ALZHEIMER'S DISEASE BIOMARKERS: DIAGNOSIS AND TREATMENT OF THE SILENT EPIDEMIC

Mireia Ribó Amezcua – Biology Degree 2014/2015

INTRODUCTION

Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder characterized by significant cognitive deficits, behaviour changes and a progressive loss of functional autonomy together with impaired judgement, decision-making and orientation.

There is a great need for biochemical markers (biomarkers) that could aid early diagnosis of AD and distinguish between AD, MCI and other dementia types. This project focuses on established biomarkers, those that have been evaluated in several studies by different research groups.

PATHOGENESIS

Hallmarks

The major pathological hallmarks of the disease are the loss and the degeneration of neurons and synapses due to brain amyloid plaques and intraneuronal neurofibrillary tangles (NFTs).

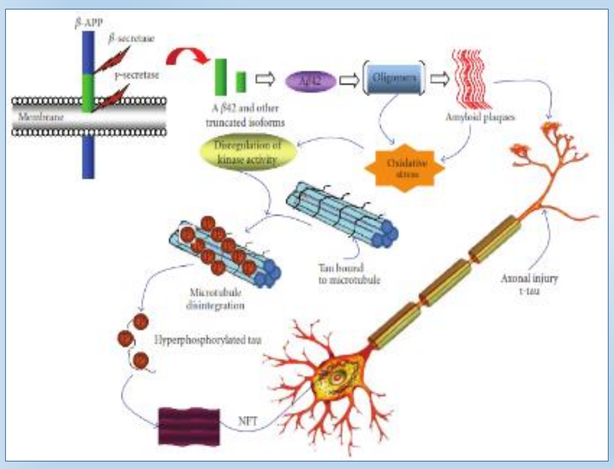


Fig 1. Pathological cascades and biomarkers of AD. [1]

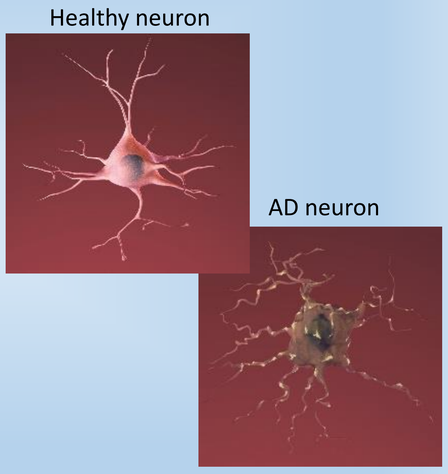
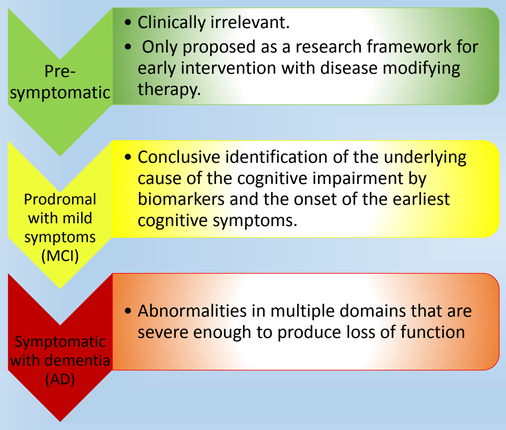
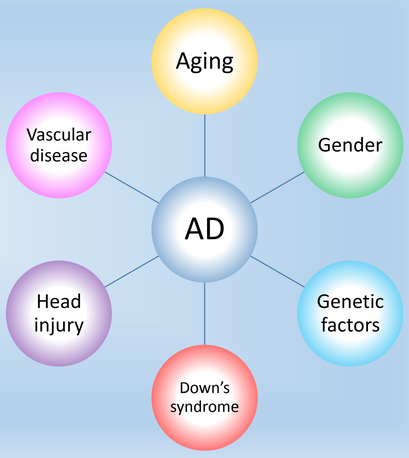


Fig 2. Aspect of a healthy and an AD neuron. [2]

Stages



Risk factors



BIOMARKERS

A biomarker is a physiological, biochemical or anatomic parameter that measures specific hallmarks of disease-related pathological changes and guides clinical diagnosis and treatment. An ideal candidate biomarker for AD should reflect the neuronal and synaptic degeneration.

A diagnostic biomarker should be highly specific and it should predict the pathological processes precisely and it should also reflect the degree of response to treatment.

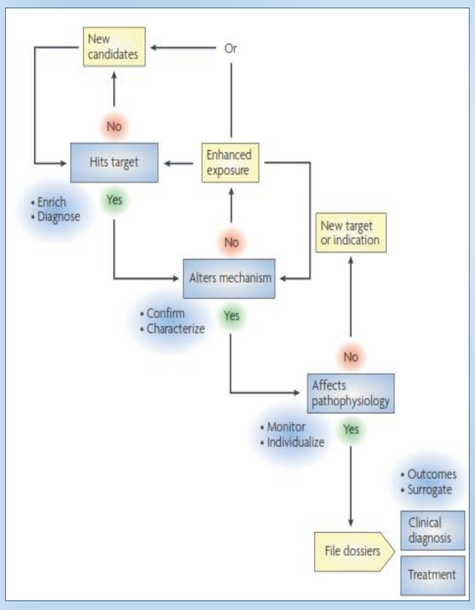


Fig 3. Validation of new candidates as biomarkers. [3]

