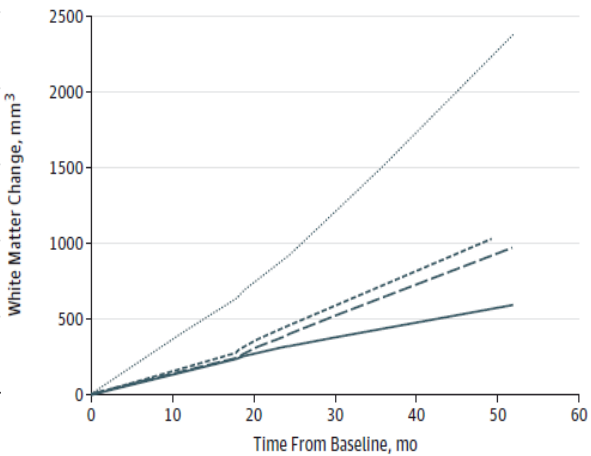
Original Investigation JAMA Neurology January 2016 Volume 73, Number 1

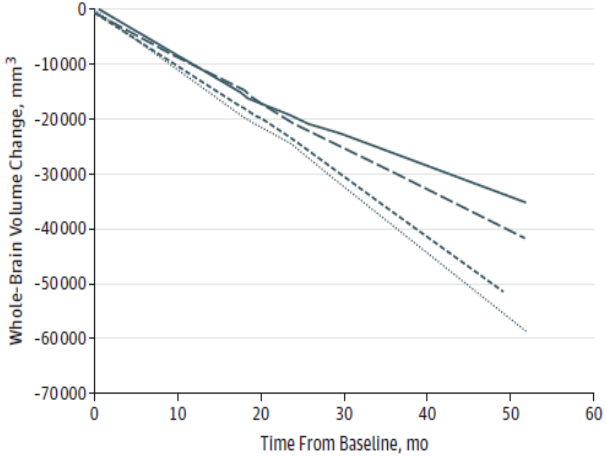
Association of Cerebrospinal Fluid Neurofilament Light Concentration With Alzheimer Disease Progression

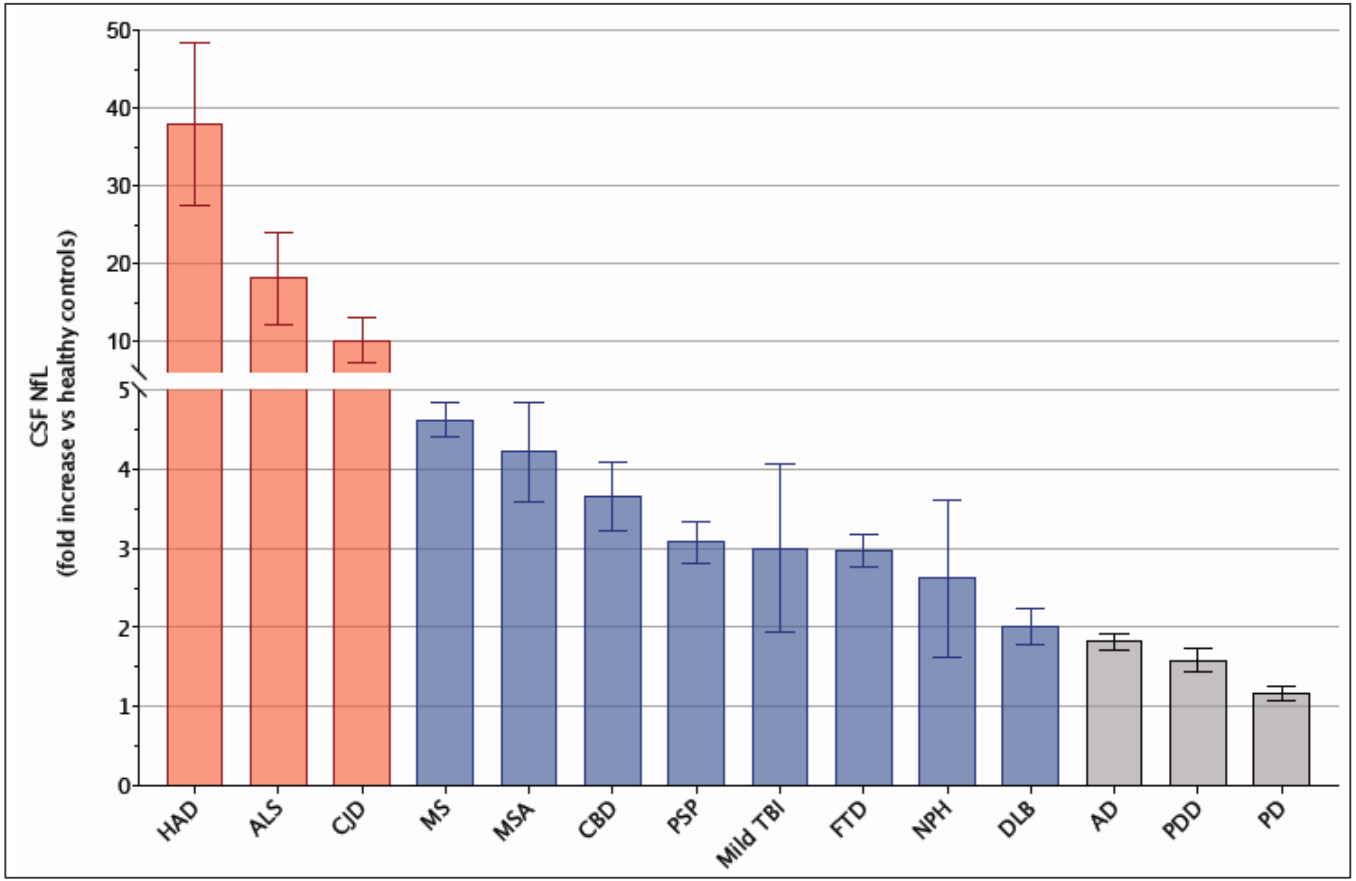
Henrik Zetterberg, MD, PhD; Tobias Skillbäck, MD; Niklas Mattsson, MD, PhD; John Q. Trojanowski, MD, PhD; Erik Portelius, PhD; Leslie M. Shaw, PhD; Michael W. Weiner, MD, PhD; Kaj Blennow, MD, PhD; for the Alzheimer's Disease Neuroimaging Initiative

