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11

Alzheimer's Diseases: Towards Biomarkers for an Early Diagnosis

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1. Introduction

Alzheimer's diseases (AD) are the most frequent dementias across the world and represent more than 60% of all neurodegenerative dementias including those with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD). Most neurodegenerative dementias are induced by aggregation of different brain proteins; they are nosologically grouped into a large pathological entity named proteinopathy. Prevalence of dementias is more than 20% in 85 years old aged population and linearly increases with the age (Ferri, Prince et al. 2005). The international impact of degenerative dementias across the world is estimated to touch more than 24 million patients with an incidence about 4.6 million new cases by year.
Diagnosis of AD is still based on the integration of clinical examination, neuropsychological data, radiological and biological analyses. The final diagnosis is established after neuropathological examination of brain and observation of typical cerebral failures, in consequence, the clinical diagnosis is "probable AD" when typical criteria are found and "possible AD" if atypical elements are present during clinical examination. Nevertheless, the clinical diagnosis performance for "probable AD" is relatively low with a sensitivity and a specificity of 80% and 70% respectively (Knopman, DeKosky et al. 2001). Because a consequent clinical overlap does exist between etiological AD and others causes of dementia, the clinical diagnosis specificity for a possible AD is less than 50%. Paraclinical analyses such as radiological and biological examinations tend to increase accuracy of differential diagnoses as well as diagnosis precocity for these patients.

2. How can we deal with the clinical diversity of Alzheimer's phenotypes?

AD is associated with a progressive disruption of the neuronal function and subsequent gradual deterioration in cognition and behaviour leading finally to the death (Khachaturian, 1985). The typical clinical beginning of AD is characterised by a progressive cognitive alteration affecting predominantly episodic memory. Other symptoms such as language deficit, visuoperceptive alterations or even dysexecutive syndromes appear during the course of the disease in relation to the progression of cerebral failures into the associative brain areas. Decrease in episodic memory is associated with radiological finding of obvious

medial temporal lobe atrophy during the first step of the disease progression (Scheltens, Fox et al. 2002). Effectively, this cerebral structure highly participates in the memory process; even more, neuropathological findings demonstrated the strong implication of typical protein depositions met in AD that occur during this medial temporal lobe atrophy (Burton, Barber et al. 2009). Nevertheless, this kind of atrophy can be met in other pathologies such as FTLD or DLB, without any cerebral pathological hallmark of AD (O'Brien, Paling et al. 2001; van de Pol, Hensel et al. 2006). Moreover, frequent clinical overlaps (Kertesz, McMonagle et al. 2005; Josephs, Petersen et al. 2006; Hort, O'Brien et al. 2010) as well as pathological co-occurrence (Merdes, Hansen et al. 2003; Amador-Ortiz, Lin et al. 2007; Schneider, Arvanitakis et al. 2009) between these 3 dementias can occur, resulting in a misleading clinical diagnosis during lifetime.

During the AD progression, other symptoms than the alteration of the episodic memory progressively appear, but they can also be clinically predominant at the first step of the disease. For example, a dysexecutive syndrome, concordant with a frontal atrophy, and then the first hypothesis of frontotemporal dementia (FTD) diagnosis can finally be an AD. As well, an aphasic clinical presentation associated with temporal cerebral areas atrophy, suggestive of primary progressive aphasia, can reveal an etiological AD. Other clinical presentations can occur in the first symptoms of AD, such as apraxic forms suggesting corticobasal degeneration (CBD) or even visual deficits associated with posterior cortical atrophy (PCA).

These focal presentations of AD are clinically difficult to distinguish from other previously adverted neurodegenerative dementias which typically begin with these kind of clinical features (Alladi, Xuereb et al. 2007). It is why there is a need to identify inside this spectrum focal presentations underlying AD as well as other pathologic processes such as FTLD or DLB.

3. Neuropathological hallmark and physiopathological pathways of AD

The two neuropathological hallmarks of AD are the deposition of extracellular amyloid plaques and accumulation of intracellular neurofibrillary tangles (NFT). The first ones are principally constituted by amyloid protein (Aß peptide), a product of proteolytic processing by secretases of the amyloid precursor protein named APP (Haass and Selkoe 1993), and the second involves phosphorylated tau protein (Masters, Simms et al. 1985; Braak and Braak 1991). Distributions of amyloid plaques and NFTs do not overlap in all anatomical regions suggesting a complex pathogenetic scenario.

