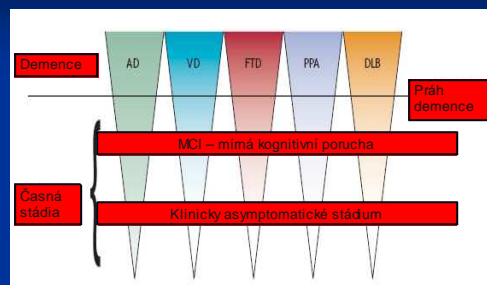


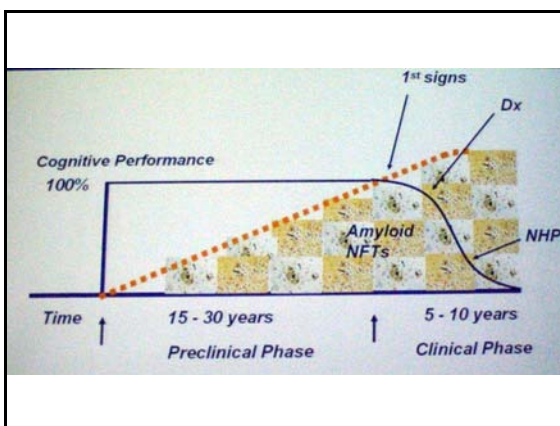
Novinky v časně diagnostice demencí

Martin Vyhňálek

Centrum pro kognitivní poruchy,
Neurologická klinika dospělých
UK, 2. lékařské fakulty a FN
Motol

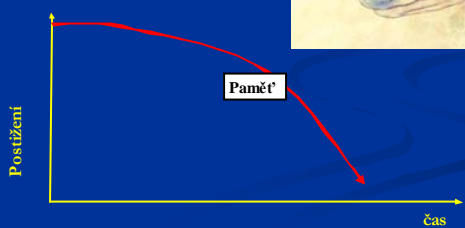


Dubois 2007

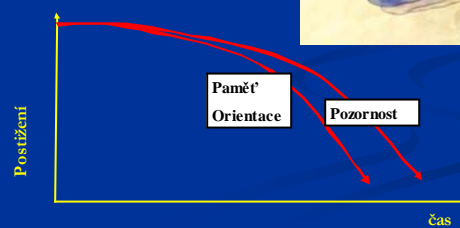


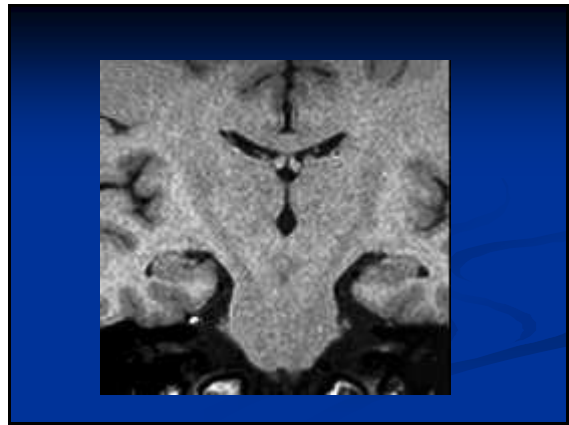
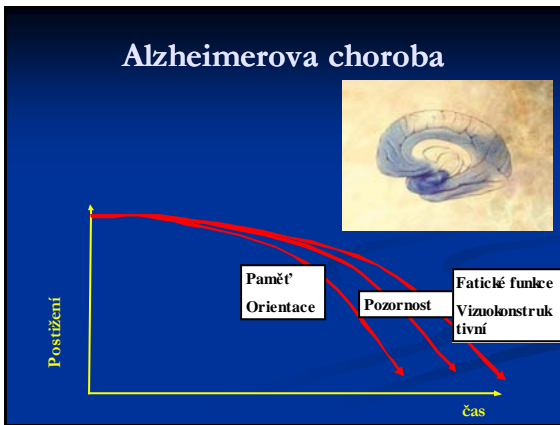
1. Znalost patobiochemických změn
2. Znalost anatomické progresse

