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Cerebrospinal Fluid Based Diagnosis in Alzheimer's Disease

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1. Introduction

The Alzheimer's disease (AD) is the most frequent form of dementia worldwide. The major neuropathological hallmarks of the disease are loss of neurons and synapse, senile plaques (extracellular aggregates primarily composed of ß-amyloid; Aß) and neurofibrillary tangles (aggregates of hyperphosphorylated forms of the microtubule-associated tau protein) throughout cortical and limbic regions of the brain. The definite diagnosis still requires histopathological conformation according to the criteria, however, in recent years substantial progress has been made in the area of early biomarker development. The use of cerebrospinal fluid as a testing platform is very promising because the CSF protein composition can reflect the pathological processes of the brain and because it is easily accessible by a lumbar puncture. Some proteins and peptides such as ß-amyloid 1-42 (Aβ1-42), ß-amyloid 1-40 (Aβ1-40), total tau (tau) and hyperphosphorylated tau (p-tau) have been reported to meet the criteria for a biomarker. Another series of publications reported transthyretin, isoprostane, BACE1 activity and other proteins and enzymes as a potential biomarkers in AD. Whereas the biomarkers mentioned first have been studied extensively and were suggested to be included into clinical AD criteria, less information is available on the others. This review will focus on the importance of CSF based biomarkers in AD, covers the data available from the literature and highlights their role in the differential diagnosis of dementia.

2. Why to use CSF as a testing platform in dementia? – Neuroanatomy driven approach

Cerebrospinal fluid (CSF) is the main component of the brain extracellular space and participates in the exchange of many biochemical products in the central nervous system (CNS). Consequently, CSF contains a dynamic and complex mixture of proteins, which reflects physiological or pathological state of CNS. Changes in CSF proteome have been described in various neurodegenerative disorders. These alterations are discussed to reflect pathological changes in the brain and thus contribute to a better understanding of the pathophysiology of the underlying disorder (Gawinecka et al. 2010).
CSF analysis is extremely important to identify autoimmune disorders and inflammatory conditions, which might lead to dementia. Although changes are non-specific, like

pleocytosis, elevated protein content, increased albumin ratio and oligoclonal IgG synthesis within the central nervous system, their presence clearly differentiate inflammatory and autoimmune disease from neurodegenerative dementia.

3. How to select a biomarker – a concept-of-pathogenesis-driven approach

Several potential biomarkers in the CSF and blood have been already suggested. Some of them like Aβ1-42 and tau (and its phosphorylated form) became important biomarker in dementia diagnosis. The advantage of these biomarkers is their clear link to the pathological process and abnormalities, which are detected in the brain of AD patients (Aß and amyloid hypothesis as well as tau pathology).

3.1 Amyloid hypothesis

The amyloid core of senile or neuritic plaques contains an amyloid-like substance formed by peptides, which originate from proteolytic cleavage of the membrane-associated precursor protein (amyloid precursor protein, APP). They are generated by a sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretase. Aβs are small hydrophobic peptides existing mainly in two lengths: Aβ1-40 and Aβ1-42. It was initially assumed that the production of Aβs occurs only under pathological conditions. Later, Aβ was shown to be constitutively released from APP and secreted to blood and CSF. In AD, Aβ peptides are involved in pathological processes and accumulate in the brain as amyloid or senile plaques. There is clear correlation between Aβ levels in CSF and plaque depositions in the brain coupled with the concept of casual involvement of APP and Aβs in the pathogenesis of AD.
The concentration of Aβs is thought to reflect disease-associated changes and is widely applied as a diagnostic biomarker of AD (Gawinecka et al. 2010).
Table 1 gives an overview of publications related to this topic from past 5 years. The vast majority of publications is related to the detection of abnormal levels of Aß1-42 in AD as compared to other dementia, however, some data are also available for Aß1-40. Recently, a ratio between both peptides has been suggested as a potential biomarker in AD (Table 2). Aß1-42 level is decreased in patients with AD, but might also decrease in other dementia, too. Test sensitivity for Aß1-42 alone is given from 60 to 96%, depending on the design of the study.
In MCI, Aß42 level is lower in patients with a subsequent AD diagnosis (De Meyer et al. 2010; Diniz et al. 2008; Mattsson et al. 2009; Stefani et al. 2006), which leads to the conclusion that this parameter might also serve as an preclinical (potential predictive?) biomarker (Stefani et al. 2006) for cognitive decline.
Aß42 level is decreased in other conditions, including prion diseases, Parkinson's disease (Siderowf et al. 2010) and DLB. In PD, decreased levels correlate well with cognitive decline, in contrast to tau/p-tau ratio (see below) (Siderowf et al. 2010). According to some studies which used patients with non-AD dementia as controls, this marker is highly sensitive for detection of dementia, but it seems that it does not allow to discriminate between various dementia types because of limited specificity (Formichi et al. 2006; Gloeckner et al. 2008).
One approach to improve test sensitivity and specificity was to calculate an Aß42/40 ratio, which is significantly decreased in AD patients. It seems also to discriminate between different dementia including AD and non-AD (vascular, mixed, FTD, alcohol toxic and controls) (Lewczuk et al. 2004). However, the significance of this finding has still to be proven on higher numbers of patients in a prospective study.