Tau protein is a microtubule associated protein expressed abundantly in the neuronal axons that promotes assembly and stability of microtubules. 6 different isoforms of tau are present in the human brain, constituted of 352 to 441 amino acids and harbouring more than 70 phosphorylation sites (Buée, Bussiere et al. 2000; Lewczuk, Esselmann et al. 2004). Its physiological function is regulated by these phosphorylations (Johnson and Hartigan 1999). The abnormal hyperphosphorylation of tau proteins in AD brain reduces their biological activity and results in disintegration of the microtubules (Uversky, Winter et al. 1998). Moreover, this phenomenon induces conformational changes of tau protein and then permits its assembly in paired helical filaments (PHF), the major constituent of NFTs (Kidd 1963; Alonso, Zaidi et al. 2001). These PHF are highly phosphorylated since more than 30 phosphorylation sites were observed in PHF deriving from NFTs (Liu, Liang et al. 2006). The stereotypic development of tau pathology with NFTs is clearly correlated with clinical

impairment of memory, starting in the transentorhinal cortex to finally involve associative areas and the whole neocortical areas (Braak and Braak 1995; Berg, McKeel et al. 1998).
In an other scheme, Aß depositions neither correlate with a given clinical presentation and seem to begin in the neocortex before involving the neuronal projections of already involved areas (Arriagada, Growdon et al. 1992). These amyloid plaques are also encountered in asymptomatic aged peoples without AD (Wolf, Gearing et al. 1999). Furthermore, metabolic imaging and particularly positron emission tomography with ^{11}C-PIB (a compound that specifically stain amyloid plaques) demonstrate that these amyloid accumulations are observed in subjects without any cognitive alteration (Villemagne, Fodero-Tavoletti et al. 2008). Although numerous proteins are associated with amyloid deposits in AD (Buée, Hof et al. 1992; Uchihara, Duyckaerts et al. 1996; Burns, Noble et al. 2003), the major proteinaceous component is the 42 amino acid Aß peptide ($Aß_{42}$) which is the most hydrophobic form of Aß (Jarrett, Berger et al. 1993; Gravina, Ho et al. 1995). Nevertheless, it was recently demonstrated that aggregation into amyloid plaques may provide truncated forms of this peptide in the N-terminal ($Aß_{4-/5-/8-/9-42}$) during the first steps of the disease (Sergeant, Bombois et al. 2003; Vanderstichele, De Meyer et al. 2005). These truncated forms could represent more than 60% of all cerebral Aß forms (Sergeant, Bombois et al. 2003).
Interestingly, the symptomatology observed in AD (or other neurodegenerative dementia) seems not due to these deposits and symptoms could appear before protein aggregations (Moechars, Dewachter et al. 1999). Several *in vitro* studies demonstrated that the toxicity against neurons is related to oligomeric forms of proteins and that the consequence is cognitive alteration in animal models (Kirkitadze, Bitan et al. 2002; Cleary, Walsh et al. 2005; Lesne, Koh et al. 2006). For AD, soluble oligomeric forms have been described, aggregating later on into amyloid plaques and it was suggested that effects of these oligomeric species could induce the first toxic events of amyloidopathy (Simmons, May et al. 1994; Kirkitadze, Condron et al. 2001; Walsh and Selkoe 2007).
Some controversy still remains on the course and distribution pattern of the Aß and tau pathologies. Some authors suggest that amyloid dysfunction is the pathogenic key leading to AD pathogenesis. This hypothesis was developed as "amyloid cascade" and the Aß metabolism dysfunction may initiate others pathologic events such as tau protein hyperphosphorylation, synaptic loss or neuroinflammation (Hardy and Higgins 1992; Hardy and Selkoe 2002). Nevertheless this hypothesis is still discussed and does not support all the AD physiopathology.
During the preclinical phase of AD, the neuronal degeneration proceeds and at a certain, yet unidentified, threshold the first symptoms appear. Otherwise, it seems that first cerebral failures begin several decades before symptoms appear (Braak and Braak 1997). Nevertheless the early and differential diagnosis remains difficult and reliable proof of AD process is difficult to obtain. An early and reliable diagnosis in order to establish appropriate drug treatment is essential to decrease symptomatology. Moreover, since research is conducted to develop treatments that could retard or stop cerebral failure progression, we need to improve AD diagnosis to identify this process before brain damages are too significant.