Alzheimerova choroba



Alzheimerova choroba

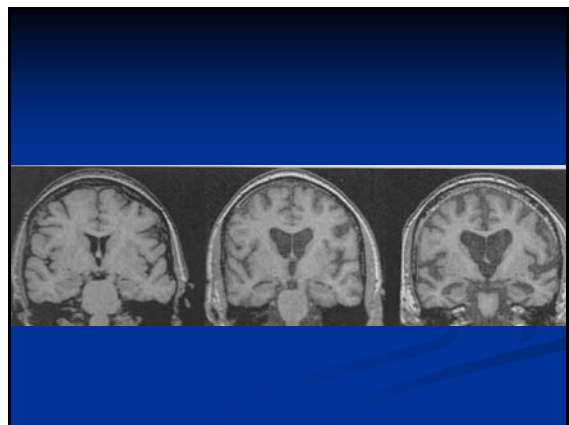
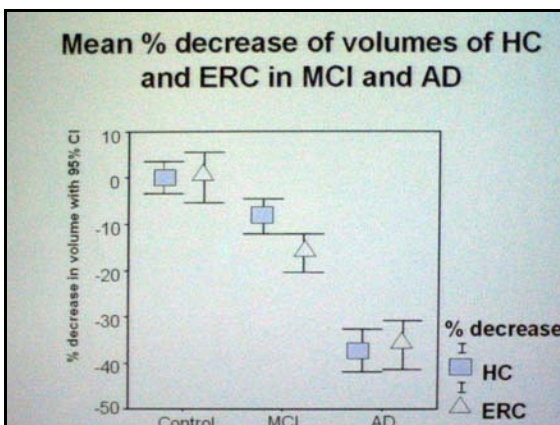


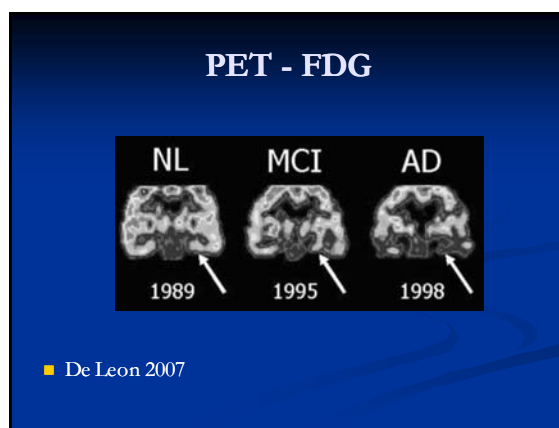
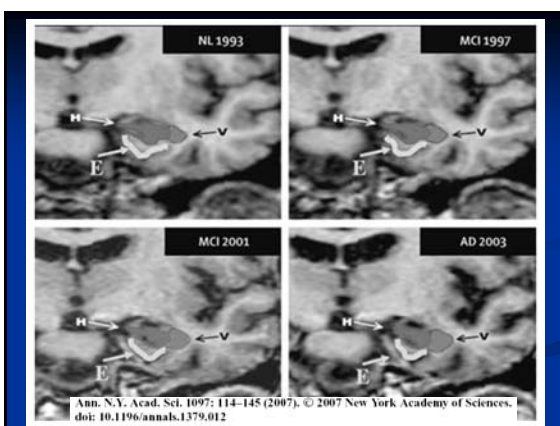


Atrofie hipokampu a entorhinální kůry

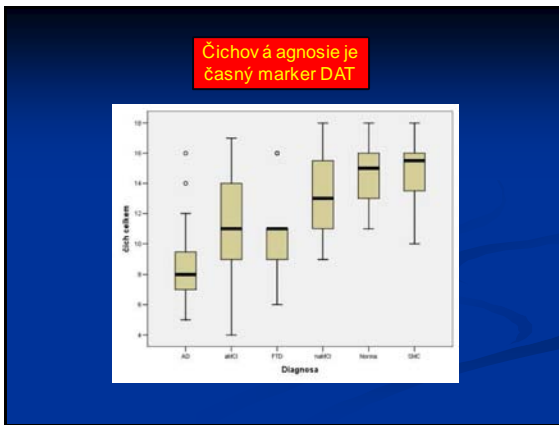
- Časný marker AD
- Ušetřeno při normálním stárnutí
- Koreluje s poruchou paměti
- Není zcela specifické pro AD (též u FTL, LBD)

Součástí návrhu nových dg. kritérií (Dubois 2007)