CONCLUSIONS AND RELEVANCE Cerebrospinal fluid NFL concentration is increased by the early clinical stage of AD and is associated with cognitive deterioration and structural brain changes over time. This finding corroborates the contention that degeneration of large-caliber axons is an important feature of AD neurodegeneration.









Gaetani et al. J Neurol Neurosurg Psychiatry 2019

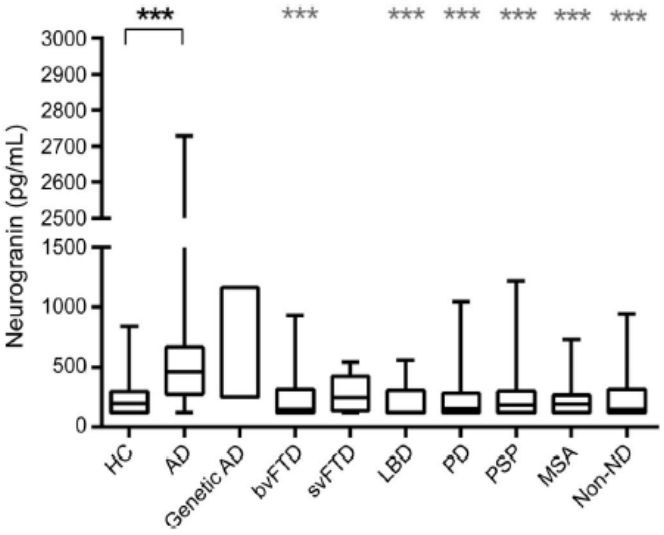
Neurogranina (Ng)

Neurology
THE MOST WIDELY READ AND HIGHLY CITED PEER-REVIEWED NEUROLOGY JOURNAL
The Official Journal of the American Academy of Neurology

Neurology. 2016 Mar 1; 86(9): 829–835.
doi: 10.1212/WNL.0000000000002423
PMCID: PMC4793782
PMID: 26826204

Increased CSF neurogranin concentration is specific to Alzheimer disease

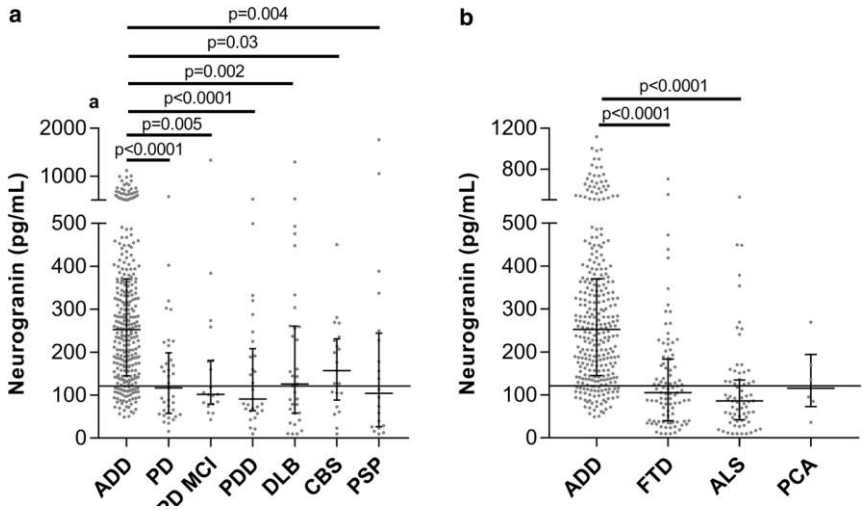
Henrietta Wellington, MRes,[✉] Ross W. Paterson, MRCP, Erik Portelius, PhD, Ulrika Törnqvist, BSc, Nadia Magdalinou, MRCP, Nick C. Fox, MD, FMedSci, Kaj Blennow, MD, PhD, Jonathan M. Schott, FRCP,[*] and Henrik Zetterberg, MD, PhD[*]



