**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).

**Stages**

- Clinically innocent
- Mildly engaged as a research framework for early intervention with disease modifying therapies
- Conclusive identification of the underlying cause of the cognitive impairment by biomarkers and the onset of the earliest cognitive symptoms
- Absence or changes in multiple domains that are severe enough to produce loss of function

**Risk factors**

- Aging
- Gender
- Genetic factors
- Vascular disease
- Head injury

**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.

**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 hyperphosphorylation 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 AB 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.

**USE OF CSF BIOMARKERS IN THE DIAGNOSIS**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>T-tau</th>
<th>P-tau</th>
<th>AB40</th>
<th>AB42</th>
<th>AB40/42</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Increase</td>
</tr>
<tr>
<td>Depression</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Absolout</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Aβ</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>PIB</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CERBL</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>VAD</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Acetyl choline</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Progressive cognitive decline</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Neuronal loss</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**CSF BIOMARKERS IN AD TREATMENT**

- **Anti-amyloid aggregation agents**
- **Anti-Aβ lowering agents**
- **Anti-Aβ oxidation**
- **Drugs interfering with tau deposition**
- **Drugs interfering with Aβ deposition**
- **Modulation of tau deposition**
- **Selective Aβ lowering agents**

**FUTURE PERSPECTIVES**

- 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**