4. Which CSF biochemical markers might allow us to detect Alzheimer's diseases?

It is convincing that we could identify these neurodegenerative processes early during the course of AD with the help of paraclinical means such as functional imaging or use of biological markers.

An ideal biomarker for Alzheimer disease would have to meet three specific criteria:

- To be a quantitative and objective measure providing an indication of disease risk and rate of disease progression long before onset of symptoms
- To be reliable, reproducible and inexpensive to measure
- To be measurable in an easily accessible tissue of the patient.

During the past years, great efforts have been made to identify reliable biomarkers for AD in body fluids of patients that are suitable for minimal invasive early diagnosis of AD, mainly cerebrospinal fluid (CSF) and blood. Cerebrospinal fluid (CSF) closely reflects the composition of the brain extracellular space and is likely to have the highest yield in biomarkers (Wiltfang, Lewczuk et al. 2005). Furthermore, CSF biological modifications seem to appear before first anatomical modifications seen on magnetic resonance imaging (Schoonenboom, van der Flier et al. 2008). Nevertheless, lumbar puncture is relatively invasive even if complications appear in less than 2% of patients (Blennow, Wallin et al. 1993). So research strives for a less invasive biological diagnosis with development of blood markers for AD.

A high number of CSF brain-derived proteins have been investigated as potential markers for AD. The more promising are proteins resulting from cerebral failures meet in AD: tau proteins with total tau (T-tau), phosphorylated tau proteins (P-tau) and $A\beta_{42}$ which are solubles in CSF. Moreover, AD diagnosis criteria were reviewed for research in 2007 and these 3 biomarkers were included (Dubois, Feldman et al. 2007).

- Aß peptide

In AD patients the CSF concentration of soluble $A\beta_{42}$ decreases and it has been suggested that this may be due to the preferential deposition of Aß peptides into cerebral amyloid plaques reflecting parenchymental sequestration with lower levels diffusing to CSF (Strozyk, Blennow et al. 2003; Wiltfang, Lewczuk et al. 2005; Fagan, Mintun et al. 2006). Interestingly, this CSF concentration is linked to ApoE genotype which was identified as a susceptibility gene to develop AD: patients with homozygote genotype of ApoE4 have lower $A\beta_{42}$ CSF concentration (Galasko, Chang et al. 1998). Nevertheless, a CSF $A\beta_{42}$ concentration decrease is also observed in other pathologies such as DLB or even Creutzfeldt Jakob disease (CJD), pathology with sometimes cerebral Aß deposits (Andreasen, Minthon et al. 2001; Wiltfang, Esselmann et al. 2003; Mollenhauer, Bibl et al. 2005). These results are in accordance with pathological overlaps observed in these diseases (Schneider, Arvanitakis et al. 2007; Schneider, Arvanitakis et al. 2009; Kovacs, Seguin et al. 2011). Nonetheless, measurement of CSF $A\beta_{42}$ concentration could differentiate AD patients from subjects without any neurodegenerative process with sensitivity and specificity of 86% and about 90% respectively (Blennow 2004). ELISA measurement of CSF $A\beta_{42}$ reveals values comprised between 600 and 1230 pg/mL in normal subjects and 260 and 500 pg/mL in AD patients (Riemenschneider, Lautenschlager et al. 2002; Riemenschneider, Wagenpfeil et al. 2002; Lewczuk, Esselmann et al. 2004).

Several works postulate that Aß aggregates will be more reliable biomarkers than soluble Aß forms, as the aggregates are directly involved in the pathologic events of AD. Monoclonal and polyclonal antibodies specific to soluble oligomeric forms of Aß were developed (Kayed et al, 2010, Ying Z et al, 2009) and used to demonstrate that these oligomers are significantly more abundant in the soluble brain extracts of AD patients (Meli et al., 2009) suggesting that diffusible oligomers would also appear in the CSF. Sensitive techniques were applied to detect CSF Aß oligomers in AD patients (Pitschke, Prior et al. 1998). Recently, a study showed that levels of CSF aggregated Aß forms are higher in AD

patients than in patients with other neurological disorders without neurodegenerative processes (Fukumoto, Tokuda et al. 2010). Moreover, the CSF oligomer concentrations correlate with cognitive alteration in AD. While detection of these CSF oligomeric forms appears to have a considerable diagnosis interest, low concentrations of these pathologic forms do not allow considering this assay routinely?.