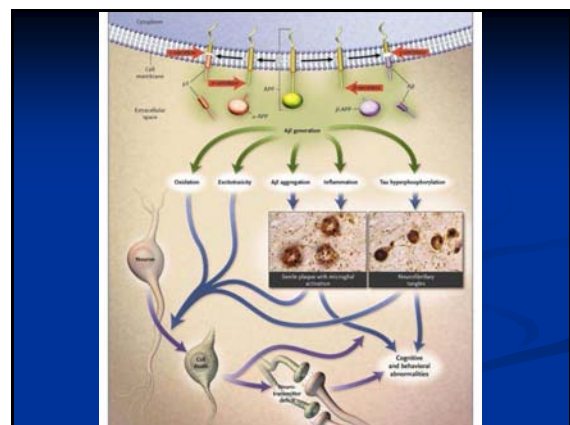
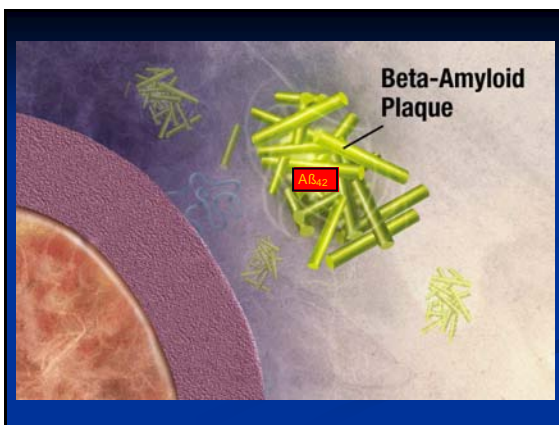
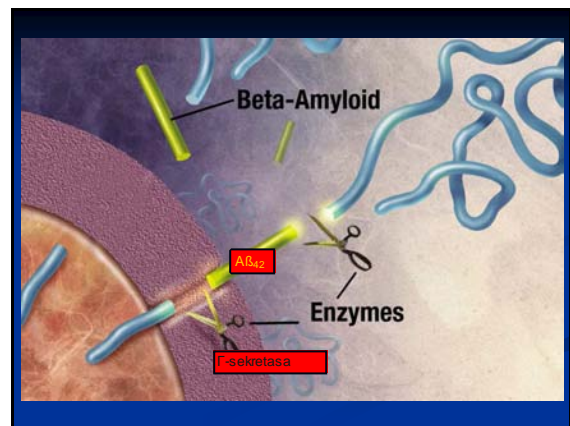
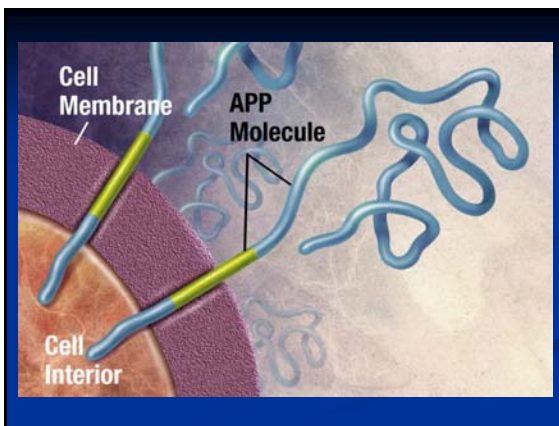




	a	b	c	d
1	gřep	borovice	paprika	karamel
2	banán	konvalinka	broskev	pomeranč
3	citron	lékořice	rybíz	šalvěj
4	růže	tulipán	fialka	med
5	borovice	meloun	karamel	višň
6	kokos	jáhoda	kadiolo	gřep
7	sefík	kiwi	hřebíček	barán
8	ocet	zázvor	rybíz	levandule
9	hruška	kadiolo	máta	kiwi
10	fialka	pomeranč	rum	jablko
11	šalvěj	jablko	pepř	skořice
12	vanilka	pepř	skořice	jedle
13	čokoláda	káva	levandule	tymian
14	zázvor	med	rum	mandarinka
15	meloun	sefík	kokos	broskev
16	vanilka	švestka	jáhoda	mandle
17	lékořice	paprika	konvalinka	rybíz
18	hřebíček	ocet	hruška	rum



Znalost patobiochemických změn

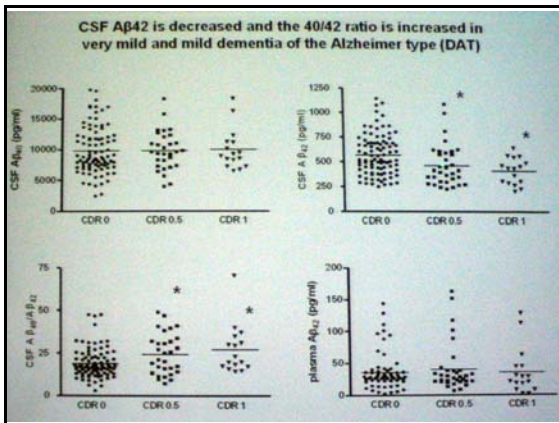
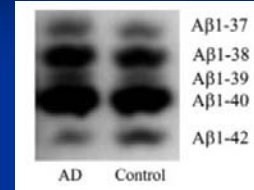


