La diagnosi di demenza: equilibrio nell’uso delle nuove tecnologie

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Un dibattito difficile

Il dibattito sulla diagnosi di demenza e sull’identificazione di possibili marker presintomatici si colloca nella logica di spostare l’attenzione verso la prevenzione (ipotetica, ma sempre “di moda”) e la diagnosi precoce (con le nuove tecnologie ad alto costo), invece che sulla terapia, area dove non sono previsti successi a breve.
Nessuno vuole fermare il progresso, anche se spesso indotto da interessi di parte. Però è necessario un approfondimento delle diverse tematiche in discussione, per evitare il prevalere di tesi non equilibrate. Il significato di questo seminario sull’importanza della diagnosi e sugli strumenti più adeguati per raggiungerla il più precocemente possibile.
In crisis, Friedman thought, the actions taken depend on the ideas that are prevalent at the time. Both reports*, released in the space of just a few weeks, have unambiguously exposed the crisis in AD prevention and laid down a useful set of ideas; now action must be taken.


* -NIH Statement on Preventing AD
- 2010 Report of Alzheimer’s Association
It is estimated that 13.5 million US citizens aged 65 and older will have AD in 2050. Moreover, the annual costs for their care will increase from US$172 billion in 2010 to $1.08 trillion in 2050. A hypothetical breakthrough intervention that could become available in 2015 and would delay onset by 5 years could reduce the number of patients in 2050 by over 40%, to less than 8 million. The cost of their care would then be reduced to $631 billion.

La diagnosi è sempre una tappa indispensabile nel processo di cura, anche indipendentemente dalla possibilità di rallentare il processo patologico.
La diagnosi di demenza: incertezze, errori, ritardi... però serve...

Eliminare l’”alibi” dalla scarsa utilità

- È’ l’inizio a qualcosa di nuovo che, per quanto terribile, è profondamente umano
- È’ premessa alla definizione di outcome realistici.
Il ritardo diagnostico impedisce il trattamento (farmacologico e non) delle fasi iniziali.
La diagnosi è un punto fermo, da cui parte l’”Individualized medical decision making” (Arch Intern Med 170:566, 2010).
Diagnosis and disease evolution

- Different forms of AD
- Predictors of drug response
- Disease progress in responders and non responders
La diagnosi e l’organizzazione dell’assistenza.
L’importanza di uscire dal “limbo clinico”.
Le ricadute sul paziente, la famiglia e la rete sociale permettono di affermare che la diagnosi di demenza è un atto medico, da compiere con gli strumenti più adeguati, tempestivamente.
In linea con l’esigenza di una diagnosi sempre più precisa la ricerca sui biomarker di demenza ha fatto notevoli progressi.
Significant Advances in Alzheimer Research Since 1984

Among the most important advances in the Alzheimer's field since the publication of the 1984 NINDS/ADRDA diagnostic criteria are:

- Alzheimer's-driven changes in the brain, as well as the accompanying cognitive deficits, develop slowly over many years with dementia representing the end stage of years of pathology accumulation. At the same time, we know that some people have the brain changes associated with Alzheimer's and yet don't show symptoms of dementia.
- Predictive genes in early onset Alzheimer's indicate that the initial events ultimately leading to both clinical symptoms and pathological brain changes begin with disordered beta amyloid metabolism.
- The e4 allele of the APOE gene is well accepted as a major genetic risk factor for late onset Alzheimer's disease, which is defined as onset at 65 or older.
- Biomarkers for Alzheimer's have been developed and are being validated. These fall into several categories:
  - Biomarkers of beta amyloid pathology, including amyloid PET imaging and levels of beta amyloid in cerebrospinal fluid (CSF).
  - Biomarkers of neuronal injury, including levels of CSF tau and phospho-tau.
  - Biomarkers of neuronal dysfunction, including decreased uptake of FDG on PET scans.
  - Biomarkers of neurodegeneration, including brain atrophy on structural MRI scans.

In addition, it has been only in the past decade that a better understanding of the distinctions and overlaps of Alzheimer's with non-Alzheimer's dementias has begun to emerge. Knowledge of the non-Alzheimer's dementias was rudimentary in 1984, and the current diagnostic criteria are vague in defining distinctions between Alzheimer's and the major alternatives. The common co-existence of Alzheimer's and cerebrovascular disease is now appreciated. Much more is known about dementia resulting from Lewy Body disease, and also about Pick's disease and other frontotemporal dementias.

http://www.alz.org/icad/2010_release_diagnostic_071310_130pm.asp
• Modificazioni strutturali
• Modificazioni funzionali
• Geni predittivi
• β amiloide, tau, ecc.
La Repubblica, 15-7-2010

Alzheimer, la svolta americana screening di massa sui 50enni

La speranza nei nuovi protocolli: cure anticipate con la diagnosi precoce
Indirizzare il progresso verso un uso clinico razionale, non verso problematiche marginali (di consumo).
Alcuni esempi di biomarker nella malattia di Alzheimer.
Alzheimer’s disease biomarker research seeks to measure changes in the structure and function of the brain (for example atrophy, regional activity changes and hypometabolism, amyloid-plaque and NFT formation, microgliosis, inflammation and oxidative stress) that might be useful for diagnosis and prognosis during the preclinical phase of the disease, before irreversible neuronal loss occurs.