	Patients (n)	Sensitivity (%)	Specificity (%)	Reference
Aß1-42	MCI -> AD (422) controls (429)	68	93	(Diniz et al. 2008)
Aß1-42	PD (109) AD (20) controls (36)	n.a.		(Alves et al. 2010)
Aß1-42	AD (131) controls (72)	92	89	(Sunderland et al. 2003)
Aß1-42	PD (45)	n.a.		(Siderowf et al. 2010)
Aß1-42	MCI	n.a.		(Okonkwo et al. 2011)
Aß1-42	AD (33) ARCD* (20) controls (50)	70-84	80-85	(Kapaki et al. 2005)
Aß1-42	MCI (750) AD (529) controls (304)	79	65	(Mattsson et al. 2009)
Aß1-42	autoptic AD (68) MCI (57)	94	n.a.	(De Meyer et al. 2010)
Aß1-42	AD	>85	>85	(Slats et al. 2010)
Aß1-42	mild AD (100) MCI (196) controls (114)	96	77	(Shaw et al. 2009)
Aß1-40	AD (82) DLB (44) controls (71)	AD vs controls 97	AD vs controls 83	(Mollenhauer et al. 2011)
Aß1-40	DLB (21) AD (23) PDD (21)	81	71	(Bibl et al. 2006a)
Aß1-40 Aß1-42	AD (23) NPH (13) DLB (23) CJD (18) DLB (23) FTD (10) controls (19)	61	78	(Gloeckner et al. 2008)

*ARCD = alcohol related cognitive disorder

Table 1. Aß40 and Aß42 in dementia diagnosis

	Diagnosis (n)	Sensitivity (%)	Specificity (%)	Reference
Aß1-42/ Aß1-40	MCI (65)	86	60	(Brys et al. 2009)
Aß1-42/ Aß1-40	AD (22)	95	88	(Lewczuk et al. 2004)
Aß1-42/ Aß1-40	AD (157)	59	88	(Shoji and Kanai 2001)
Aß1-42/ Aß1-40	AD (69)			(Spies et al. 2010)
Aß1-42/ Aß1-40	AD (18)	AD vs control: 100 AD vs DLB: 100 AD vs both groups: 100	AD vs control: 93 AD vs DLB: 68 AD vs both groups: 77	(Bibl et al. 2006b)
Aß1-42/ Aß1-40	AD (109)	AD vs control: 79 AD vs all: 70	AD vs control: 71 AD vs all: 71	(Brettschneider et al. 2006)

