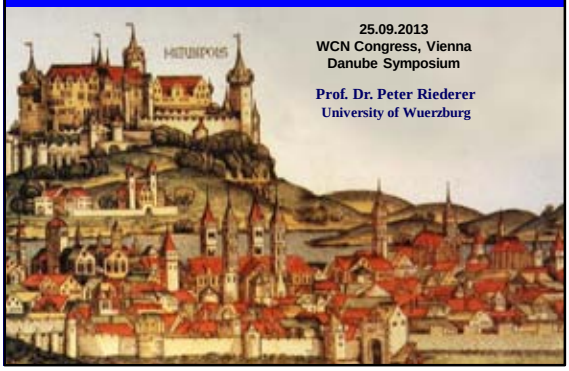
Current Status on Biomarkers in Alzheimer's Disease



25.09.2013
WCN Congress, Vienna
Danube Symposium

Prof. Dr. Peter Riederer
University of Wuerzburg

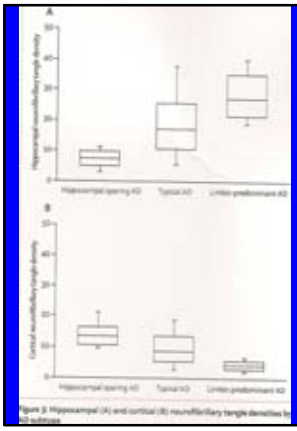
Sporadic Alzheimer Disease

- more than 15 million people worldwide
- multiple subtypes
- multiple phenotypes
- mutation-related stimulus is lacking
- causation is enigmatic

RISK FACTORS FOR

AD	Hippocampal atrophy
• Age	• Hypertension
• Gender	• Diabetes
• Education	• Hyperlipidaemia
• Pathol. Events	• Seizures
• Head Injury	• Affective disturbances
• Biometals	• Stress
• OS	• APOE?4 genotype
• Smoking	
• Genetic pathology (APP, PS1, PS2, APOE?4)	
• Depression	
• Folic acid	

Dhikav and Amand 2011



hippocampal sparing	(11 %)	(H)
typical	(75 %)	(T)
limbic predominant	(14 %)	(L)

Murray et al. 2011

Dementias

- Alzheimer Dementia (AD)
- Neurodegeneration + / - vascular pathology

  Amyloid
  ?au - Pathology
  Synapse

- Multiple Pathologies in most of aged people
  multi infarct dementia
  strategic infarct dementia
  AD + SVD (small vessel disease)
  AD + CAA or SVD

Dementias

- FTLD (Pick): CA1, CA 4 round inclusions; early (50 – 70 yrs.)
- PSP (Progressive Supranuclear Palsy): astrocytes; (60 – 100 yrs.)
- CBD (Cortico Basal Disease): 60 – 90 yrs.
- AGD (Argyrophilic Grain Disease): ?au-pathol. in spines; (60 – 100 yrs.)
- FTLD-TDP: nuclear inclusions in nerve-cells subtypes
- LBD (Lewy Body Disease): Lewy neurites, LB

Braak, Thal 2011; Thal 2012
Montine 2012

Criteria for biological markers (1)

- **Features of an ideal biomarker**

(Shaw et al. 2007: Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. Nature Reviews 6: 295-303)

- linked to fundamental features of the neuropathology
- validated in neuropathologically confirmed cases
- able to detect the disease early in its course and distinguish it from other dementias
- non-invasive, simple to use and inexpensive
- not influenced by symptomatic drug treatment

Gerlach, Riederer et al. 2012

Criteria for biological markers (2)

- **Criteria that must be evaluated before acceptance as a biomarker**

(Shaw et al. 2007. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. Nature Reviews 6: 295-303)

- Sensitivity (>85%; 100% indicates that all patients are identified with the disease)
- Specificity (>85%; 100% a test identifies all individuals free of the disease)
- Prior probability (the background prevalence of the disease in the population tested)
- Positive predictive value (>80%; refers to % of people who are positive for the biomarker and have definite the disease at autopsy)
- Negative predictive value (The % of people with a negative test, no disease at autopsy)

Gerlach, Riederer et al. 2012

Relevance of BIOMARKERS

?á **PRESYMPTOMATIC DIAGNOSIS**

?$ **EVIDENCE FOR PROTECTIVE THERAPY**

? **DIFFERENTIATING „DEMENTIAS“**

CSF BIOMARKERS

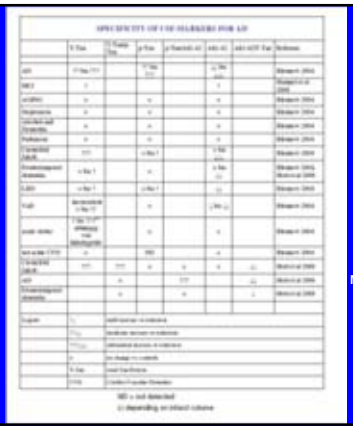
Core CSF changes in sporadic AD are

- decreased amyloid ß(1-42)
- increased total ?au
- increased phospho-?áu

positive predictive value for the combination remained stable with ageing, while the negative predictive value decreased with age.