In parallel to $A\beta_{42}$, numerous N- and C- terminal truncated forms have been identified in clinical samples from AD patients (Gabelle, Roche et al. 2010). Most abundant Aß peptides in CSF are, in increasing order concentrations, $A\beta_{40}$, $A\beta_{38}$ and $A\beta_{42}$ (Wiltfang, Esselmann et al. 2002). Concentration measurements of the major form $A\beta_{40}$ in CSF are greatly instructive because they well reflect total amount of Aß peptide release in this biological fluid (Wiltfang, Esselmann et al. 2007). By the APP metabolism and the amyloidogenic way, strong cerebral producers of Aß peptides have higher Aß CSF levels (and thus also $A\beta_{42}$) than weak producers. Instauration of $A\beta_{40}$ CSF measurements associated with $A\beta_{42}$ could permit to rectify mistakes in interpretation of biological results with CSF $A\beta_{42}$ levels alone.

In addition to CSF $A\beta_{40}$, $A\beta_{38}$ and $A\beta_{42}$, other forms of this peptide are produced by physiological regulation of γ-secretase (Gabelle, Roche et al. 2010). Numerous both cerebral and CSF truncated forms of Aß peptide were identified in AD and MCI patients using immunobloting or mass spectrometry analyses (such as SELDI-TOF) (Lewczuk, Esselmann et al. 2003; Sergeant, Bombois et al. 2003; Vanderstichele, De Meyer et al. 2005). Part of research concentrates on identification of novel Aß truncated forms that could allow better predictive power and specificity of biological diagnosis (Bibl, Mollenhauer et al. 2007). Indeed, new $A\beta_{13}$, $A\beta_{14}$ or else $A\beta_{16}$ peptides were described within CSF of AD patients and surprisingly $A\beta_{16}$ CSF levels increase in AD patients (Portelius, Zetterberg et al. 2006). Identification of these Aß fragments in the CSF could lead to a more specific differential diagnosis since it may exist distinct CSF Aß fragment profiles between AD, DLB or FTD, these profiles could reflect distinct physiopathological events between these pathologies (Bibl, Mollenhauer et al. 2007). So, the use of these new biomarkers could lead to novel diagnostics and therapeutics approaches for Alzheimer's diseases.

- Tau proteins

Increase of T-tau CSF levels was found in AD patients as well as MCI patients who will develop later an AD (Riemenschneider, Buch et al. 1996; Andreasen, Minthon et al. 2001; Riemenschneider, Lautenschlager et al. 2002; Hansson, Zetterberg et al. 2006). Measurement of T-tau levels with ELISA test (Innotest hTau Ag, Innogenetics) reveal concentrations between 150 pg/mL and 450 pg/mL in control subjects and between 300 and 1100 pg/mL in AD patients (Riemenschneider, Lautenschlager et al. 2002; Lewczuk, Esselmann et al. 2004; Grossman, Farmer et al. 2005). Nevertheless, increase of T-tau CSF levels is not AD specific since it is also observed in different concentrations in CJD or even an acute stroke (Otto, Wiltfang et al. 1997; Hesse, Rosengren et al. 2000). T-tau CSF levels in patients with sporadic CJD are higher than those observed in patients with other neurodegenerative dementias including AD (Otto, Wiltfang et al. 1997; Otto, Wiltfang et al. 2002). Threshold for CSF T-tau concentration in sporadic CJD was determined at 1300pg/mL in 2002 in a study conducted on 300 patients with CJD with 109 neuropathological confirmations (Otto, Wiltfang et al. 2002). In other forms of CJD as new variant, CSF T-tau levels are lower than those observed in sporadic disease (Sanchez-Juan, Green et al. 2006).Thus, T-tau is more a neuronal death marker than a specific AD biomarker. Several diseases are neuropathologically linked to tau dysfunction such as in some FTD, progressive supranuclear palsy (PSP) and CBD. Numerous studies have investigated measurement of CSF T-tau levels in FTD but results are

in accordance with pathological heterogeneity of FTD (neuropathological tau inclusions or without tau inclusions) since existence of discordance between studies with increase of CSF T-tau levels or not (Riemenschneider, Wagenpfeil et al. 2002; Pijnenburg, Schoonenboom et al. 2004; Grossman, Farmer et al. 2005). Any biological argument does exist with T-tau CSF levels in pathologies like FTD or other tauopathies as PSP and CBD (Urakami, Wada et al. 2001). Interestingly, a distinct profile of T-tau in electrophoretic separation was observed in CSF of sporadic CJD patients in a very recent study (Chen, Shi et al. 2010).