Biomarkers and Alzheimer’s disease: proposed changes in biomarkers in relation to the time course of pathological and clinical stages.

I diversi marker sono in grado di “costruire una storia” della malattia, che nei prossimi anni troverà sempre maggiori approfondimenti.
L’esempio di PK 11195 PET, marker dei recettori periferici delle benzodiazepine, indicatore di microgliosi, e quindi di infiammazione, correlata alle funzioni cognitive.
Fluid biomarkers

CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment

**Conclusions**  This multicenter study found that CSF Aβ42, T-tau, and P-tau identify incipient AD with good accuracy, but less accurately than reported from single-center studies. Intersite assay variability highlights a need for standardization of analytical techniques and clinical procedures.

Figure 1. Percentage of Patients With MCI Who Developed Alzheimer Disease by Quintiles of CSF T-Tau and CSF Aβ42/P-Tau Ratio

Quintiles with less than 5 cases are excluded from the graph. CSF indicates cerebrospinal fluid.

Evaluation of Cerebrospinal Fluid Tau/Beta-Amyloid(42) Ratio as Diagnostic Markers for Alzheimer Disease

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PIB (Pittsburgh Compound-B): un progresso importante, legato anche alla progressiva diffusione della PET.
Reaction scheme for the radiochemical synthesis of PIB.

\[ \text{Annals Neurol 55:306-319, 2004.} \]
This report describes the first human study of a novel amyloid-imaging positron emission tomography (PET) tracer, termed Pittsburgh Compound-B (PIB), in 16 patients with diagnosed mild AD and 9 controls. Compared with controls, AD patients typically showed marked retention of PIB in areas of association cortex known to contain large amounts of amyloid deposits in AD. In the AD patient group, PIB retention was increased most prominently in frontal cortex (1.94-fold, $p = 0.0001$). Large increases also were observed in parietal (1.71-fold, $p = 0.0002$), temporal (1.52-fold, $p = 0.002$), and occipital (1.54-fold, $p = 0.002$) cortex and the striatum (1.76-fold, $p = 0.0001$). PIB retention was equivalent in AD patients and controls in areas known to be relatively unaffected by amyloid deposition (such as subcortical white matter, pons, and cerebellum). Studies in three young (21 years) and six older healthy controls (69.5 ± 11 years) showed low PIB retention in cortical areas and no significant group differences between young and older controls. In cortical areas, PIB retention correlated inversely with cerebral glucose metabolism determined with 18F-fluorodeoxyglucose. This relationship was most robust in the parietal cortex ($r = -0.72; p = 0.0001$). The results suggest that PET imaging with the novel tracer, PIB, can provide quantitative information on amyloid deposits in living subjects.
a) Relationship of PIB PET to cerebrospinal fluid $\alpha_42$ concentration in cognitively normal individuals.

b) Axial (horizontal) view of Alzheimer’s brain, imaged to quantify amyloid (PIB PET), annual rates of regional atrophy (quantitative MRI) and hypometabolism in relation to dementia severity (fluorodeoxyglucose PET).
Quando aumenta il binding PIB, le concentrazioni liquorali di Abeta sono basse. Ciò significa che una volta formate le placche, Abeta solubile è intrappolata nelle placche stesse.
Conversion of amyloid positive and negative MCI to AD over 3 years
An 11C-PIB PET study

ABSTRACT

Background: Patients with amnestic mild cognitive impairment (MCI) represent an important clinical group as they are at increased risk of developing Alzheimer disease (AD). 11C-PIB PET is an in vivo marker of brain amyloid load.

Objective: To assess the rates of conversion of MCI to AD during a 3-year follow-up period and to compare levels of amyloid deposition between MCI converters and nonconverters.

Methods: Thirty-one subjects with MCI with baseline 11C-PIB PET, MRI, and neuropsychometry have been clinically followed up for 1 to 3 years (2.68 ± 0.6 years). Raised cortical 11C-PIB binding in subjects with MCI was detected with region of interest analysis and statistical parametric mapping.