Author	n	Main outcome	Stage
CSF T-tau vs Aβ ₄₂			
Polvik and co-workers*	154	T-tau in patients aged <50 years, most prominently in APOE ε4 carriers	Preclinical
Kawar and co-workers*	191	T-tau vs Aβ ₄₂ was highly correlated with age, CDR of 1-1, and APOE ε4. PSN1 mutation identified in a patient with greatly reduced Aβ ₄₂ concentrations	Preclinical, prodrome, dementia
Sunderland and co-workers*	292	T-tau, but no change in tau in APOE ε4 carriers and T-tau in AD dementia	Preclinical, dementia
Fagan and co-workers**	139	T-tau and T-tau in patients with CDR-sb <5	Prodrome, dementia
Wozniak and co-workers**	223	T-tau and T-tau in amnesic MCI and AD dementia compared with non-amnesic MCI, T-tau in AD dementia compared with amnesic MCI	Prodrome, dementia
Sunderland and co-workers**	203	T-tau and T-tau in AD	Dementia
Andersen and co-workers**	241	T-tau and T-tau in AD dementia, T-tau in AD dementia compared with VD, MCI, DLB, and controls	Prodrome, dementia
Andersen and co-workers**	121	T-tau in AD and non-AD	Dementia
Calabisi and co-workers**	215	T-tau and T-tau in AD, APOE ε4 genotype effect on Aβ ₄₂ concentrations	Dementia
Rowman and co-workers**	375	T-tau and T-tau in AD dementia and T-tau in older controls	Dementia
Rowman and co-workers**	137	T-tau and Aβ ₄₂ in MCI that progressed to AD over 4 years	Prodrome
Kawar and co-workers**	129	T-tau/Aβ ₄₂ predicted progression to MCI in AD dementia over 10 months	Preclinical
CSF tau P218			
Fagan and co-workers**	139	T-tau in patients with CDR-sb <5	Prodrome, dementia
Wozniak and co-workers**	223	T-tau in amnesic MCI and AD dementia compared with non-amnesic MCI	Prodrome, dementia
Rowman and co-workers**	375	T-tau in AD compared with controls and in older controls compared with younger controls	Dementia
CSF tau P217			
Glück Sobanska and co-workers**	78	T-tau in APOE ε4 carriers	Preclinical
Wagner and co-workers**	131	T-tau in MCI and AD dementia	Prodrome
Wagner and co-workers**	132	T-tau in AD compared with controls, TTD, VD, and DLB	Dementia
Evans and co-workers**	145	T-tau in MCI that converted to AD over 14-28 months	Prodrome

www.thelancet.com/neurology Vol 7 August 2008

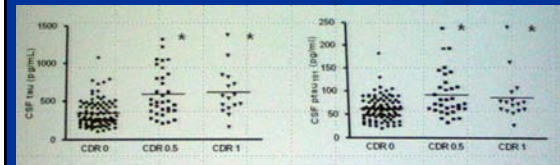
Aβ₄₂ v MM

- Aβ₄₂ – sníženo o 50% u pacientů s DAT i aMCI (Hulstaert – Neurology 1999)
- Snížená hladina Aβ₄₂ u pacientů s MCI predikuje konverzi do DAT (Hansson 2007)
- Hladina se nemění s progresí choroby
- Ale:
 - Velká interindividuální variabilita
 - Není specifické pro DAT



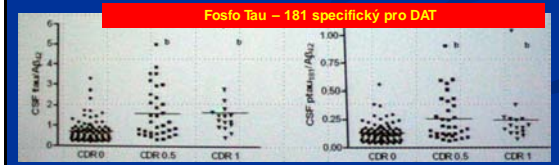
Protein Tau v MM

- Celkový tau protein zvýšený 2-3x (Sonnen 2008)
- Hyperfosforylovaný tau zvýšený i řádově



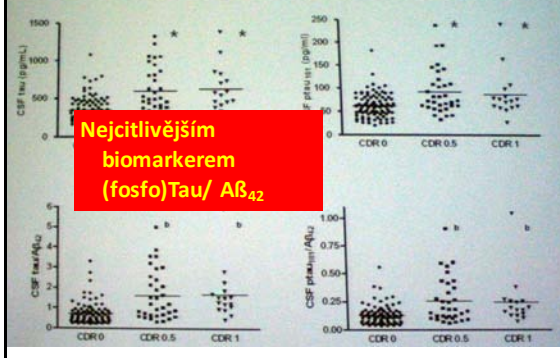
Protein Tau v MM

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Fosfo Tau – 181 specifický pro DAT