The diagnostic accuracies decrease with age.

Mattson et al. 2012
Sarazin et al. 2012
Blennow et al. 2010



Mollenhauer et al 2011

OTHER POSSIBLE BIOMARKERS ARE UNSPECIFIC

?á **OXIDATIVE STRESS PARAMETERS**

- ?† **MITOCHONDRIAL DYSFUNCTION**
- ?S **NITROTYROSINE**
- ?' **ISOPROSTANE**
- ?ô **8-HYDROXY-2-DEOXY GUANOSINE**
- ?Á **ALZHEIMER ASSOCIATED PROTEIN (ALZACS)**

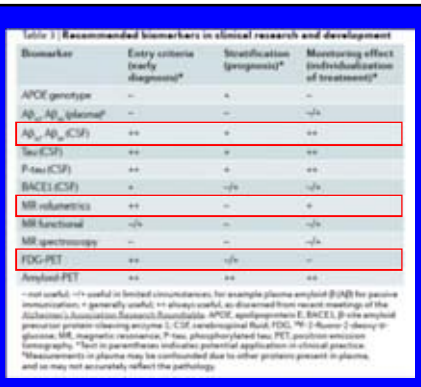
?– **INFLAMMATORY PARAMETERS**

- ?b **IL-1?b**
- ?? **IL-6-RECEPTOR COMPLEX**
- ? **IL-6**
- ?Đ **TNF-?Đ**

?¥ **VASULAR RISK-FACTORS**

- ?r **HOMOCYSTEINE**

?F **APO E ?F-allele (sensitivity 65%, specificity 68%)**



Hampel et al. 2010

GENETIC BIOMARKERS (1)

- 513 families worldwilde (by August 2011) are suffering from hereditary AD
  - APP gene mutations: 89 families (17,3 %)
  - PS 1 gene mutation: 402 families (78,4 %)
  - PS 2 gene mutation: 22 families (4,3 %)

RISK GENES FOR SPORADIC LATE-ONSET AD

- LARGE SCALE GENOME-WIDE ANALYSES (GWAS)
  - ?“ APOE?‘4
  - ? CLU
  - ?± PICALM
  - ?B CR1
  - ?î BIN1

  no correlation between SNPs and CSF Aß(42) or ?(181) (Kauwe et al. 2011)
- ALZGENE DATABASE
  - ?ŸAPOE, CLU, PICALM, EXOC3L2, BIN1, CR1, SORL1, TNK1, IL 8, LDLR, CST3, CHRNB 2, SORCS 1, TNF, CCR 2
- TREM2 variants — Jonsson et al. 2013
- COPY NUMBER VARIATION GWAS — Chapman et al. 2013
- GWAS OF CSF ?au / p-?au ?D3 loci — Cruchaga et al. 2013
- DNA MODIFICATIONS
  - ? HYPO- and HYPERMETHYLATED AD-RELATED SUSCEPTIBILITY GENES

Alexopoulos et al. 2010, Elias-Sonnenschein et al. 2013, Harold et al. 2011, Olgiati et al. 2011, Seshadri et al. 2010, Szigeti et al. 2013, Zetzsche et al. 2010

Problems with GWAS - studies

- significance levels too high; loss of information
- subtyping spectrum disorder
- high N means many clinical subtypes included!
- interaction clinicians / basic researchers is missing

- regional gene expression different?
- social support
- life events

- epigenetics
- copy number variation
- Splicing
- de novo mutations
- gene interactions

Systems biology in Alzheimer‘s disease (AD)

H. Hampel et al. / Alzheimer's & Dementia 8 (2012) 312–336

Proteomics: 366 proteins — Zürbig and Jahn 2012
5 plasma proteins (Aß associated) — Guo et al. 2013

Conclusion

Current evidence based on clinical, pathological, (molecular) biological and genetic studies and evaluation of such data by using algorithm-based processes point to conclude that

„ … there will never be a valid biomarker for AD!“

„… rather there will be distinct biomarkers for sAD subtypes.“