More interestingly, some modifications as truncated forms can be identified on tau proteins. A recent study permitted to demonstrate differences in CSF levels of truncated forms of tau in PSP patients compared with other neurodegenerative diseases (FTD, CBD, AD, DLB and Parkinson disease) or control subjects (Borroni, Gardoni et al. 2009). Other proteolytic processes on tau protein can occur in neurodegenerative disorders and could be identified.

CSF P-tau level specifically increase in AD patients compared with those with FTD, vascular dementia or control subjects (Hampel, Buerger et al. 2004). Regarding DLB, results are more conflicting with studies describing increase of P-tau CSF levels and others reporting normal concentrations (Vanmechelen, Vanderstichele et al. 2000; Parnetti, Lanari et al. 2001). So, an increase in P-tau CSF levels is observed in AD and MCI patients (Itoh, Arai et al. 2001; Andreasen, Vanmechelen et al. 2003; Herukka, Hallikainen et al. 2005). Moreover, cognitive decline is correlated with CSF increasing levels of P-tau, these CSF tau species might specifically mark a cerebral degenerative process (Maccioni, Lavados et al. 2006; Wallin, Blennow et al. 2006). While other P-tau species have been measured, only CSF levels of tau proteins phosphorylated at serine 181 ($P\text{-}tau_{181}$) or threonine 231 ($P\text{-}tau_{231}$) seem to clearly improve the accuracy of the diagnostic of AD (Buerger, Zinkowski et al. 2002; Hampel and Teipel 2004; Mitchell 2009). Some phosphorylations are more specific for AD, CSF $P\text{-}tau_{181}$ significantly increases in AD patients compared to patients without neurodegenerative processes as well as patients with other neurodegenerative dementias (Vanmechelen, Vanderstichele et al. 2000; Vanderstichele, De Vreese et al. 2006). The P-tau181 assay in CSF is now routinely used for biological differential diagnosis between AD and other forms of dementias. ELISA measurements of this protein (Innotest phospho-$tau_{(181P)}$, Innogenetics) reveal CSF levels between 30 pg/mL and 50 pg/mL in control subjects and between 75 pg/mL and 100 pg/mL in AD patients (Lewczuk, Esselmann et al. 2004). This phosphorylated form of tau protein permits to distinguish an AD from all other neurodegenerative etiologies with great sensitivity and specificity (Hampel, Buerger et al. 2004). $P\text{-}tau_{181}$ CSF measurement is able to differentiate AD patients from FTD patients with a sensitivity of 85% and a specificity more than 80% (Schoonenboom, Pijnenburg et al. 2004). These results are similar in differentiation of AD and all other neurodegenerative dementias (Hampel, Buerger et al. 2004). Furthermore this measurement improves distinction of AD and DLB patients (Parnetti, Lanari et al. 2001; Vanderstichele, De Vreese et al. 2006).

Other phosphorylated species of tau protein allow to improve accuracy of biological diagnosis. The $P\text{-}tau_{231}$ appears early during AD pathogenesis (Augustinack, Schneider et al. 2002). This form of tau in CSF differentiates patients with AD from control subject with high sensitivity and specificity (more than 90%) (Mitchell 2009), nevertheless its interest for differential diagnosis appears to be less important than $P\text{-}tau_{181}$ except for distinction of AD and FTD (Hampel, Buerger et al. 2004). Moreover $P\text{-}tau_{231}$ well reflects AD neuropathology because its CSF concentration is correlated with amounts of NFT found at the autopsy (Buerger, Ewers et al. 2006). Since this form of phosphorylated tau permits to identify AD within a population of patients presenting a mild cognitive impairement (MCI), it seems