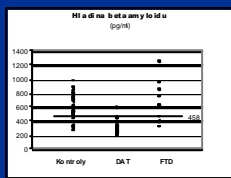
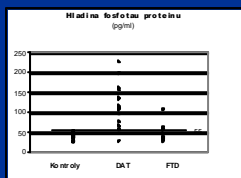
Tau and p-Tau181 are increased in CSF of very mild and mild DAT



Nejcitlivějším biomarkerem (fosfo)Tau/ Aβ₄₂

Biomarkery v moku

Součástí návrhu nových dg. kritérií (Dubois 2007)



Hon et al 2006

Biomarkery DAT v plazmě a moči.....

- Slibný nález zvýšení **V2 isoprostanu** nebyl v dalších studiích zreprodukován (Hřezany 2007)
- **Plazmatická hladina $A\beta_{1-42}$** výsledky velmi nejednoznačné – zvýšení i snížení – zatím není užitečný marker (Lopez 2008)

....nejednoznačné závěry... zatím bez klinické aplikace

- Slibný nález zvýšení **V2 isoprostanu** nebyl v dalších studiích zreprodukován (Hřezany 2007)
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Zobrazovací metody v dg. demencí

Imaging technique	Biological process
CT	Atrophy, space-occupying lesions
MRI	Atrophy, space-occupying lesions, white-matter hyperintensity
$[^{18}F]FDG$ -PET	Glucose metabolism
$[^{123}I]C$ -HMPAO SPECT	Blood flow
$[^{18}F]DDNP$ -PET	Amyloid plaques and tau tangles
$[^{11}C]PiB$ -PET	Amyloid plaques
$[^{11}C]SB-13$ PET	Amyloid plaques
$[^{18}F]$ -BA94-9172-PET	Amyloid plaques
$[^{18}F]$ MPPF-PET	Hippocampal neuronal integrity
Functional MRI	Blood flow, functional connectivity
DTI	Neuronal connectivity, white-matter integrity
MRS	Metabolite concentrations
$[^{11}C]$ -nicotine PET	Nicotinic binding sites
$[^{11}C]$ (R)-PK11195 PET	Microglial activation (inflammation)
$[^{11}C]$ β -CFT PET	Dopamine reuptake

Table: Imaging techniques and the biological processes they measure

Small 2008

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Small 2008

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Table: Imaging techniques and the biological processes they measure

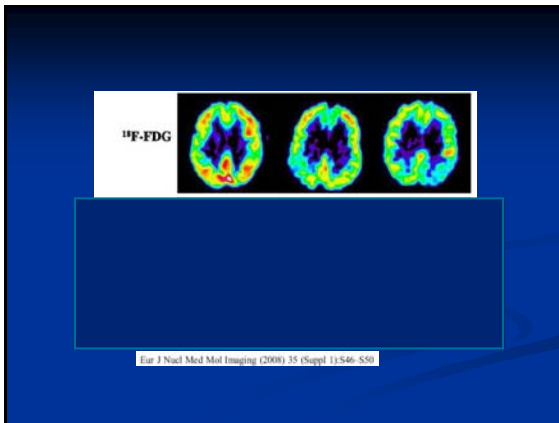
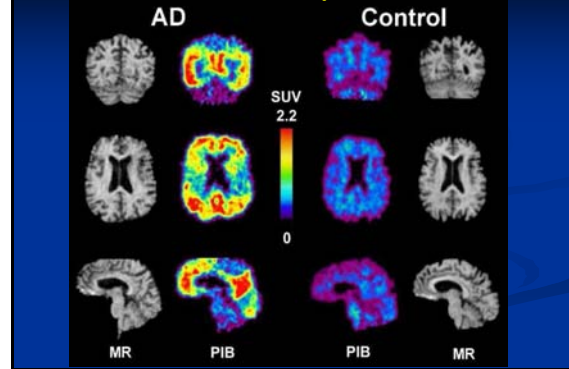
Small 2008

