Marking the Markers of Alzheimer’s: Too good to diagnose, too bad to use?

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One of the most important neurodegenerative diseases of our time is Alzheimer’s disease, which mainly affects the elderly population. The accumulation of β-amyloid and tau protein in the brain tissue is the most characteristic pathomechanical event of the disease, later causing neuronal cell death. Setting up an accurate diagnosis of Alzheimer’s disease has essentially changed recently, since besides psychometry, neurochemical and neuroimaging examinations are also gaining greater importance in the clinical routine. Thanks to the widening of diagnostic methods, in the future the disease could be recognised even during the preclinical phase. The most remarkable source of brain-derived compounds is the cerebrospinal fluid. Although obtaining cerebrospinal fluid is greatly unpleasant, it poses a low risk and is frequently used as part of the diagnostic procedure. The assay of cerebrospinal fluid means the identification of the level of β-amyloid(1-42), tau and phospho-tau and their ratio, but to get more specific and sensitive investigations there is intensive research work both on the utility of their combination and on finding even more specific biomarkers. This review gives a summary of the biomarkers that are being used and being researched for the diagnostic tests of both familial and sporadic forms of Alzheimer’s disease. Other notable sources of neurochemical compounds are the serum and the plasma, however, the identification of their biomarkers is under preclinical examinations. Unfortunately neither the validation of these markers nor the consistent acceptance of the experimental results is possible due to the wide range of protocols in international research. The importance of biomarkers in the development of potential drug candidates is also discussed.

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Keywords: Alzheimer’s disease, β-amyloid, tau protein, biomarker, cerebrospinal fluid, diagnostic tool

WHY BIOMARKERS?

It is claimed that biomarkers are specifically proven indicator molecules of biological and pathological processes, and their level shows notable changes as a pharmacological response. The ideal biomarker of Alzheimer’s disease (AD) was defined in 1998 by the Ronald and Nancy Reagan Research Institute of the Alzheimer’s Association and the National Institute on Aging Working Group as "it should detect the fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases, and it should have a sensitivity of >80% for detecting AD and a specificity of >80% for distinguishing from other dementias; it should be reliable, non-invasive; simple to perform and inexpensive" (Rosenmann, 2011).

Currently the diagnosis of AD is based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) or the National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria, but setting up the accurate diagnosis has some limitations, because the early psychological symptoms are very similar to the symptoms of frontotemporal dementia, Parkinson’s disease, diffuse Lewy body disease, Creutzfeldt-Jacob disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (de Rino et al., 2011). Distinguishing AD from other forms of dementia includes various types of examinations, such as medical history, physical examination, neurophysiological elucidation, laboratory tests and neuroimaging tests.
Since the available treatments have the greatest benefits at the early stage of the disease, our current aim is to establish the diagnosis of AD before the memory decline reaches the level of dementia. There are new, multidisciplinary diagnostic criteria compiled by Dubois et al. (2009; 2010), based on various imaging and laboratory investigations. As for the new criteria, to recognize AD minimum one of the minor criteria should be fulfilled in addition to the major criterion. The major criterion is the presence of memory impairment, and the minor ones are medial temporal atrophy, pathological sites on neuroimaging of positron emission tomography (PET) and abnormal cerebrospinal fluid (CSF) markers. Abnormal CSF markers include elevated tau and phospho-tau levels and reduced amyloid level.

One of the greatest advantages of CSF examination is that it is the direct environment of the brain, consequently it contains markers of the chemical changes occurring there. Despite the fact that biomarkers for AD are known, diagnostic procedures accurate enough to screen for presymptomatic patients have not been developed yet (Mattsson et al., 2009a, Mattsson et al., 2012). Distinguishing early or preclinical AD from other dementias has remained challenging until today, even in specialized dementia centres. However, there are several ongoing studies to identify and validate novel biomarkers to meet this urgent need. Fagan & Holzman (2010) summarized why more useful and reliable biomarkers have not been found:

• the identification of biomarkers strongly depends on the accurate diagnosis of the patient
• the golden standard of confirming AD is post-mortem histological analysis
• to draw up an adequate healthy control group (age and gender matched) is extremely difficult
• limited number of CSF samples [lack of adjustment according to age, gender, ethnicity and apolipoprotein E (APO E4) genotype]
• there is no standard protocol of sample collection, preparation and analysis for laboratories
• misinformation of patients results in enrolment difficulties in studies