	Specificity, %
AD vs controls	84
AD vs non-AD (−controls)	76
AD vs bvFTD	75
AD vs svFTD	62
AD vs LBD	77
AD vs PD	77
AD vs PSP	74
AD vs MSA	90
AD vs non-ND	74

Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology

Erik Portelius[1,2] · Bob Olsson[1,2] · Kina Höglund[1,2] · Nicholas C. Cullen[1] · Hlin Kvartsberg[1] · Ulf Andreasson[1,2] · Henrik Zetterberg[1,2,3,4] · Åsa Sandelius[1] · Leslie M. Shaw[5] · Virginia M. Y. Lee[5] · David J. Irwin[6] · Murray Grossman[6] · Daniel Weintraub[7,8] · Alice Chen-Plotkin[6] · David A. Wolk[6] · Leo McCluskey[6] · Lauren Elman[6] · Jennifer McBride[5] · Jon B. Toledo[5,9] · John Q. Trojanowski[5] · Kaj Blennow[1,2]



In conclusion, CSF Ng is a biomarker specifically reflecting synaptic pathology in ADD and its concentration is linked to the extent of plaque pathology in the hippocampus and amygdala. The findings support the use of CSF Ng as a biomarker for diagnosing ADD and also for treatment trials, where disease-modifying drugs are evaluated, to monitor if treatment restores synaptic function in the patients.

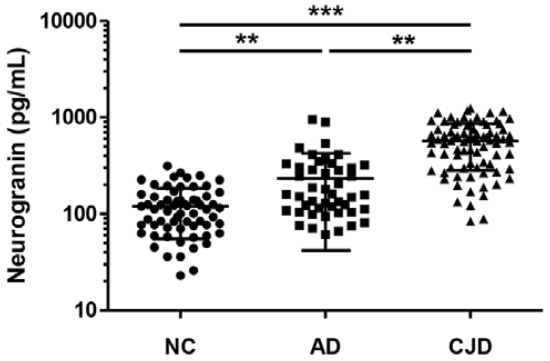
Portelius et al. Acta Neuropathol 2018

Neurodegeneration

RESEARCH PAPER

CSF neurogranin as a neuronal damage marker in CJD: a comparative study with AD

Kaj Blennow,[1,2] Daniela Diaz-Lucena,[3] Henrik Zetterberg,[1,2,4,5] Anna Villar-Pique,[6] Andre Karch,[7] Enric Vidal,[8] Peter Hermann,[6] Matthias Schmitz,[6,9] Isidro Ferrer Abizanda,[3,10] Inga Zerr,[6,9] Franc Llorens[3,6,10]



Blennow et al. Neurol Neurosurg Psychiatry 2019

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- ❑ *Perché è utile l’analisi liquorale*

CSF in CJD

MRI-CJD Consortium criteria for sporadic Creutzfeldt–Jakob disease

- Clinical signs
  - Dementia
  - Cerebellar or visual signs
  - Pyramidal or extrapyramidal signs
  - Akinetic mutism
- Tests
  - Periodic sharp wave complexes (PSWC) in EEG
  - 14-3-3 detection in CSF (in patients with a disease duration less than 2 years)
  - High signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal-parietal-occipital) either in DWI or FLAIR.

SE 92% SP 80% *(Muayqil et al., Neurology 2012)*

A diagnostic sensitivity of 94% and specificity of 90% were achieved for **tau-protein** at a cut-off of 1,300 pg/mL (Otto *et al*, *Neurology* 2002).

In some dementia due to inflammation, where a 14-3-3 test might be **false positive**, low levels of tau might be helpful in discriminating forms of neurodegenerative dementia

JAMA Neurology | Original Investigation

Diagnosis of Human Prion Disease Using Real-Time Quaking-Induced Conversion Testing of Olfactory Mucosa and Cerebrospinal Fluid Samples

JAMA Neurol. 2017;74(2):155-162.