Zobrazení betaamyloidu in vivo

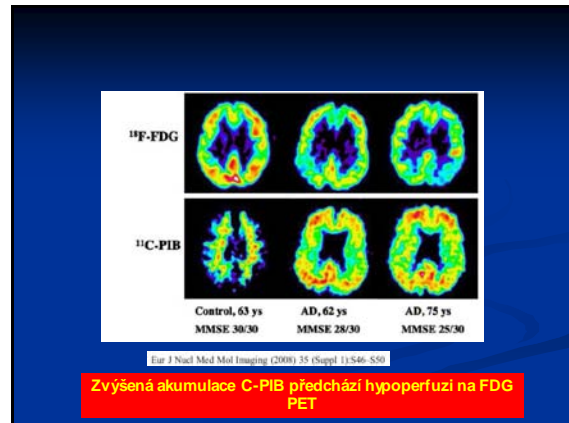
[¹⁸ F]FDDNP-PET	Amyloid plaques and tau tangles
[¹¹ C]PIB-PET	Amyloid plaques
[¹¹ C]SB-13 PET	Amyloid plaques
[¹⁸ F]-BAY94-9172-PET	Amyloid plaques

■ Specificita a senzitivita přes 90%

Zobrazení Betaamyloidu in vivo

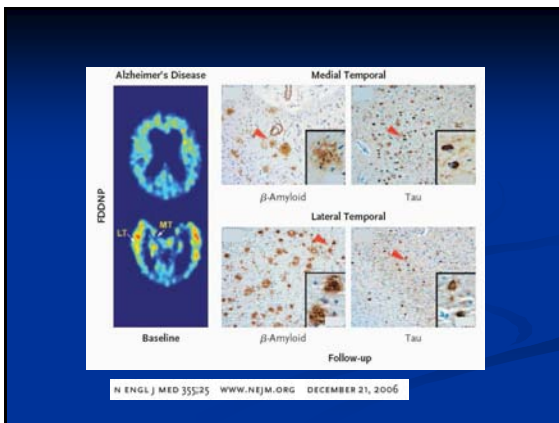


Eur J Nucl Med Mol Imaging (2000) 35 (Suppl 1):S46-S50



Eur J Nucl Med Mol Imaging (2000) 35 (Suppl 1):S46-S50

Zvýšená akumulace C-PIB předchází hypoperfuzi na FDG PET



N ENGL J MED 355:25 WWW.NEJM.ORG DECEMBER 21, 2006

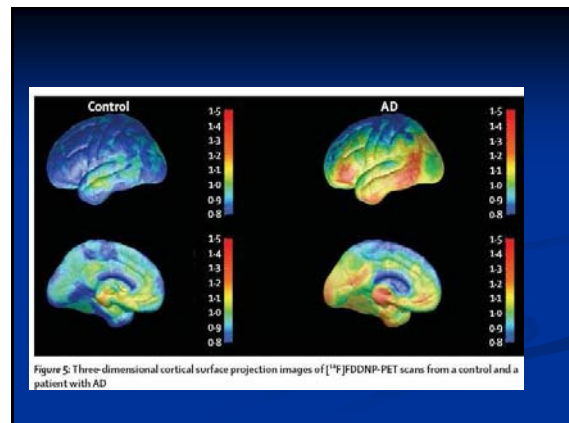
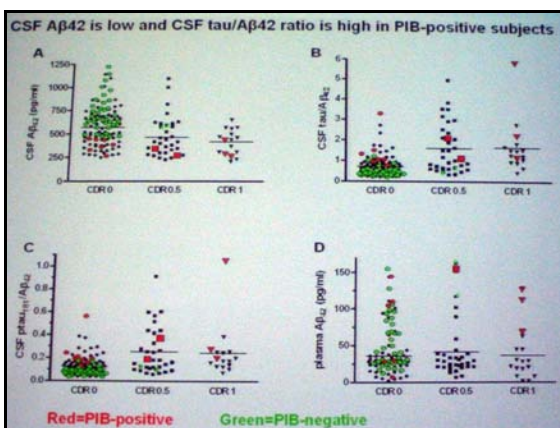
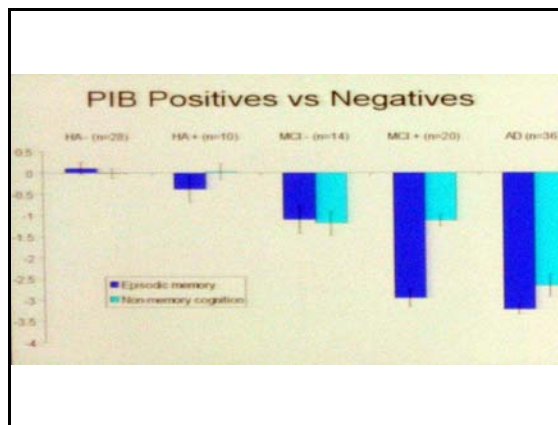


Figure 5: Three-dimensional cortical surface projection images of [¹⁸F]FDDNP-PET scans from a control and a patient with AD

PET s PIB je schopno predikovat konverzi do demence

Forsberg A, Engler H, Ahnkvist O, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging*. 2007 May 10 (in press).