“CORE BIOMARKERS” IN CONNECTION WITH PATOMECHANISM

The “core biomarkers” of AD include β-amyloid 1-42 (Aβ(1-42)), tau and phospho-tau (P-tau). Aβ42 is involved in amyloid pathology and the formation of senile plaques. Tau and P-tau are in correlation with neurofibrillary tangles (Ballard et al., 2011). As for the amyloid hypothesis, altered amyloid processing causes amyloid burden in the brain tissue, and it may cause dementia due to cell death (Struble et al., 2010). Amyloid precursor protein (APP) is cleaved by three types of protease enzymes, α-, β- and γ-secretases. Two of them (β and γ) are constitutively active and they are involved in the amyloidogenic pathway. If APP is cleaved by β-secretase, the level of the large part of ectodomain (APPSβ) will increase; if it is cleaved by γ-secretase, the level of Aβ(1-40) or Aβ(1-42) peptide will increase. These truncated peptides may accumulate and form pathological senile plaques (Fnder, 2011). β-secretase 1 is a promising drug target, because its inhibition can reduce the level of APPsβ, Aβ(1-40) or Aβ(1-42) (Haass et al., 2012). Tau protein is a soluble microtubule-associated protein, and if it is hyperphosphorylated, it will form insoluble tangles (Meraz-Rios et al., 2010). Many phosphokinases are involved in the pathological hyperphosphorylation of tau filaments, for example glycogen syntase kinase (GSK3β), cyclin-dependent kinase 5, extracellular-related kinase 1/2 (ERK1/2) and dual specificity tyrosine-phosphorylation-regulated kinase1A (Lee et al., 2011).

CURRENT STATUS OF DIAGNOSTICAL BIOMARKERS OF FAMILIAL ALZHEIMER’S DISEASE

According to international databases, approximately 1–6% of all AD cases have the familial form with the development of the diseases between 30 to 65 years of age. Almost 60% of them have multiple cases of AD in the family, and nearly 13% are inherited in the autosomal dominant form of the illness (at least 3 generations are affected) (Campion et al., 1999). Early onset familial AD (EAOFAD) is caused by the mutations of presenilin-1 (PSEN1) or presenilin-2 (PSEN2) or (APP) (Bekris et al., 2010). In presymptomatic patients carrying some of these mutations the development of AD can be predicted with 100% certainty (Ringman et al., 2012). There are several advantages of examining these patients to find new biomarkers.

• They are more homogenous, so a smaller cohort size is needed.
• They are younger, thus they have fewer age-dependent neurologic and somatic changes.

On the other hand, the disadvantages of these examinations are that the pathogenesis of EAOFAD is in connection with the overproduction of Aβ(1-42)
instead of the decline of Aβ(1-42) degradation, which is the main pathomechanism in late-onset, sporadic AD (Bekris et al., 2012; Ringman et al., 2012).

Table 1 presents specifications of the three most important EAOFAD mutations, which are also used in the diagnosis (Bettens et al., 2010).

**CURRENT STATUS OF DIAGNOSTICAL BIOMARKERS OF LATE ONSET, SPORADIC ALZHEIMER’S DISEASE**

**Sensitivity and specificity of CSF biomarkers in recognising AD**

NINCDS-ARDA criteria show 80% sensitivity and much lower specificity in recognising AD, while an ideal marker should have >85% sensitivity and >75% specificity with a standardized protocol, according to the National Institute on Aging (Knopman et al., 2001). Early diagnosis is absolutely necessary to delay memory loss with the availability of new, disease-modifying drugs on the market in the future. The prediction of mild cognitive impairment (MCI) switching to AD based on the changed level of a single marker has a specificity and sensitivity lower than 50% (Brandt et al., 2008). When we use the internationally validated combination of the three biomarkers to diagnose AD, the specificity and sensitivity will be much higher than 80% (Blennow et al., 2010). Table 2 shows the values of CSF biomarkers obtained from AD patients and control subjects (Humpel, 2011). Welge et al. (2009) used the combination with a sensitivity and specificity of 88%. Bibl et al. (2008) found that the oxygenated form of Aβ(1-40) was elevated in the CSF of AD patients compared to vascular dementia patients and controls. As huge variations in findings may be experienced in the research centers, Mattsson et al. (2009b) published the results of a multicentered study, concluding that the ratio of Aβ(1-42)/tau and Aβ(1-42)/P-tau may predict the conversion of MCI to AD with 83% sensitivity and 72% specificity.