particularly interesting for the early diagnosis (Brys, Pirraglia et al. 2009). The CSF P-tau$_{231}$ levels decrease with time during the AD process; this will enable to approach dementia severity (Hampel, Buerger et al. 2001). CSF P-tau$_{199}$ measurement and determination of its phosphorylation, that seems precociously involved during AD pathogenesis and NFT formation (Maurage, Sergeant et al. 2003), are able to discriminate AD patients from other degenerative dementias with a sensitivity and a specificity of 85% and 80% respectively (Itoh, Arai et al. 2001). Phosphorylation of tau protein on both amino acid 231 and 235 might be predictive of MCI conversion into AD (Arai, Ishiguro et al. 2000). In the same way, CSF level of P-tau$_{396/404}$ is elevated in AD compared to vascular dementia, and control subjects (Hu, He et al. 2002). Nevertheless these results have to be confirmed on patients with other degenerative disorders.

- Combination of etiological markers

The use of combinations of these CSF markers (Aβ_{42}, T-tau and P-tau$_{181}$) improves biological diagnosis performance for dementias in terms of differential or early diagnosis (Andreasen, Minthon et al. 2001; Riemenschneider, Wagenpfeil et al. 2002; Pijnenburg, Schoonenboom et al. 2004). These CSF biomarkers are also prognosis markers since a recent prospective study conduct on 150 AD patients for 5 years revealed that extreme CSF biomarkers levels (high T-tau and P-tau$_{181}$ and low Aβ_{42}) are associated with more aggressive diseases leading to an earlier death (Wallin, Blennow et al. 2010).

Recently, a clinical study of the Alzheimer Disease Neuroimaging Initiative Project has detected an Alzheimer disease signature in the CSF levels of, Aß$_{42}$ T-tau and P-tau181 in more than one third of cognitively normal subjects (De Meyer, Shapiro et al. 2010). This finding suggests that this CSF signature is present and detectable early during the neurodegenerative process. A recent study including 43 patients with a clinical dementia disorder and conducted in Sweden failed to show a concordance between T-tau and Aß CSF levels and pathological symptoms (Brunnstrom, Rawshani et al. 2010). Further, it has been suggested that low CSF Aß$_{42}$ may also be a marker of diffuse plaques in addition to fibrillar plaques. Indeed, Fagan and colleagues have studied the relationship between *in vivo* brain amyloid and CSF markers of proteins (T-tau, P-tau$_{181}$ and Aß$_{42}$) in cognitively normal individuals ranging in age from 43-89 years (Fagan, Mintun et al. 2009). In this study they have identified a new class of non demented individuals who present low CSF Aß$_{42}$ with cerebral amyloid deposition. The authors suggested that CSF Aß$_{42}$ drop prior to amyloid becomes detectable and may reflect the presence of diffuse plaques and/or oligomeric Aß species. These data demonstrate that CSF Aß$_{42}$ may be considered as a biomarker for plaque burden and prognosis providing the very earliest clue to identify preclinical AD.

Combination of CSF T-tau and Aβ_{42} allows to distinguish AD from FTD patients with both sensitivity and specificity of 85% (Riemenschneider, Wagenpfeil et al. 2002). Moreover the use of this combination permits to identify AD in MCI patients with sensitivity and specificity of 95% and 83% respectively (Hansson, Zetterberg et al. 2006). Interestingly, predictive value of P-tau$_{181}$ is better than T-tau for prediction of conversion of MCI in AD patients (Parnetti, Lanari et al. 2006). Association of 3 biomarkers is clearly useful to identify a degenerative process concordant with AD in atypical clinical presentation. A study with 9 patients presenting PCA revealed CSF levels of these 3 biomarkers similar to those observed in AD (Baumann, Duyar et al. 2010). In the same way, very recent prospective study conducted on 22 ACP patients demonstrated that a majority of patients with this syndrome (90%) have intrathecal biomarker levels compatible with AD (Seguin, Formaglio et al. in press).