Zobrazení betaamyloidu in vivo

[¹⁸ F]FDNDP-PET	Amyloid plaques and tau tangles
[¹¹ C]PIB-PET	plaques
[¹¹ C]SB-13 PET	plaques
[¹⁸ F]-BAY94-9172-PET	Amyloid plaques

Součástí návrhu nových dg. kritérií (Dubois 2007)

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria

Bruno Dubois, Howard H. Gaster, Claudia Jacova, Simon T. DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, Andre Delacourte, Douglas Galaski, Serge Gauthier, Gregory Jicha, Kenneth Mogera, John D. Breit, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Subbarao, Yasuko Sano, Pedro V. Van, Philip Scheltzer*

Lancet Neurol 2007; 6: 734-46
 Published Online July 8, 2007
 DOI:10.1016/S1473-3099(07)70128-7

The NINCDS-ADRDA and the DSM-IV-TR criteria for Alzheimer's disease (AD) are the prevailing diagnostic standards in research; however, they have now fallen behind the unprecedented growth of scientific knowledge. Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses. This progress provides the impetus for our proposal of revised diagnostic criteria for AD. Our framework was developed to capture both the earliest stages, before full-blown dementia, as well as the full spectrum of the illness. These new criteria are centred on a clinical core of early and significant episodic memory impairment. They stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid β or tau protein. The timeliness of these criteria is highlighted by the many drugs in development that are directed at changing pathogenesis, particularly at the production and clearance of amyloid β as well as at the hyperphosphorylation state of tau. Validation studies in existing and prospective cohorts are needed to advance these criteria and optimise their sensitivity, specificity, and accuracy.

Dg. Kritéria DAT

A: Základní dg. kritéria

- Porucha epizodické paměti
 - Trvající déle než 6 měsíců a postupně progredující
 - Hipokampálního typu (není efekt nápovědy)
 - Může být doprovázena dalším kognitivním deficitem


Dg. Kritéria DAT

Podpůrná dg. kritéria- biomarkery

- B. Atrofie mesiálních struktur na MRI
- C. Charakteristická hypoperfuzie na PET
- D. Positivní biomarkery v moku
- E. Positivní genetické vyšetření na známé AD mutace

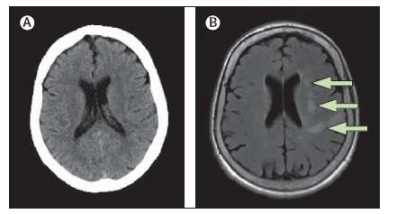
Vaskulární demence

- VD je klinická diagnosa
- Neexistují PET studie s PIB
- Z komplementárních metod dominantní role MRI

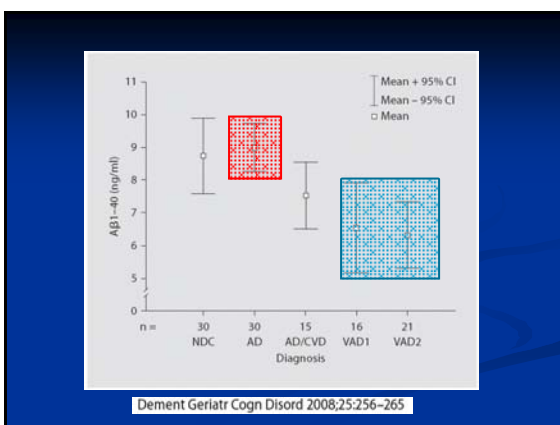
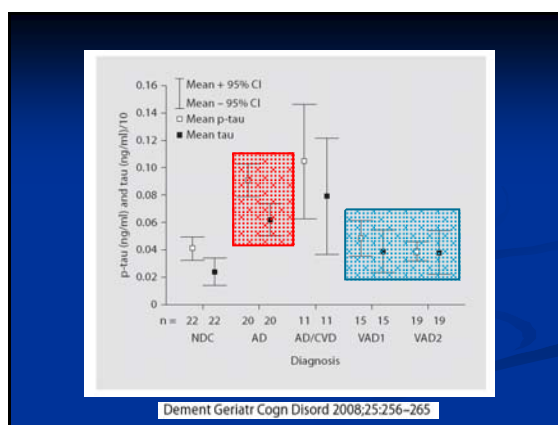
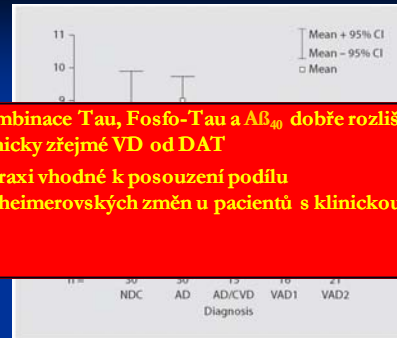