Another large international study by cNEUPRO (involving 14 academic research partners) investigated new biomarkers and tried to unify sample handling protocols (Spitzer et al., 2010). They examined sAPPα, sAPPβ, total tau and Aβ(1-42) levels of MCI and AD

| Table 1 | The specifications of the three most important mutations of EAOFAD |
| --- | --- | --- |
| **Prevalence of all EAOFAD** | 10% to 15% | 18% to 50% | Rare |
| **Mutation** | 32 (in 80 families) | 178 (in 393 families) | 14 (in 23 families) |
| **Age of development** | mid 40s-50s | as early as 30s | 45-88 years |
| **Localization** | 21q21 | 14q24.2 | 1q42.13 |
| **Protein** | APP695 | presenilin 1 (467aa) | presenilin 2 (448aa) |
| **Alternative splicing** | APP714, APP751, APP770, APP563 | not identified | tissue-specific |
| **Function** | primary function is not known | impact on regulation of synapse formation processed in the endosomal-lysosomal pathway implicated in mitochondrial dysfunction | PSEN1, nicastrin, Aph-1, PSEN enhancer 2 are required for the stability and activity of γ-secretase complex | component of γ-secretase |
| **Changes in levels of markers** | increased Aβ42 level relative to levels of other Aβ isoforms | relative increase in the ratio of Aβ to Aβ40 peptides | relative increase in the ratio of Aβ to Aβ40 peptides |
| **Reasons** | increasing Aβ42 | decreased Aβ40 | combination of them |
| | decreasing Aβ40 | increasing Aβ42 while decreasing Aβ40 | combination of them |
patients with high sensitivity. To further enhance the specificity and sensitivity more biomarkers should be used. The researchers of cNEUPRO identified other markers not related to APP processing. They found that the level of ERK1/2 is responsible for the elevation oftau hyperphosphorylation (Klafki et al., 2009). The level of glial fibrillary acidic protein, a marker of astrogliosis did not increase significantly (Jesse et al., 2009). The level of 3-nitrotyrosine, the marker of nitrosative stress, was also higher compared to controls (Korolainen & Pirttilä, 2009). Surprisingly, they did not find any change in total carbonylation, a marker of oxidative stress, which is one of the initial events of AD (Ryberg et al., 2004). They found that the level of ubiquitin (a small molecule related to protein degradation) also increased, however, it was not specific in AD but characteristic of all dementias examined (Blennow et al., 1994). The level of s100 calcium binding protein, an astroglial marker, also increased not only in the CSF but in the serum as well (Jesse et al., 2009).

Besides biochemical markers, neuroimaging studies like PET or MRI investigations are also available, and by putting various data together we may get a much clearer picture of the patient’s status (de Leon et al., 2004). As for De Souza et al. (2011), hippocampus atrophy significantly correlated with the altered level of P-tau, but the rate of atrophy did not have any implications for the Aβ level. Vos et al. (2011) showed that the altered Aβ(1-42)/P-tau ratio may also predict a reduction in hippocampal volume, but the cutoff values should be validated in all of these cases.

### Biomarkers in blood

Although the CSF is a really good source of new biomarkers, its utility in clinical routine is low, since invasive procedures may have various side-effects. That is why serum and plasma are getting more important in identifying new biomarkers (de Souza et al., 2011). Obtaining blood samples is really easy and poses minimal risks, but the standardisation of the measured difference and the replicability of results are quite problematic since the proteom of blood may be modified by comorbid diseases including obesity (Costa et al., 2011), diabetes (Hong & Lee, 1997) or metabolic syndrome (Schönknecht et al., 2002).

Just as in the case of CSF, specificity and sensitivity for the blood markers are as high as 71-99% and 91% if we use them in combination to follow the progression of AD (Ait-Ghezala et al., 2008). The altered level of tau has the most predictive value, however, measuring tau in blood samples is very difficult, consequently researchers focus on the change of Aβ. Although the protein extract of CSF is 200 times lower, it contains 10 times more Aβ than plasma (Song et al., 2009; Ewers et al., 2011). As we know, the circulating Aβ is not derived exclusively from the brain tissue, its level may also increase due to liver catabolism or renal excretion (Salin et al., 2008) and platelets can also secrete Aβ (Chen et al., 1995). Another problem is the circulating Aβ binding to albumin, so when it is depleted, most of the markers are lost (Maler et al., 2007). Gloeckner et al. (2008) found that the level of Aβ in blood, especially Aβ(1-42), decreased in patients with various types of dementia. The results of cNEUPRO showed the same Aβ(1-42)/Aβ(1-40) ratio, decreased in the early stage of AD, and this reduction may elevate the risk of rapidly developing dementia (Spitzer et al., 2010).