Results: Seventeen of 31 (55%) subjects with MCI had increased 11C-PIB retention at baseline and 14 of these 17 (82%) clinically converted to AD during follow-up. Only one of the 14 PIB-negative MCI cases converted to AD. Of the PIB-positive subjects with MCI, half (47%) converted to AD within 1 year of baseline PIB PET, these faster converters having higher tracer-retention values than slower converters in the anterior cingulate (p = 0.027) and frontal cortex (p = 0.031). Seven of 17 (41%) subjects with MCI with known APOE status were ε4 allele carriers, this genotype being associated with faster conversion rates in PIB-positive subjects with MCI (p = 0.035).

Conclusions: PIB-positive subjects with mild cognitive impairment (MCI) are significantly more likely to convert to AD than PIB-negative patients, faster converters having higher PIB retention levels at baseline than slower converters. In vivo detection of amyloid deposition in MCI with PIB PET provides useful prognostic information.
Figure 1  Amyloid deposition in mild cognitive impairment (MCI) subgroups

Scatter plot showing the distribution of individual Pittsburgh compound B (PIB) retention values in PIB-positive MCI subgroups: fast, slow, and nonconverters compared to controls (top line = Turku control mean; bottom line = London control mean).

Cognitively unimpaired HIV-positive subjects do not have increased $^{11}$C-PiB

A case-control study

ABSTRACT

Objectives: Diagnostic challenges exist for differentiating HIV dementia from Alzheimer disease (AD) in older HIV-infected (HIV+) individuals. Similar abnormalities in brain amyloid-$\beta_{42}$ ($\text{A}{\beta}_{42}$) metabolism may be involved in HIV-associated neuropathology and AD. We evaluated the amyloid-binding agent $^{11}$C-Pittsburgh compound B ($^{11}$C-PiB), a biomarker for $\text{A}{\beta}_{42}$ deposition, in cognitively unimpaired HIV+ ($n = 10$) participants and matched community controls without dementia ($n = 20$).

Methods: In this case-control study, all participants had an $^{11}$C-PiB scan within 2 years of concomitant CSF studies and neuropsychometric testing. Statistical differences between HIV+ and community controls for demographic and clinical values were assessed by $\chi^2$ tests. Participants were further divided into either low ($\leq 500$ pg/mL) or normal ($\geq 500$ pg/mL) CSF $\text{A}{\beta}_{42}$ groups with Student $t$ tests performed to determine if regional differences in fibrillar amyloid plaque deposition varied with CSF $\text{A}{\beta}_{42}$.

Results: Regardless of CSF $\text{A}{\beta}_{42}$ level, none of the HIV+ participants had fibrillar amyloid plaques as assessed by increased $^{11}$C-PiB mean cortical binding potential (MCBP) or binding potential within 4 cortical regions. In contrast, some community controls with low CSF $\text{A}{\beta}_{42}$ (<500 pg/mL) had high $^{11}$C-PiB MCBP with elevated binding potentials (>0.18 arbitrary units) within cortical regions.

Conclusions: Cognitively unimpaired HIV+ participants, even with low CSF $\text{A}{\beta}_{42}$ (<500 pg/mL), do not have $^{11}$C-PiB parameters suggesting brain fibrillar amyloid deposition. The dissimilarity between unimpaired HIV+ and preclinical AD may reflect differences in $\text{A}{\beta}_{42}$ production and/or formation of diffuse plaques. Future longitudinal studies of HIV+ participants with low CSF $\text{A}{\beta}_{42}$ and normal $^{11}$C-PiB are required. Neurology $^{c}$ 2010;75:111-115
Selettività dei depositi di amiloide fibrillare nella malattia di Alzheimer.
The role of C-PIB (and similar ligands for β-amyloid deposits) in routine clinical practice needs to be further defined, relative to other diagnostic markers of AD. Moreover, the relation between C-PIB uptake and cognitive decline in subjects without dementia with non-amnestic MCI and subjective cognitive impairment, or in subjects without any cognitive impairment, needs further study.

PIB: il merito di aver richiamato l’attenzione su metodologie oggettive per studiare l’evoluzione del disturbo cognitivo. Ora è necessario confermare in studi su larga scala la relazione con la condizione clinica.
MRI and CSF biomarkers in normal, MCI, and AD subjects

Predicting future clinical change

ABSTRACT

Objective: To investigate the relationship between baseline MRI and CSF biomarkers and subsequent change in continuous measures of cognitive and functional abilities in cognitively normal (CN) subjects and patients with amnestic mild cognitive impairment (aMCI) and Alzheimer disease (AD) and to examine the ability of these biomarkers to predict time to conversion from aMCI to AD.

Methods: Data from the Alzheimer’s Disease Neuroimaging Initiative, which consists of CN, aMCI, and AD cohorts with both CSF and MRI, were used. Baseline CSF (t-tau, Aβ1-42, and p-tau181P) and MRI scans were obtained in 399 subjects (109 CN, 192 aMCI, 98 AD). Structural Abnormality Index (STAND) scores, which reflect the degree of AD-like features in MRI, were computed for each subject.