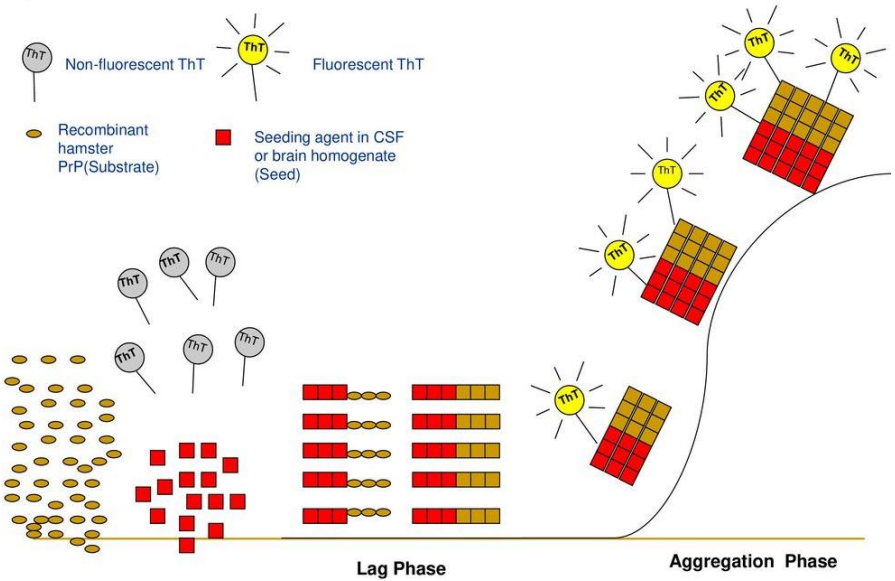
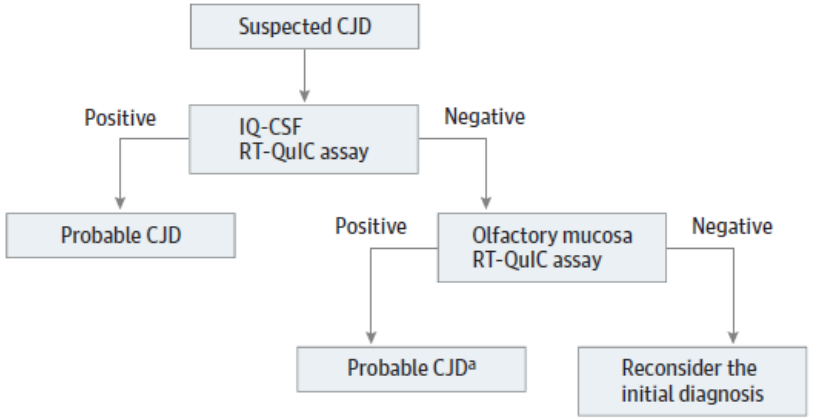


Figure 2. Algorithm for In Vivo Diagnosis of Probable Creutzfeldt-Jakob Disease (CJD)



IQ-CSF RT QuIC SE 95% SP 100%
Combinazione CSF+OM: accuratezza 100%

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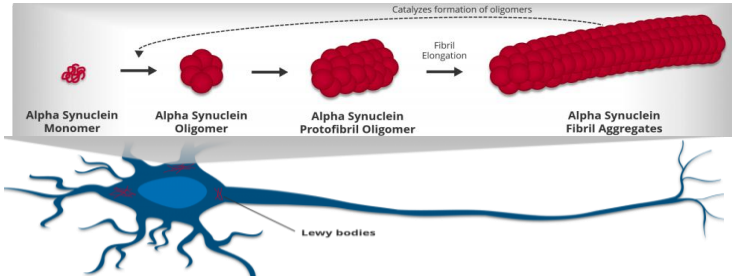
CSF nelle alfa-sinucleinopatie



1) Alfa-sinucleina

- CSF a-syn totale ↓ in PD ma ↑ ancora di più in neurodegenerazione → bassa accuratezza, non utile
- a-syn oligomerica e fosforilata ↑ in PD → necessità di studi ulteriori

↑ **o-a-syn/t-a-syn ratio**

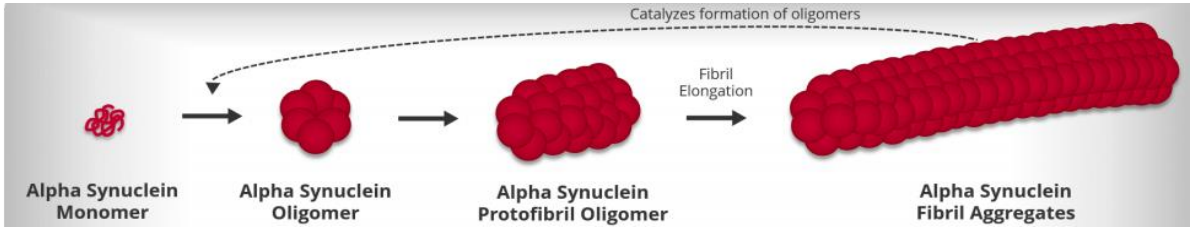
AUC 0.79 PD vs NC

- Problemi analitici
- Contaminazione eritrocitaria

"…sensitivity and specificity were far from being optimal for both a-syn species. This suggests a limited usefulness of total and oligomeric a-syn as standalone biomarkers for discriminating PD and controls."