### Biomarkers in the focus of the research

Recent publications reported that CSF biomarkers beyond tau and Aβ supported the additional diagnostic information given by multiple antibody-based screens. Researchers found changes in the levels of some proteins involved in neurodegeneration, blood brain barrier, early role of inflammation, oxidative stress and synapse turnover (Ringman et al., 2012).

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AD (pg/ml)</th>
<th>Controls (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-42</td>
<td>&lt;500</td>
<td>794±20</td>
</tr>
<tr>
<td>Total tau</td>
<td>&gt;600</td>
<td>341±171</td>
</tr>
<tr>
<td>P-tau-181</td>
<td>&gt;60</td>
<td>23±2</td>
</tr>
</tbody>
</table>

**Table 2** Internationally validated biomarkers in CSF
Figure 1 Different types of biomarkers in the development of potential drug candidates

Table 3 shows a summary of the most important markers with their characteristics, which may help to distinguish late onset, sporadic AD from other dementias. Some CSF biomarkers shown in Table 3 can also be found in either plasma or serum. Potential blood markers could be APOE, clusterin, progranulin, cAMP-dependent protein kinase 1 subunit a1 (CDKα1) and a1-antitrypsin (Harold et al., 2009). Carriers of the APOE4 allele had a higher rate of nitration and glycation, which may also be indicators of the early stage of AD (Lambert et al., 2009). APOE and sortilin-related receptor L1 (SORL1) have shown lower specificity and sensitivity in diagnostic trials, but phosphatidylinositol-binding clathrin assembly protein (PICALM) and complement receptor 1 (CR1) were also associated with late onset, sporadic AD (Mayeux & Schupf, 2011). Bridging integrator 1 (BIN1) showed decrease but it was not significant (Harold et al., 2009).

The compounds of the molecular mechanism of AD may serve as potential disease-modifying drug targets. The studies of molecular biology of Aβ, tau protein, hyperphosphorylated tau, intracellular signal pathways, mitochondrial dysfunction, synaptic abnormalities and cell death have shown that pharmacologic manipulation of these pathological events could be an effective therapeutic strategy. According to the Food and Drug Administration (FDA), potential biomarkers should be integrated into clinical development (Good said & Frueh, 2007), because of their wide-ranged utility shown in Figure 1 (Cummings, 2011).

There have been only a few studies so far that aimed to show the effectiveness of compounds on CSF markers. In spite of the difficulties in examining CSF markers, few compounds were proven effective on CSF markers. Table 4 summarizes the list of examined drug candidates.
### Table 3  Potential biomarkers of late onset, sporadic AD

