Malattia di Alzheimer: ***un'entità clinica*** VS un'entità biologica

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Definizione di demenza

Major and Mild Neurocognitive Disorders

Major Neurocognitive Disorder

Diagnostic Criteria

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

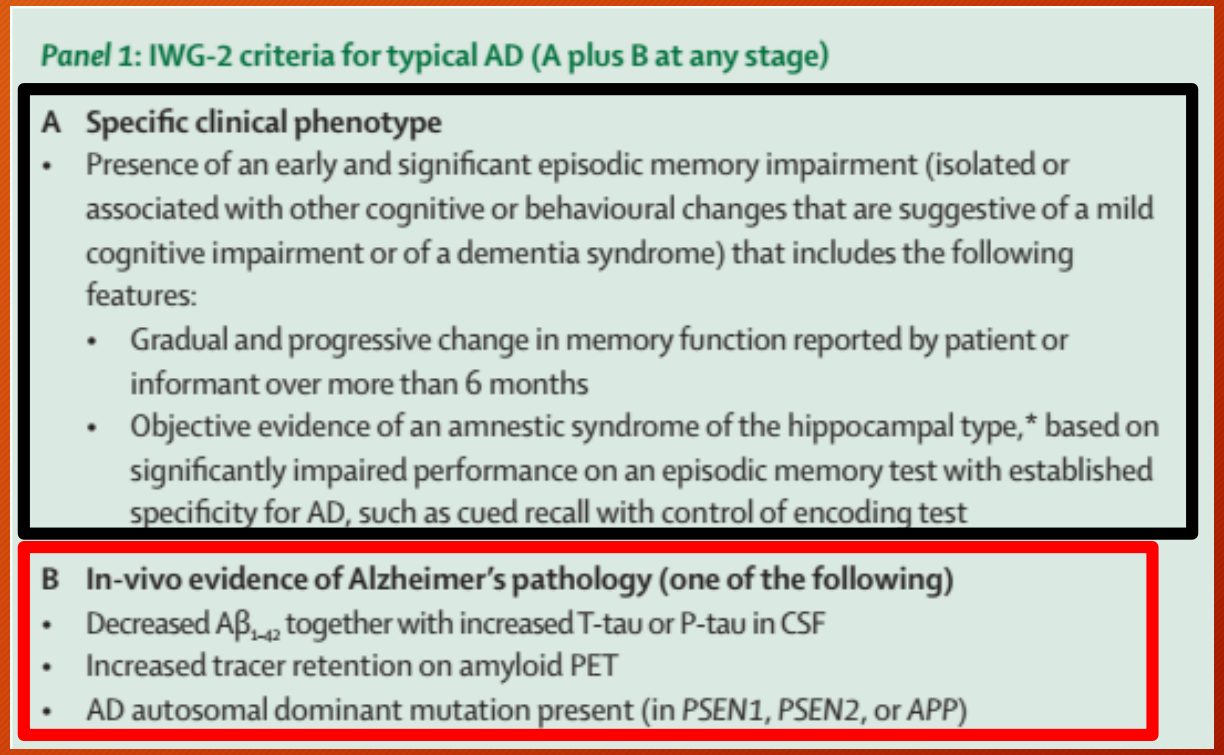
B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

DSM-5
Disturbo in almeno un dominio cognitivo che impatta sulle attività quotidiane!!!

I criteri clinici



Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

La diagnosi è in primo luogo uno specifico fenotipo clinico

Sebbene siano indicati anche marker biologici

L’ipotesi biologica: realmente una singola entità?

THE AMYLOID HYPOTHESIS ON TRIAL

With the continued failure of potential drugs for Alzheimer’s disease, is it time to look beyond amyloid-ß as the root cause of the condition?

Laboratory Investigation
https://doi.org/10.1038/s41374-019-0231-z

REVIEW ARTICLE

The amyloid cascade and Alzheimer’s disease therapeutics: theory versus observation

Rudy J. Castellani[1,2] · Germá

Another major drug candidate targeting the brain plaques of Alzheimer’s disease has failed. What’s left?