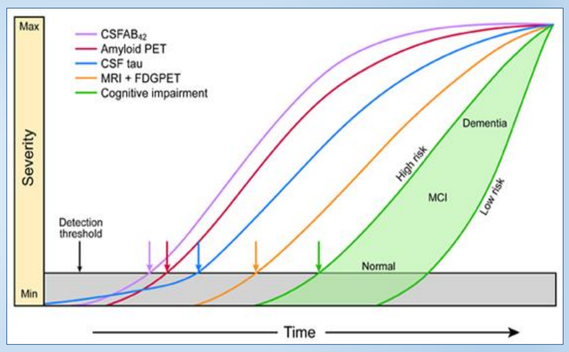


Fig 4. Model for biomarkers during the development of AD. [4]

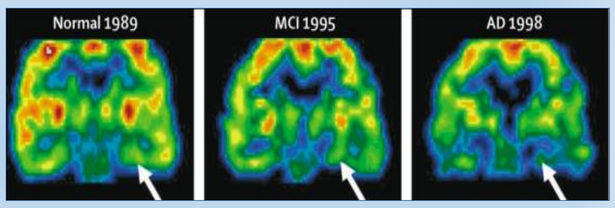


Fig 5. Longitudinal metabolic reductions on FDG-PET.[5]

CSF MARKERS OF AD

CSF Total-tau (T-tau)

Pathogenic events change a soluble protein to its insoluble aggregated form which makes up neurofibrillary tangles.

The concentration of tau protein in CSF reflects the intensity of neuronal degeneration in chronic neurodegenerative disorders.

CSF Phosphorylated-tau (P-tau)

In some chronic neurodegenerative disorders the protein undergoes hyperphosphorylated at many sites. As a result of this aberrant phosphorylation the protein loses its ability to act as a "glue" promoting the aggregation of tau with subsequent formation of NFTs.

CSF Aβ isoforms (Aβ40/Aβ42)

Aβ is a cleavage product from the amyloid precursor protein (APP) which is generated as a soluble protein during normal cellular metabolism and is secreted to CSF.

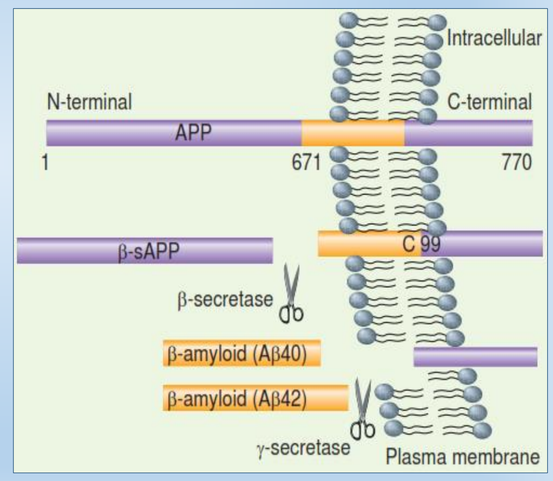


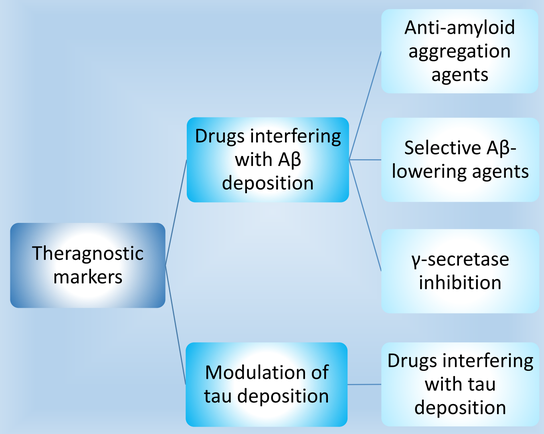
Fig 6. Schematic drawing of Aβ isoforms formation. [6]

USE OF CSF BIOMARKERS IN THE DIAGNOSIS

	T-tau	P-tau	Aβ42	Aβ40	Aβ42/Aβ40	T-tau/Aβ42 P-tau/Aβ42
AD	Marked increase	Marked increase	Marked decrease	No difference	Marked decrease	Increase
Normal aging	Normal	Normal	Normal			
Depression	Normal	Normal	Normal			
Alcoholic dementia	Normal	Normal	Normal			
FTD	Mild increase	Normal / mild increase	Mild decrease			
LBD	Mild increase	Normal	Mild decrease			
PD	Normal	Normal	Normal			
CJD	Very marked increase	Normal	Normal / marked decrease			
VAD	Increase	Normal	Normal / mild increase			
Acute stroke	Increase	Normal	Normal			
Progressive supranuclear palsy	Normal		Normal			
Amyotrophic lateral sclerosis		Normal	Normal			
Multiple system atrophy			decrease			

Table 1. CSF biomarkers in AD and other dementias diagnosis.

CSF BIOMARKERS IN AD TREATMENT



FUTURE PERSPECTIVES

CSF Aβ42 and CSF tau have stood the test of time being potential predictors of cognitive decline and future dementia.

The most efficient AD treatment may be a multi-modal drug such *Cerebrolysin* (CBL), CBL is a brain derived peptide preparation purified from pig brains.

Collaborations between geriatricians, neuroimaging specialists, neuropsychiatrists and molecular and cellular neurobiologists are being promoted.

CONCLUSIONS

- Biomarkers increase the diagnosis accuracy.
- Further discovery and validation of CSF biomarkers is essential to improve early diagnosis and accelerate the development of new therapies.
- There are three main uses of biomarkers in clinical trials:
  - As diagnostic tools to exclude between AD dementia, MCI due to normal aging and other dementias.
  - To identify and monitor the biochemical effect of a drug to facilitate its development.
  - To allow early and specific detection of side effects of the drug.
- Early diagnosis can be thought of as an opportunity for patients to plan for future.

REFERENCES

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