Table 2. Aß1-42/ Aß1-40 ratio as potential biomarkers in AD

3.2 Tau hypothesis

Intracellular neurofibrillary tangles (NFT), which are neuronal inclusions consisting of abnormal cytoskeletal elements of hyperphosphorylated tau protein are another characteristic pathological feature of AD. These tangles are found throughout the neocortex, in the nucleus basalis Meynert, thalamus, and in the mammillary bodies. Tau protein is a microtubule-associated protein (MAP), which interacts with tubulin and promotes microtubule assembly and stability; it is also involved in neurogenesis, axonal maintenance and axonal transport. There are six different tau isoforms present in the human adult brain, which are generated by an alternative mRNA splicing from a single gene (Goedert et al. 1989). Tau is a phosphoprotein, with 79 putative serine or threonine phosphorylation sites on the longest tau isoform. The hyperphosphorylated tau has a reduced affinity for microtubules and reduced ability to promote their assembly (Lindwall and Cole 1984). In AD, tau detaches from microtubules and aggregates in paired helical filaments (PHFs). Tau isolated from these aggregates is found to be about 4 times more phoshorylated than tau isolated from nondemented individuals (Alonso et al. 2001; Kopke et al. 1993, Gawinecka and Zerr 2010).

The elevated CSF level of nonphosphorylated and phosphorylated tau is one of AD hallmarks (Andreasen et al. 1999; Arai et al. 1997; Galasko et al. 1997; Ishiguro et al. 1999; Itoh et al. 2001; Mecocci et al. 1998). Since the first description of this abnormality and availability of an ELISA test, extensive research has been conducted. Data on tau level in AD and other dementia are given in Table 3. Again, elevated levels can be observed in other conditions than AD too, the test sensitivity and specificity seems to be above 80% in majority of the cases (Table 3). However, it has to be kept in mind that tau levels increase in CSF with age and this physiological finding hast to be kept in mind when cut-off level are established (Figure 1). In pathological conditions, total tau levels in MCI patients indicate increased AD risk (Hertze et al. 2010; Mattsson et al. 2009; Pauwels et al. 2009) and increased level correlates well with disease severity (Buchhave et al. 2009; Stefani et al. 2006). Some studies even demonstrated that extremely high tau levels might be indicator of poor prognosis (Snider et al. 2009).

Patients (n)	Sensitivity (%)	Specificity (%)	Reference
MCI (166)	78	83	(Hertze et al. 2010)
AD (131)	92	89	(Sunderland et al. 2003)
AD, CJD, LBD, FTD, VD	73-91	74-98	(van Harten et al. 2011)
AD (33) ARCD* (20)	88-94	95-96	(Kapaki et al. 2005)
AD NPH	91-93	78-96	(Kapaki et al. 2007)
MCI (750) AD (529)	86	56	(Mattsson et al. 2009)
AD, other dementia, psychiatric (219)	88	80	(Ibach et al. 2006)
early AD (269) mild AD (468) late AD (495)	n.a.		(Stefani et al. 2006)
MCI -> AD	82	87	(Pauwels et al. 2009)
mild AD (100) MCI (192) autoptic AD (56) controls (114)	70	92	(Shaw et al. 2009)
MCI -> AD (422) controls (420)	68	93	(Diniz et al. 2008)
DLB (34) AD (31) other dementia (4)	85	95	(Kasuga et al. 2010)

*ARCD = alcohol related cognitive disorder

Table 3. Total tau level in cerebrospinal fluid in AD and other dementia

Regarding phosphorylated tau level in CSF, a recent metaanalysis on 51 publications from the area revealed that p-tau contributed to the separation of MCI from healthy individuals with a sensitivity of 80% and specificity of 84% (Mitchell 2009). CSF p-tau is a good diagnostic biomarker of AD too, with test sensitivity mostly >80% (see Table 4). MCI patients with low Aß1-42 and high p-tau levels are at a clear AD risk (Hertze et al. 2010). AD patients with higher p-tau level have greater hippocampal atrophy, poorer neuropsychological test results and it is also indicator of disease progression (Henneman et al. 2009). Whereas p-tau levels indicate AD or development of AD with good accuracy, unfortunately, this biomarker is also less adequate in separating AD from other dementias (Mitchell 2009).

Due to these considerations, several studies tried to analyse the diagnostic potential of p-tau/total tau ratio. Some of them reported test sensitivity between 88-96% with a specificity of 60-100%. While its ratio is promising, again, it has to be analysed in a prospective setting since the numbers of analysed patients so far are too low for any definite conclusions (Buerger et al. 2006; Hu et al. 2002; Kapaki et al. 2007).