(Eusebi et al, Mov Dis 2017)

2) RT-Quic



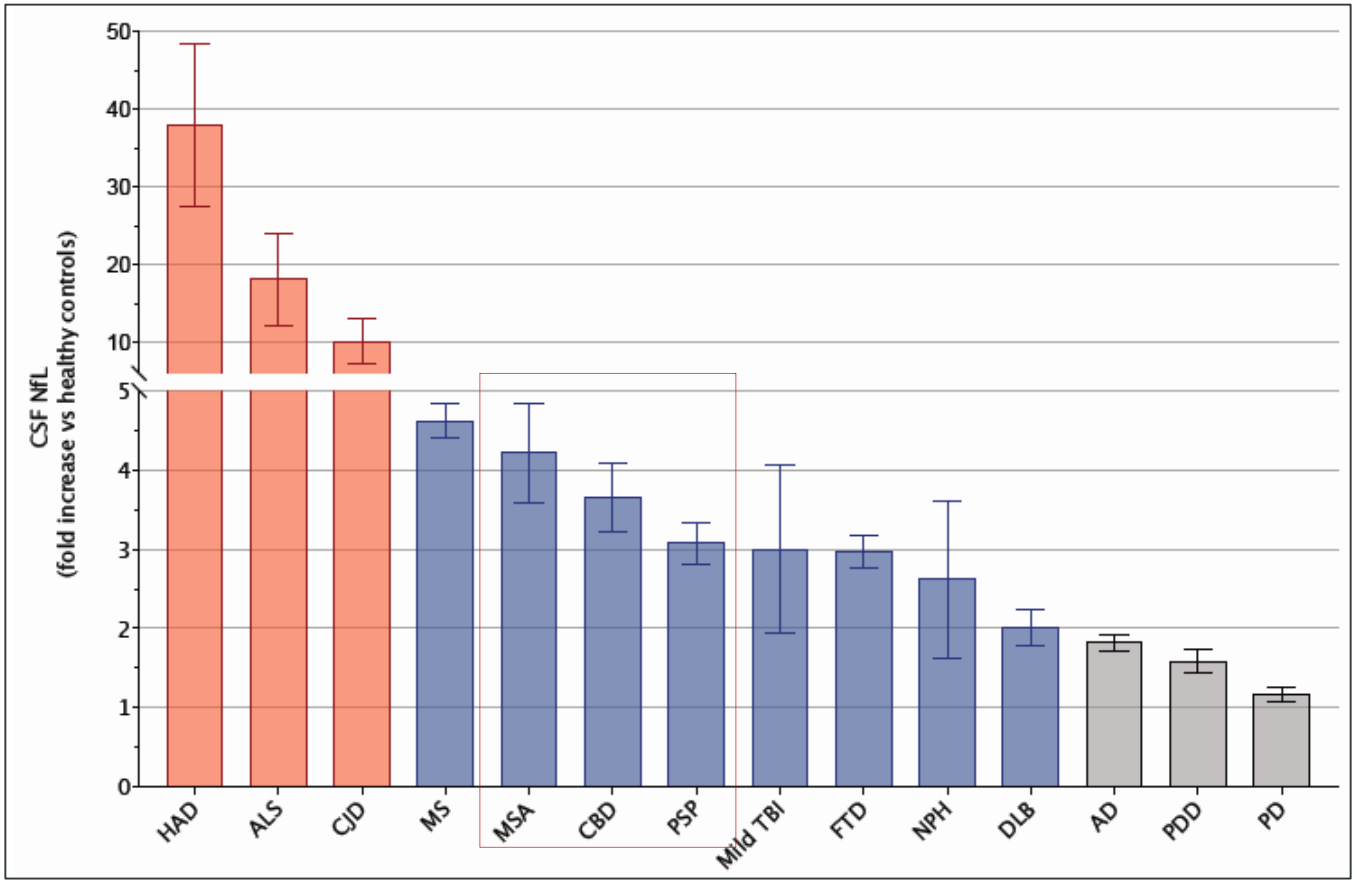
ANNALS of Clinical and Translational Neurology
Open Access
American Neurological Association
BRIEF COMMUNICATION
Annals of Clinical and Translational Neurology 2016; 3(10): 812–818

Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies

Graham Fairfoul[1], Lynne I. McGuire[1], Suvankar Pal[1,2], James W. Ironside[1], Juliane Neumann[3], Sharon Christie[4], Catherine Joachim[4], Margaret Esiri[4], Samuel G. Evetts[3], Michal Rolinski[3], Fahd Baig[3], Claudio Ruffmann[3], Richard Wade-Martins[5], Michele T. M. Hu[3], Laura Parkkinen[3] & Alison J. E. Green[1]

- **SE 92% (DLB) - 95% (PD)**
  SP 100%
- **NEG in CBD and PSP**
- **POS in RBD-high risk**

3) Neurofilamenti leggeri (NfL)

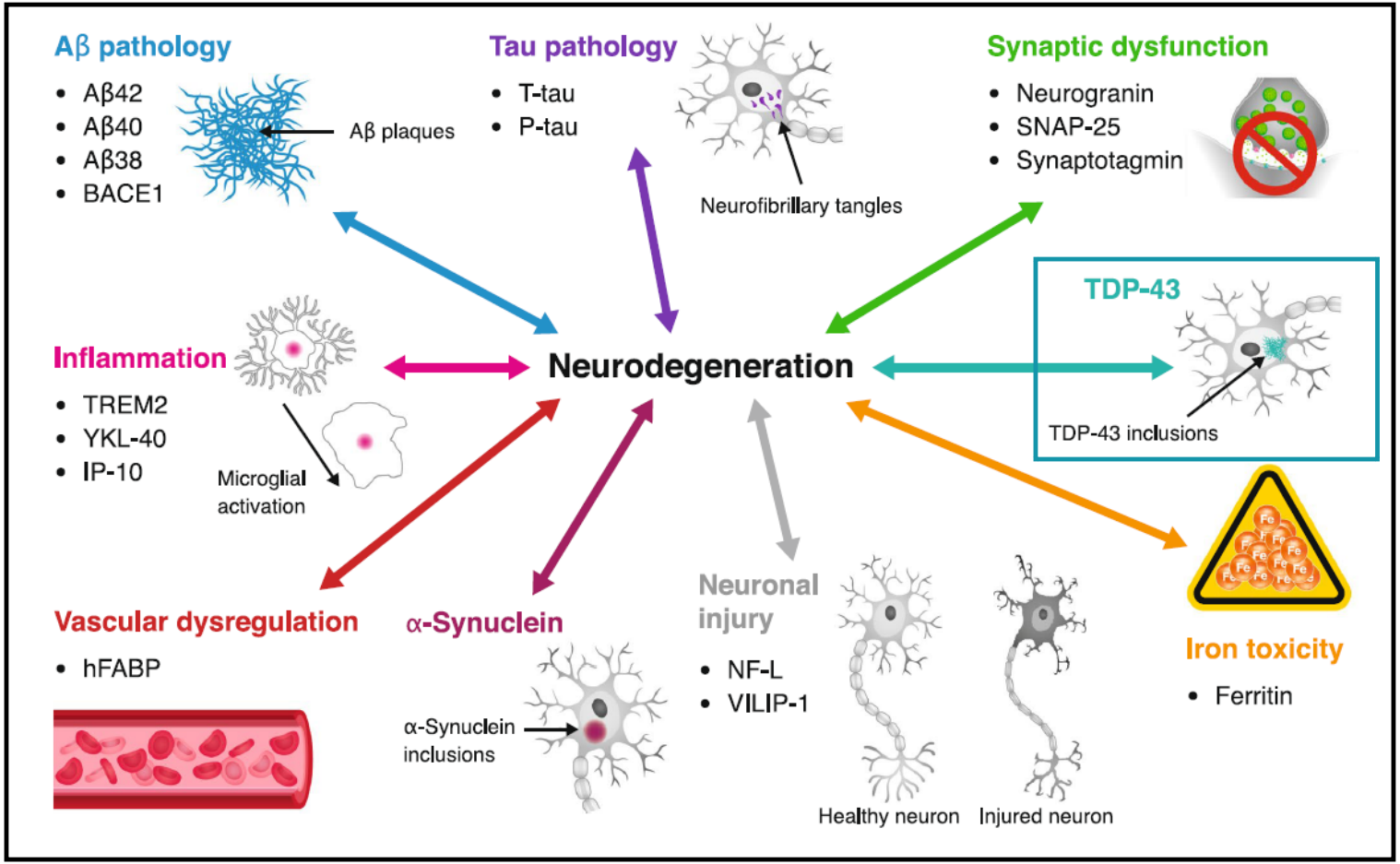


Gaetani et al. J Neurol Neurosurg Psychiatry 2019

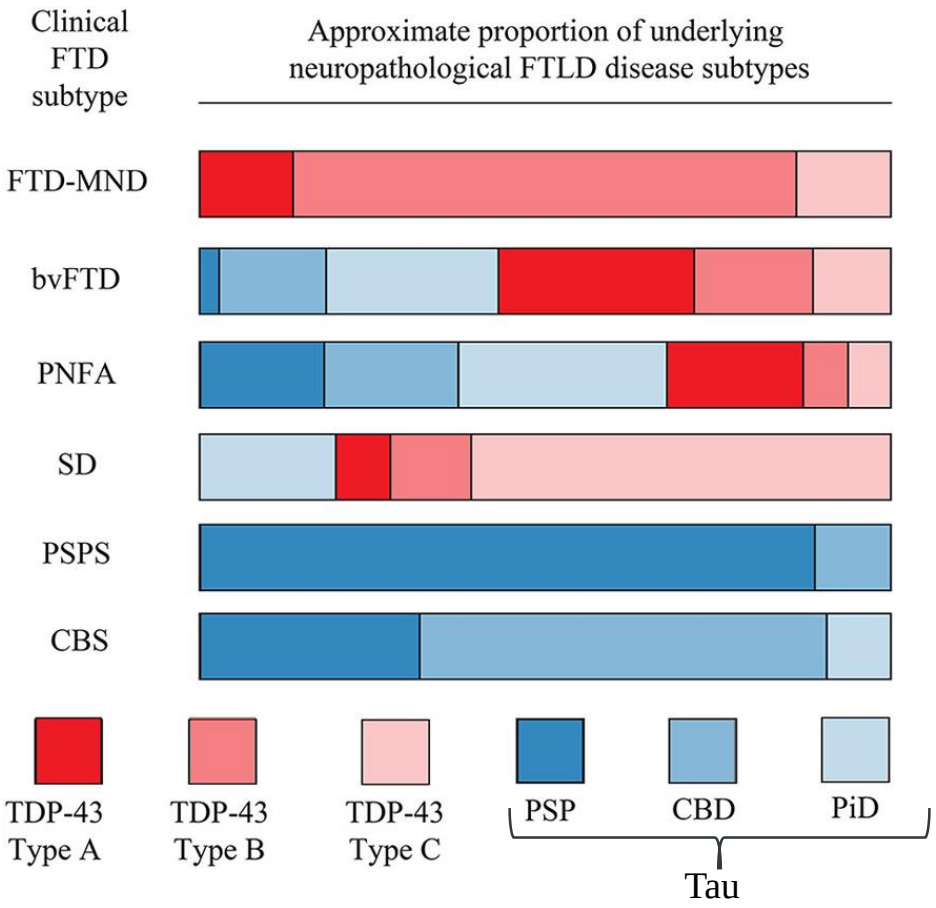
Sommario

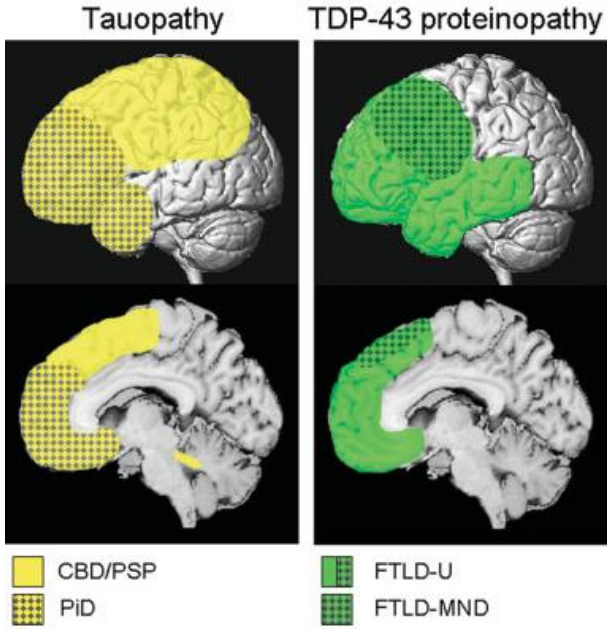
- ❑ *‘AD signature’ e rapporto Aβ42/Aβ40*
- ❑ *Nuovi biomarcatori nella AD: NfL e Ng*
- ❑ *Il liquor nella CJD*
- ❑ *Il liquor nelle alfa-sinucleinopatie*
- ❑ ***Focus su TDP-43***

- ❑ *Perché è utile l’analisi liquorale*



Molinuevo et al. Acta Neuropatol 2018





D'Alton et al. Front. Aging Neurosci 2014

Diagnosi differenziale: Tau-patia o TDP43-patia?