<http://neurology.thejco.com Vol7 March 2008>

Vaskulární demence



<http://neurology.thejco.com Vol7 March 2008>

- Kombinace Tau, Fosfo-Tau a Aβ₄₀ dobře rozliší klinicky zřejmé VD od DAT
- V praxi vhodné k posouzení podřlu Alzheimerovských změn u pacientů s klinickou dg. VD

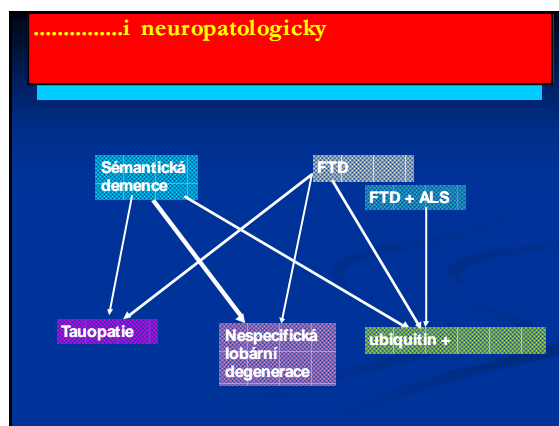
Dement Geriatr Cogn Disord 2008;25:256-265

Frontotemporální lobární degenerace je diagnosa heterogenní klinicky.....

Frontotemporální demence

Sémantická demence

Progressivní nonfluentní afázie



MRI JP, MMSE 27/30

Sc 5 TSEM SL13

Sc 2 TSEM SL8

Sc 2 TSEM SL9

22/28 pacientů s klinickou dg. FTLD mělo negativní PIB

PIB je užitečné v dif.dg.DAT a FTLD

FTD NEGATIVE

FTD POSITIVE

HEALTHY CONTROL

AD

Fig. 1. PIB standardized uptake values (SUV) of four representative subjects. FTD PIB negative: patient no 8 (Table 1). FTD PIB positive: patient no 4 (Table 1). AD: scan of a typical patient with Alzheimer's disease. SUV were obtained using the time interval 40-60 min.

Eur J Nucl Med Mol Imaging (2008) 35:100-106

FTLD – další diagnostické metody

- V porovnání s DAT - není výrazný rozdíl v hladině T au a Aβ₄₀
- U FTLD je normální hladina fosfoTau 181 v porovnání s DAT (Kapaki 2008)

FosfoTau je užitečný v dif.dg.DAT a FTLD

Demence s Lewyho tělísky

Sensitivity and specificity of dopamine transporter imaging with ¹²³I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study

Sensitivita 77% , specifita 90%

Odhalí i pacienty s LBD bez klinického Parkinsonismu (Walker JNNP 2007)

UZ mesencefala

ORIGINAL COMMUNICATION

Ulrich Mikler,
Dink Shrivastava,
Alexandra Weidner,
Martina Witznigg,
Bogdan Cernak,
Robert Blohse

Sonographic discrimination of dementia with Lewy bodies and Parkinson's disease with dementia



Hyperechogenita SN u všech pacientů s LBD, u 80% bilaterální (x30% PDD)

Demence s Lewyho tělísky – další diagnostické metody

- **PIB Výrazně pozitivní** – není klinicky využitelné (Rowe 2007)
- **fosfo-Tau 181 vhodné** k odlišení od DAT (sensitivita a specificita 80%) (Aarsland 2008)

Závěr

- Degenerativní demence mají velmi dlouhou preklinickou a predementní fázi
- Samotná demence je manifestace již výrazně pokročilého patologického procesu a kauzální ovlivnění je v této fázi již problematické
- V predikci budoucího rozvoje demence výrazná role biomarkerů v MM moku a vyšetření PET
- Populační screening demence???????????
- Ale zatím málo studií s patologickou confirmací