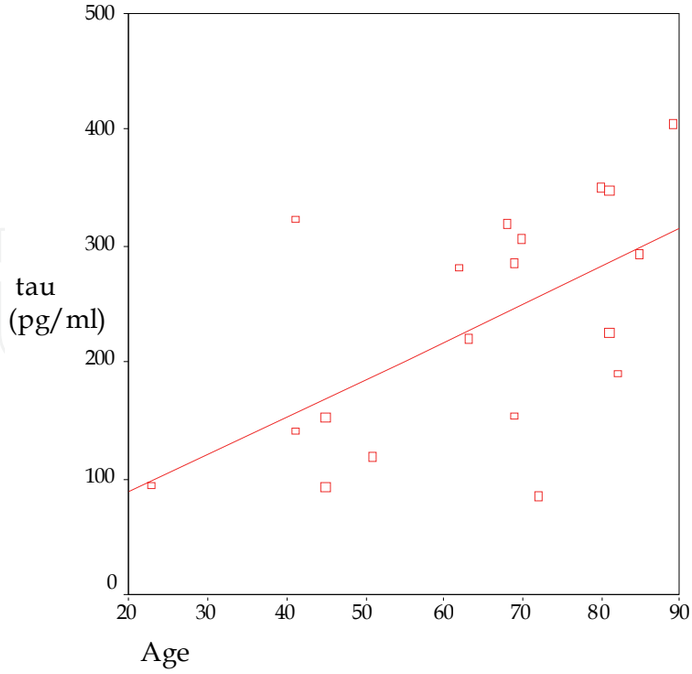

Fig. 1. Total tau level in cerebrospinal fluid stratified by age in healthy controls (Gloeckner et al. 2008)

	Patients (n)	Sensitivity (%)	Specificity (%)	Reference
p-tau	AD neurological controls (46)	>85	79-91	(Scheurich et al. 2010)
p-tau	AD (94) MCI (166) depression (29) controls (38)	>85	79-91	(Hertze et al. 2010)
p-tau	AD (49)	46	94	(Snider et al. 2009)
p-tau	AD (251) controls (122)	62	93	(Formichi et al. 2006)
p-tau	AD, CJD, LBD, FTD, vascular dementia	79-88	78-83	(van Harten et al. 2011)
p-tau	AD, NPH, controls	89	87	(Kapaki et al. 2007)
p-tau	AD, other dementia, psychiatric, controls	89	87	(Ibach et al. 2006)
p-tau	AD (31) MCI (25)	72-81	78-88	(Henneman et al. 2009)

	Patients (n)	Sensitivity (%)	Specificity (%)	Reference
p-tau	autoptic AD (68) MCI (57)	AD 94 MCI 100		(De Meyer et al. 2010)
p-tau	mild AD (100) MCI (196) autoptic AD (56) controls (114)	68	73	(Shaw et al. 2009)
p-tau	MCI (750) AD (529) Controls (304)	84	47	(Mattsson et al. 2009)
p-tau/total tau	AD (52) controls (56) non AD (37) vascular dementia (46)	96	94	(Hu et al. 2002)
p-tau/total tau	AD (67) NPH (18) controls (72)	88-93	60-100	(Kapaki et al. 2007)
p-tau/total tau	AD (37) CJD (21) controls (10)	91	97	(Buerger et al. 2006)
p-tau/total tau	AD (71) FTD (18) CJD (20) controls (43)	ratio AD: 1,27 (mean) ratio FTD: 1,13 (mean) ratio CJD: 0,05 (mean) ratio controls: 1,7 (mean)		(Riemenschneider et al. 2003)
p-tau/total tau	CJD (21) AD (49) neurol. controls (164)	86	90	(Bahl et al. 2009)

Table 4. Phosphorylated tau level in cerebrospinal fluid in AD and other dementia

In general, many studies on Aß1-42, total tau level and its phosphorylated isoform have been performed. In most studies, the number of patients per group is limited and various criteria and diagnostic techniques have been applied. Of importance, a recent multicenter study demonstrated once again that CSF Aß1-42, total tau and p-tau identify incipient AD with good sensitivity and specificity, however, the data are less reliable than reported from single-center studies (Mattsson et al. 2009). Thus, improvements are necessary, with respect to standardisation protocols between centers, but also with respect to identification of further disease- specific biomarkers in biological fluids.