Using of ratio T-tau/$A\beta_{42}$ increases the diagnosis specificity of AD compared with control subjects and other degenerative dementias (Gomez-Tortosa, Gonzalo et al. 2003; Kapaki, Paraskevas et al. 2003). Specificity of this ratio in differentiation of AD from vascular dementias is higher than 80% nevertheless this ratio is less efficient for differentiating AD and DLB (Gomez-Tortosa, Gonzalo et al. 2003). Finally, ratio T-tau/$A\beta_{42}$ could be early instructive since its increase permits to predict cognitive alterations in asymptomatic subjects within 8 years (Fagan, Roe et al. 2007). Similarly, the ratio P-tau_{181}/$A\beta_{42}$ appears as an important element for differential diagnosis. It allows to distinguish AD patients from those with FTD with a sensitivity and a specificity of more than 90% (de Souza, Lamari et al. 2010). Furthermore this ratio is able to discriminate patients with semantic dementia from AD patients with an excellent sensitivity of 98% and a specificity of 84%. Ratios with other forms of Aβ peptides such as $A\beta_{42}$/$A\beta_{38}$ and $A\beta_{42}$/$A\beta_{37}$ combined with T-tau CSF levels are able to differentiate AD from DLB with a sensitivity of 100% and a specificity of 92% (Bibl, Mollenhauer et al. 2006).

Since CSF T-tau levels in sporadic CJD are clearly elevated comparing to all other neurodegenerative disorders and P-tau_{181} is in normal concentrations, the use of P-tau_{181}/T-tau ratio seems interesting to identify CJD patients (Riemenschneider, Wagenpfeil et al. 2003). This ratio is inferior to 0.05 in CJD and superior to 1.25 in AD even in very early stages of the disease. Similar results were found with P-tau_{231}/T-tau (Buerger, Otto et al. 2006). It is important to note that CSF P-tau_{181} level in new variant CJD are higher than in sporadic CJD, and this inversely to T-tau CSF level (Goodall, Head et al. 2006). So, this ratio P-tau_{181}/T-tau is able to differentiate sporadic CJD from new variant with an elevated ratio. Nevertheless, biological levels overlap, particularly between new variant CJD and AD, thus does not permit to attain a differential diagnosis value.

Other combinations with different P-tau are useful for biological diagnosis. Combining CSF P-tau_{181} and P-tau_{231} enables to identify AD patients with a sensitivity of 94%, but a weak specificity of 66% confronting with all neurodegenerative disorders (Hampel, Buerger et al. 2004). More interestingly, ratio of P-$tau_{396/404}$ and T-tau is able to distinguish AD patients from others dementias with a sensitivity and a specificity of 96% and 86% respectively and have an excellent specificity (100%) in the distinction of AD and vascular dementias (Hu, He et al. 2002).

- Others potential biological markers

Numerous other molecules have been investigated as biological CSF markers and are liable to participate on etiological dementia diagnosis. We briefly deal with some of them which seem to supply advantage for differential and early diagnosis.

Implication of oxidative stress hypothesis and inflammation in AD or other neurodegenerative disorders opened some research ways. It is known that inflammation is associated with parenchymal Aß deposits in AD (Schmidt, Schmidt et al. 2002). Inflammation markers have been investigated in CSF to reveal potential inflammatory process linked to these pathological deposits. Inflammatory mediators such as chemokines might be increased into AD patients CSF (Galimberti, Schoonenboom et al. 2006; Galimberti, Schoonenboom et al. 2006). The concentration of classical complement cascade C1q subunit decreases in CSF of AD patients and is correlated with disease severity (Smyth, Cribbs et al. 1994). However, this intrathecal molecule only attests for microglial reactions met in AD and also during physiological aging (Lue, Walker et al. 2001; Schuitemaker, van der Doef et al. 2011). Similarly isoprostane CSF levels, an oxidative stress marker, clearly increase in biological fluid (CSF, blood and urine) proportionally to cognitive decline and might be an

early biomarker of AD in MCI patients (Pratico, Clark et al. 2000; Pratico, Clark et al. 2002). If these molecules seem interesting for understanding physiopathological mechanisms which occur in neurodegenerative disorders (oxidative stress and microglial activation particularly), these biomarkers cannot be a specific part of differential diagnosis since they are frequently involved during cerebral aging (Montine, Peskind et al. 2011).