- **NfL** is higher in FTD than AD and PSY, no differences between Tau and TDP43 pathology

- **pTau/tTau** ratio is lower in FTD than AD and PSY, with good accuracy in discriminating Tau and TDP43 pathology

Towards a TDP-43-Based Biomarker for ALS and FTLD

Emily Feneberg[1,2] · Elizabeth Gray[1] · Olaf Ansorge[3] · Kevin Talbot[1] · Martin R. Turner[1]

Molecular Neurobiology (2018) 55:7789–7801

Abstract

TDP-43 accumulates in nerve cells of nearly all cases of amyotrophic lateral sclerosis (ALS; the commonest form of motor neuron disease) and in the majority of Tau-negative frontotemporal lobar degeneration (FTLD). There is currently no biochemical test or marker of disease activity for ALS or FTLD, and the clinical diagnosis depends on the opinion of an experienced neurologist. TDP-43 has a key role in the pathogenesis of ALS/FTLD. Measuring TDP-43 in easily accessible biofluids, such as blood or cerebrospinal fluid, might reduce diagnostic delay and offer a readout for use in future drug trials. However, attempts at measuring disease-specific forms of TDP-43 in peripheral biofluids of ALS and FTLD patients have not yielded consistent results, and only some of the pathological biochemical features of TDP-43 found in human brain tissue have been detected in clinical biofluids to date. Reflecting on the molecular pathology of TDP-43, this review provides a critical overview on biofluid studies and future directions to develop a TDP-43-based clinical biomarker for ALS and FTLD.

Meeter et al. Neurology 2018
Rivero-Santana et al., JAD 2017

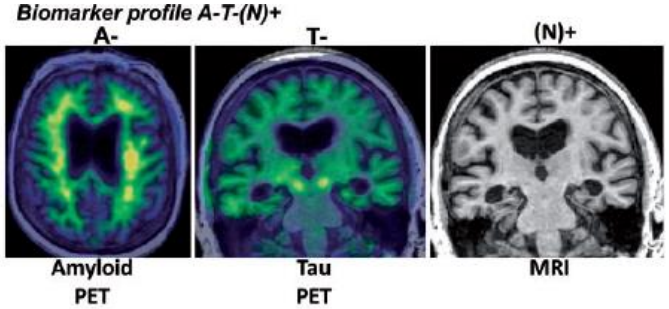
doi:10.1093/brain/awz099 BRAIN 2019: 0; 1–25 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Neuropathological indices	Fraction attributable % (95% CI)[a]
Alzheimer's disease (ADNC)	39.4 (31.5–47.4)
Vascular disease pathology[b]	24.8 (17.3–32.1)
LATE-NC	**17.3** (13.1–22.0)
α-Synucleinopathy/Lewy body pathology	11.9 (8.4–15.6)



Box 1 LATE and LATE-NC summary points

- LATE-NC features
  - A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
    - Stage 1: amygdala only
    - Stage 2: +hippocampus
    - Stage 3: +middle frontal gyrus
  - Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC
- LATE-NC is present in >20% (up to 50%) of individuals past age 80 years according to large community-based autopsy series
- LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome ('dementia of the Alzheimer's type')
- The overall public health impact of LATE is on the same order of magnitude as Alzheimer's disease neuropathological changes; the diseases are often comorbid, but which pathology is more severe varies greatly between individuals
- Genetic risk factors for LATE have some overlap with FTLD-TDP and with Alzheimer's disease
- There is no molecule-specific biomarker for LATE. This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer's disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE

Nelson et al., Brain 2019

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- ❑ ***Perché è utile l’analisi liquorale***

Conclusioni – Perché il liquor?

- Riflette lo stato metabolico e patologico del SNC
- Accessibile in molti centri
- Economico
- Rare controindicazioni o complicanze

- Diagnosi precoce ed accurata
- Progressione della neurodegenerazione
- Valore prognostico (cognitivo/motorio)

- "*due piccioni con una fava*"

Nuovi biomarcatori
Assays più accurati
Standardizzazione mondiale

DISEASE-MODIFYNG THERAPIES

In futuro si potranno avere diagnosi specifiche ed accurate basate sulla combinazione di biomarcatori

		Future biomarkers		Diagnoses
Aβ+	P-Tau+	α-Synuclein+	TDP-43+	
+	-	-	-	Presumed preclinical Alzheimer's disease (AD)
+	+	-	-	"Pure" AD
-	-	+	-	"Pure" Lewy body disease (LBD)
-	-	-	+	"Pure" LATE
+	+	+	-	AD+LBD
+	+	-	+	AD+LATE
+	+	+	+	AD+LBD+LATE
-		+	+	LBD+LATE
-	+	-	-	"Pure" Tauopathy
-	+	-	+	Tauopathy+LATE
-	+	+	-	Tauopathy+LBD

Nelson et al. Brain 2019

GRAZIE PER L'ATTENZIONE!