Results: Change on continuous measures of cognitive and functional performance was modeled as average Clinical Dementia Rating—sum of boxes and Mini-Mental State Examination scores over a 2-year period. STAND was a better predictor of subsequent cognitive/functional change than CSF biomarkers. Single-predictor Cox proportional hazard models for time to conversion from aMCI to AD showed that STAND and log (t-tau/Aβ1-42) were both predictive of future conversion. The age-adjusted hazard ratio for an interquartile change (95% confidence interval) of STAND was 2.6 (1.7, 4.2) and log (t-tau/Aβ1-42) was 2.0 (1.1, 3.4). Both MRI and CSF provided information about future cognitive change even after adjusting for baseline cognitive performance.

Conclusions: MRI and CSF provide complimentary predictive information about time to conversion from amnestic mild cognitive impairment to Alzheimer disease and combination of the 2 provides better prediction than either source alone. However, we found that MRI was a slightly better predictor of future clinical/functional decline than the CSF biomarkers tested.
Serial MRI and CSF biomarkers in normal aging, MCI, and AD

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ABSTRACT

Objective: To compare the annual change in MRI and CSF biomarkers in cognitively normal (CN), amnestic mild cognitive impairment (aMCI), and Alzheimer disease (AD). Comparisons were based on intergroup discrimination, correlation with concurrent cognitive/functional changes, relationships to APOE genotype, and sample sizes for clinical trials.

Methods: We used data from the Alzheimer’s Disease Neuroimaging Initiative study consisting of CN, aMCI, and AD cohorts with both baseline and 12-month follow-up CSF and MRI. The annual change in CSF (total-tau [t-tau], Aβ1-42) and MRI (change in ventricular volume) was obtained in 312 subjects (92 CN, 149 aMCI, 71 AD).

Results: There was no significant average annual change in either CSF biomarker in any clinical group except t-tau in CN; moreover, the annual change did not differ by clinical group in pairwise comparisons. In contrast, annual increase in ventricular volume increased in the following order, AD > aMCI > CN, and differences were significant between all clinical groups in pairwise comparisons. Ventricular volume increase correlated with concurrent worsening on cognitive/functional indices in aMCI and AD whereas evidence of a similar correlation with change in CSF measures was unclear. The annual changes in MRI differed by APOE ε4 status overall and among aMCI while annual changes in CSF biomarkers did not. Estimated sample sizes for clinical trials are notably less for MRI than the CSF or clinical measures.

Conclusions: Unlike the CSF biomarkers evaluated, changes in serial structural MRI are correlated with concurrent change on general cognitive and functional indices in impaired subjects, track with clinical disease stage, and are influenced by APOE genotype. Neurology® 2010;75:143-151
Structural and Functional Patterns in Healthy Aging, Mild Cognitive Impairment, and Alzheimer Disease

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Abstract: The aim of this study was to analyze the combined contribution of magnetic resonance imaging and magnetoencephalography (MEG) to the diagnosis of mild cognitive impairment (MCI) and AD. To whole—head MEG recordings were obtained from three diagnosis groups: Alzheimer disease (AD), MCI, and control. Magnetic resonance imaging volumetric data of global brain, temporal lobe, and hippocampal volumes, were also obtained. Results indicated that a reduction of volume in the hippocampal structure allowed the discrimination between AD and MCI patients as compared with controls. The percentage of correct classification was 91.3% when AD versus controls was compared, and 83.3% when we compared MCI versus control. MEG data showed that AD patients exhibit higher θ and δ activity than MCI and controls. Such higher activity was significant in parietal, temporal, and occipital areas. Left parietal theta classified controls versus MCIIs with 78.3% rate of correct classification. Right occipital theta and the left parietal delta allowed the discrimination of controls versus ADs, with 81.8% rate of correct classification. Left parietal theta discriminated between ADs and MCIs with 56.6% rate of correct classification. In addition, the combination of both techniques significantly improved the rate of correct classification, thus indicating that a multidisciplinary perspective of techniques may improve the diagnostic capabilities.

Key Words: magnetoencephalography, MRI volumetry, Alzheimer disease, mild cognitive impairment

(Alzheimer Dis Assoc Disord 2010;24:1–10)
Il rischio che la diagnosi (e la funzione predittiva) richiedano strumenti plurimi e costosi. Chi potrà fruirne?
Alla ricerca di un equilibrio tra la tecnologia concentrata in pochi centri e l’esigenza assistenziale diffusa.
Il ruolo delle UVA e la loro “dignità” diagnostica anche senza tecnologie.
Use of Alzheimer Disease Biomarkers
Potentially Yes for Clinical Trials but Not Yet for Clinical Practice

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Però... è un inizio...
Il progresso è anche incertezza!
La diagnosi clinica non deve essere trascurata.
La lunga strada verso una EBM delle demenze.