By Kelly Servick | Mar. 21, 2019 , 6:00 PM

Neuron

Multiscale Analysis of Independent Alzheimer’s Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus

Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer’s Disease

Fuyuki Kametani and*

Department of Dementia and H

SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

***Porphyromonas gingivalis* in Alzheimer’s disease brains: Evidence for disease causation and treatment with small-molecule inhibitors**

Review

The Vascular Hypothesis of Alzheimer’s Disease: A Key to Preclinical Prediction of Dementia Using Neuroimaging

Le indagini in vivo

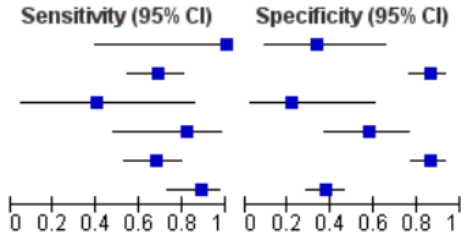
- Il 20-30% di individui cognitivamente sani o affetti da demenza non AD e fino al 50% degli anziani portatori di allele apoE4 sono positivi alla PET amiloide (Bergeron et al 2018)
- La PET tau dimostra ancora numerose criticità (scarsa concordanza ante- e post-mortem, off-target binding) (Leuzy et al 2019)
- L'analisi del liquor attualmente ha una variabilità interlaboratorio ed intracampione del 20-35% (Blennow et al 2015)

I tassi di conversione

Cochrane review 2017

Figure 7. Forest plot of 2 CSF p-tau conversion to AD dementia.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fellgiebel 2007	4	8	0	4	1.00 [0.40, 1.00]	0.33 [0.10, 0.65]
Hansson 2006	39	11	18	66	0.68 [0.55, 0.80]	0.86 [0.76, 0.93]
Koivunen 2008	2	7	3	2	0.40 [0.05, 0.85]	0.22 [0.03, 0.60]
Monge-Argiles 2011	9	11	2	15	0.82 [0.48, 0.98]	0.58 [0.37, 0.77]
Palmqvist 2012	35	11	17	70	0.67 [0.53, 0.80]	0.86 [0.77, 0.93]
Visser 2009	31	77	4	46	0.89 [0.73, 0.97]	0.37 [0.29, 0.47]



Cosa ci dirà lo studio Interceptor???

Table 3 The 10 single predictors and the five best two- to four-predictor classification results predicting progression from MCI to AD dementia

Predictors	AUC	Youden index	Sensitivity	Specificity	PPV	NPV
Single predictors						
t-Tau	0.77	1.48	0.62	0.86	0.42	0.93
HCV	0.74	1.45	0.63	0.82	0.42	0.92
CDR-sb	0.73	1.38	0.45	0.93	0.35	0.95
CERAD-DR	0.72	1.39	0.64	0.75	0.40	0.89
MMSE	0.71	1.36	0.68	0.68	0.40	0.87
p-Tau	0.69	1.41	0.81	0.61	0.50	0.86
Aβ42	0.68	1.38	0.74	0.64	0.44	0.87
Aβ42/Aβ40	0.66	1.34	0.59	0.75	0.37	0.88
Aβ40	0.55	1.15	0.76	0.39	0.34	0.80
APO E	0.50	1.05	0.41	0.64	0.26	0.47

Frolich et al 2017

Storia naturale

JAMA Neurology | Original Investigation

Association of Amyloid and Tau With Cognition in Preclinical Alzheimer Disease
A Longitudinal Study

4. After 7 years of cognitive follow-up, criteria for MCI owing to AD were met in a subset of 6 participants with high PiB (35%). These observations, suggesting higher rates of tau accumulation with clinical progression, are consistent with previous studies showing higher rates of tau accumulation in patients with symptomatic AD than in clinically normal older adults.[9,27] The sequence from subthreshold Aβ accumulation to MCI was not observed in any participant, suggesting it requires longer than 7 years. We did not observe any MCI owing to non-AD etiologies.

Suspected non-Alzheimer pathology

- Sono patologie diverse o sono un continuum clinico?
- Una percentuale di SNAP evolve in AD
- La distinzione si basa sull'ipotesi della cascata amiloide: è veramente così?

Review

Suspected non Alzheimer's pathology – Is it non-Alzheimer's or non-amyloid?