3.3 The role of ApoE

The presence of the apolipoprotein E allele is a well documented risk factor for AD (Lamb et al. 1998; Saunders et al. 1993) and is associated with a decreased age of clinical onset, with a higher stage of ß-amyloid deposition and neurofibrillary change formation, severe disease course, higher brain atrophy and a more rapid disease course (Ohm et al. 1999). The ApoE polymorphism includes three common alleles (ε2, ε3, ε4) at a single gene locus resulting in

six ApoE genotypes ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4, ε3/ε4. The ApoE ε4 allele is an established risk factor for AD (Saunders et al. 1993) and there is a large body of evidence for a role of ApoE in the pathogenesis of AD (Davidson et al. 2006; Varges et al. 2011).

CSF marker	Patients (n) [diagnosis confirmed]	Influence of ApoE ε4 allele	Reference
Aß1-42	82	dose-dependent reduction	(Galasko et al. 1998)
tau		heterozygous: elevation homozygous: reduction	
Aß1-42	50	dose-dependent reduction	(Riemenschneider et al. 2000)
Aß1-42	84	dose-dependent reduction	(Hulstaert et al. 1999)
Aß1-42	73	more reduced levels in ε4 carriers	(Smach et al. 2008)
tau		no influence	
Aß1-42	60	no influence	(Ewers et al. 2008)
Aß1-42	50	no influence	(Engelborghs et al. 2007)
tau		no influence	
tau	19	dose-dependent elevation	(Golombowski et al. 1997)
Aß1-42	121 [41 NP]	more reduced levels in ε4 carriers	(Tapiola et al. 2000)
tau		more elevated levels in ε4 carriers	
Aß1-42	563	more reduced levels in ε4 carriers	(Prince et al. 2004)
Aß1-42	150	more reduced levels in ε4 carriers	(Sunderland et al. 2004)

Table 5. Influence of the ApoE ε4 allele on CSF markers in AD (modified from Varges et al. 2011)

The ApoE ε4 allele status is important to be analysed in the context of CSF biomarker. Some studies report no association between ApoE ε4 allele and tau level, whereas others show higher tau level among ApoE ε4 carriers when compared to non-carriers among AD patients. The situation seems to be clearer for ß-amyloid 1-42: several studies report correlations between Aß1-42 levels and the ApoE ε4 allele (Table 5) (modified from Varges et al. 2011). Although the pathological links are not clearly identify at the moment, it is apparent that the ApoE genotype has to be taken into consideration.

4. Clinical criteria for AD

CSF biomarkers play an important role in clinical diagnosis and differential diagnosis of neurodegenerative dementia. A lot of research in this area has been already conducted. Recently, these markers which are associated with disease pathology in the brain namely Aß1-42 as a parameter of the amyloid cascade and tau and its phosphorylated isoforms have been suggested to be included into diagnostic criteria for AD. The typical AD signature comprises low CSF Aß1-42 levels and high total tau/p-tau level and it was suggested as a parameter of one of the supportive features at the same level as structural and functional brain imaging for probable AD diagnosis (Dubois et al. 2007).

5. Conclusions

The PubMed search on 31.1.2011 using keywords cerebrospinal fluid and Alzheimer reveals 2336 hits. Although not all are dealing directly with biomarker discovery and identification of novel proteins for diagnosis, they are linked to the topic and demonstrate once again the importance of the area. Adequate biomarker, which can be easily analysed in CSF and, even better, blood, will have a great potential for clinical and also preclinical diagnosis of the disease. In neurodegenerative disorders, we have to meet the problem of early disease diagnosis, because it is likely that neuroprotective and other pharmacological strategies will allow better treatment response in earlier disease stages.

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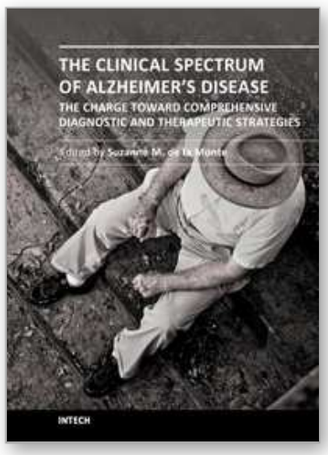

The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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