<table>
<thead>
<tr>
<th>gene</th>
<th>name</th>
<th>chromosome</th>
<th>SNP</th>
<th>function</th>
<th>shared biological pathways</th>
<th>presents in CSF</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICALM</td>
<td>phosphatidylinositol-</td>
<td>11</td>
<td>rs3851179</td>
<td>*clathrin mediated endocytosis  *VAMP2 trafficking  *functional integrity of synapses</td>
<td>*immune system response  *vesicle-mediated transport  *cellular membrane organisation</td>
<td>no data</td>
<td>Harold et al. (2009) Hu et al. (2011) Schjeide et al. (2011)</td>
</tr>
<tr>
<td>EXOC3L2</td>
<td>exocyst complex</td>
<td>19</td>
<td>rs597668</td>
<td>*vesicle targeting during exocytosis</td>
<td>*vesicle-mediated transport</td>
<td>no data</td>
<td>Morgan (2012)</td>
</tr>
<tr>
<td>BIN1</td>
<td>bridging integrator 1</td>
<td>2</td>
<td>rs744373</td>
<td>*member of BAR adapter family  *endocytosis  *intracellular endosome trafficking</td>
<td>*vesicle-mediated transport  *cellular membrane organisation</td>
<td>no data</td>
<td>Hu et al. (2011)</td>
</tr>
<tr>
<td>CR1</td>
<td>complement component receptor 1</td>
<td>1</td>
<td>rs3818361</td>
<td>*inhibition of classical and alternative pathway C3 and C5 convertases</td>
<td>*immune system response</td>
<td>no data</td>
<td>Lambert et al. (2009) Hu et al. (2011) Schjeide et al. (2011)</td>
</tr>
<tr>
<td>SORL1</td>
<td>receptor 1</td>
<td>11</td>
<td>rs2282649</td>
<td>*regulates trafficking and processing of APP</td>
<td>*vesicle-mediated transport  *cellular membrane organisation  *alcohol metabolic process  *lipid transport  *steroid metabolic process  *cholesterol metabolic process</td>
<td>yes</td>
<td>Kauwe et al. (2010) Reitz et al. (2011) Patel et al. (2011)</td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>SNP</td>
<td>Functions</td>
<td>Other Functions</td>
<td>Data Availability</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>--------</td>
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<td>---------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>TNK1</td>
<td>nonreceptor tyrosine kinase 1</td>
<td>rs1554948</td>
<td>*TNFα-induced apoptosis</td>
<td>apoptosis/cell death</td>
<td>no data</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>IL8</td>
<td>interleukin 8</td>
<td>rs4073</td>
<td>*proinflammatory cytokines</td>
<td></td>
<td>yes</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>LDLR</td>
<td>low density lipoprotein receptor</td>
<td>rs5930</td>
<td>*cholesterol metabolism</td>
<td>vesicle-mediated transport, cellular membrane organisation</td>
<td>yes</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>CST3</td>
<td>cystatin c</td>
<td>rs1064039</td>
<td>*inhibitor of lysosomal proteinases</td>
<td>protein degradation</td>
<td>yes</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>CHRN2</td>
<td>nAChR protein β2 subunit</td>
<td>rs4647198</td>
<td>*sleep, fatigue and arousal, anxiety and attention, pain perception, memory</td>
<td></td>
<td>no data</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>SORCS1</td>
<td>SorCS protein</td>
<td>rs600879</td>
<td>*member of Vsp10p family, binds to NGF propeptide</td>
<td>growing</td>
<td>no data</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
<td>rs7678</td>
<td>*induces the production of β-amyloid</td>
<td></td>
<td>yes</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
<tr>
<td>CCR3</td>
<td>chemokine receptor 2</td>
<td>rs1799864</td>
<td>*coupled with MAP-kinase pathway</td>
<td></td>
<td>no data</td>
<td>Morgan (2012)</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUDING REMARKS

In the last decade significant steps have been taken in the process of using promising biomarkers in the diagnosis of AD. The combined analysis of CSF Aβ and tau proteins increased the sensitivity and specificity, so that they became suitable for a more exact diagnosis of AD. However, the accurate pathophysiological role of new biomarkers in the development of AD remains to be clarified. The further progress of research requires application of biomarkers not only from CSF, but also from the blood.

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Abbreviations. AD Alzheimer’s disease
APO E4 Apolipoprotein E4 allele
APP amyloid precursor protein
Aβ amyloid beta protein
BIN1 bridging integrator 1

CDKα1 cAMP dependent protein kinase 1 subunit α1
CR1 complement receptor 1
CSF cerebrospinal fluid
EAOFAD early-onset familial Alzheimer’s disease
ERK 1/2 extracellular-related kinase 1/2
FDA Food and Drug Administration
GSK3β glycogen syntase kinase 3 beta
MCI mild cognitive impairment
NINCDS-ADRDA National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association
PET positron emission tomography
PICALM Phosphatidylinositol binding clathrin assembly protein
PSEN-1 presenilin 1
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Aβ amyloid beta protein
BIN1 bridging integrator 1

CDKα1 cAMP dependent protein kinase 1 subunit α1
CR1 complement receptor 1
CSF cerebrospinal fluid
EAOFAD early-onset familial Alzheimer’s disease
ERK 1/2 extracellular-related kinase 1/2
FDA Food and Drug Administration
GSK3β glycogen syntase kinase 3 beta
MCI mild cognitive impairment
NINCDS-ADRDA National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association
PET positron emission tomography
PICALM Phosphatidylinositol binding clathrin assembly protein
PSEN-1 presenilin 1
PSEN-2 presenilin 2
P-tau phosho-tau
SNP single nucleotid polymorphism
SORL1 sortilin-related receptor L1
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Marking the Markers of Alzheimer’s...


Az Alzheimer-kór markereinek jelentősége: diagnosztikai haszon, korlátozott alkalmazhatóság?


Kulcsszavak: Alzheimer-kór, β-amiloid, tau protein, biomarker, cerebrospinalis folyadék, diagnosztikai módszerek