Melanie Dani[a], David J. Brooks[a,b,d], Paul Edison[a,c,*]

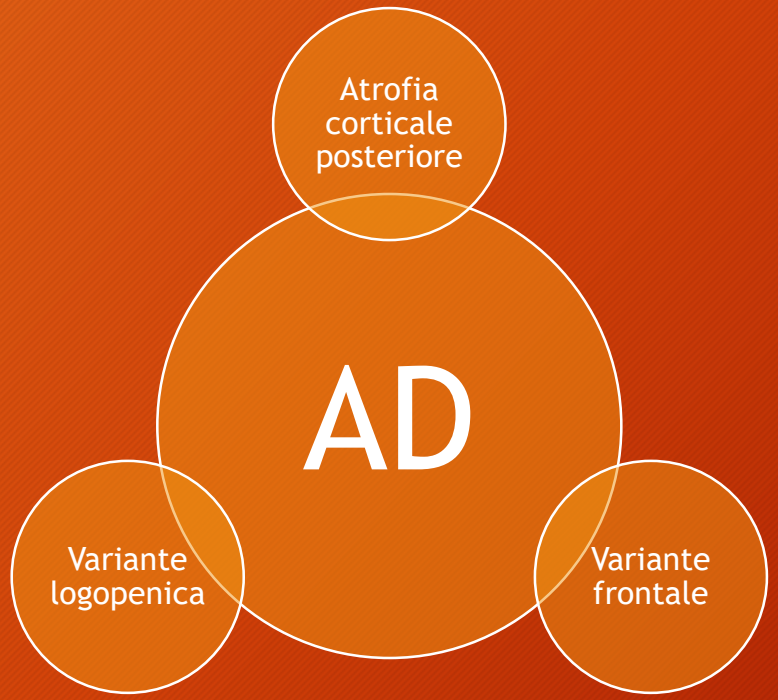
OPINION

Suspected non-Alzheimer disease pathophysiology — concept and controversy

Limbic-predominat age-related TDP-43 encephalopathy

- Recentissima review su Brain
- Accumulo di TDP-43 ± sclerosi ippocampale
- Fattori di rischio e patogenesi sovrapposta? (PART, AD)
- Evidenza di performance cliniche differenti (solo memoria, evoluzione + lenta)
- Nessun biomarker *in-vivo*

La varianti «atipiche»



Generalmente biomarcatori della malattia di AD
MA
Associati anche ad altra patogenesi (corpi di Lewy, FTLD, CJD…)

La comunicazione della diagnosi

- Certezza dell'evoluzione? Terapie disease-modifying?
- In Italia il 60% dei familiari non vuole che venga comunicata la diagnosi all'assistito (Pucci et al. 2003)
- AD preclinico → soggetto asintomatico a rischio di AD (solo a scopo di ricerca) (Gauthier et al 2012)
- Ricadute su lavoro, assicurazione, relazioni familiari

La parola all'esperto

On the path to 2025: understanding the Alzheimer's disease continuum

Paul S. Aisen[1*], Jeffrey Cummings[2], Clifford R. Jack Jr[4], John C. Morris[6], Reisa Sperling[7], Lutz Frölich[3], Roy W. Jones[5], Sherie A. Dowsett[8], Brandy R. Matthews[8], Joel Raskin[9], Philip Scheltens[10] and Bruno Dubois[11]

Support for the disease continuum concept is growing, yet how this will be successfully integrated into clinical practice is not yet clear. For example, even with the currently available biomarkers and clinical tools, identifying individuals who will progress along the AD spectrum, as well as the trajectory of decline, is still fraught with challenges. Indeed, patients and caregivers only raise con-

Profile

Bruno Dubois: transforming the diagnosis of Alzheimer's disease

Dubois. "It's a disease which starts with the first clinical symptoms. Within the preclinical state we can identify two different situations: preclinical Alzheimer's disease, where patients are mutation carriers and will definitely develop the disease, and a second group that we call 'asymptomatic at risk', meaning those people who are biomarker-positive for Alzheimer's disease, but cognitively normal, and we don't know whether they will develop the disease".

Conclusioni

- La malattia di Alzheimer è una patologia complessa la cui fisiopatologia non è stata ancora completamente chiarita
- Centralità della clinica
- Evitare un approccio riduzionista (troponina ↑ ≠ infarto)
- Ma non dimentichiamo l'importanza dei biomarker = entità clinico-biologica