Molecules with an implication in protein catabolism are present within CSF and their levels may reflect cerebral damages. An increase of the intrathecal neprisylin activity was observed and correlated to T-tau CSF level and cognitive decline in AD patients and patient with prodromal form of AD (Maruyama, Higuchi et al. 2005). Nevertheless this activity is modestly predictive for MCI conversion to dementia. Ubiquitine, another catabolic signal protein might be linked to aggregated tau proteins in the cerebral cortex and its CSF levels might increase in AD patients (Iqbal, Flory et al. 2005). Moreover ubiquitine CSF levels correlate with those linked with cerebral tau aggregates in AD (Kudo, Iqbal et al. 1994). Nevertheless, elevated ubiquitine CSF levels were observed in other non-AD dementias (Iqbal and Grundke-Iqbal 1997).

A protein largely present in CSF and blood, tranthyretin, has higher CSF levels in AD and MCI stage. CSF measurements can distinguish AD from control subjects with sensitivity of 100% and specificity of 93% (Lovell, Lynn et al. 2008). In the same way, CSF concentrations of the mitochondrial protein cytochrome c are increased in AD and permit to identify AD process in MCI patients with a sensitivity of 100% and specificity of 75% (Papaliagkas, Anogianakis et al. 2009). However, a specificity problem is present regarding other neurodegenerative dementia such as FTD (Ruetschi, Zetterberg et al. 2005).

Recently, Zhong and colleagues have quantified the levels and the activity in the CSF of ß-secretase (BACE 1), an enzyme involved in the cleavage of APP to Aß (Zhong, Ewers et al. 2007). An elevated BACE 1 activity was observed in CSF of MCI and AD subjects compared with normal controls. Moreover, this activity was correlated with CSF BACE 1 protein and Aß peptide levels. A more recent study showed that CSF BACE1 activity correlates with CSF $Aß_{40}$, total T-tau and $P\text{-}tau_{181}$ levels but surprisingly not with intrathecal $Aß_{42}$ concentration (Mulder, van der Flier et al. 2010). These results are promising and suggest that BACE 1 could be a potential candidate as a biomarker of early-stage AD, but additional studies are necessary to confirm this hypothesis.

4. Peripheral biomarkers

Because the CSF collection by lumbar puncture is an invasive, expensive and time-consuming procedure, the detection of biomarker molecules in blood would be more widely applicable. However, in comparison with CSF biomarkers, efforts to discover reliable biomarkers for Alzheimer's disease in peripheral blood have not been successful and do not allow developing a solid diagnostic. The use of many different sensitive ELISA tests for the detection of $A\beta_{40}$ and $A\beta_{42}$ allowed the detection and quantification of Aß in human plasma (for review see Irizarry, 2004; Mehta, 2007). According to these studies, some controversy persists concerning the changes in blood Aß levels in relation with the severity of the disease suggesting that plasma Aß levels cannot allow differentiating sporadic AD from control cases. As the pool of circulating Aß includes multiple C-terminal truncated fragments, and possibly oligomeric species, it has been suggested that the use of of antibodies to various forms of Aß with different affinities may explain these differences. Nevertheless, the ELISA assay may not be an ideal method to measure Aβ levels in blood. Indeed, the two major

difficulties in the measurement of Aβ in plasma consist in the low concentration of the plasma peptide, needing a more sensitive quantification assay, and in the interaction of the beta peptide with different carrier proteins present in plasma, that can mask the epitopes of Aβ and interfere with the detection of the peptide (Kuo et al., 2000).

Nowadays, the development of more sensitive and more specific assays for the detection of plasma Aβ levels is needed for proposing plasma Aβ as a biomarker for diagnosis. To overcome the Aβ low levels different new promising strategies have been developed based on purification and concentration steps prior to the Aβ peptides analysis. Using a denaturing solid-phase extraction (SPE) combined with an ELISA assay, Lanz and co-workers (Lanz & Schachter, 2008) have compared the Aβ detection in plasma and CSF bio-fluids of normal individuals. But, while human CSF exhibit, in comparison with non-SPE samples, the most robust recovery (≥ 90%), the human plasma showed a lower recovery (between 40 and 60% in function of the extraction process used, guanidine or acid formic, respectively) suggesting that the use of a SPE step does not improve the detection of the protein comparatively to the non-denatured plasma. Slemmon and collaborators (Slemmon et al., 2007) have linked to the SPE a reverse-phase HPLC (SPE-HPLC) compatible with analysis by ELISA. In this study, the detection of Aβ peptides from the whole blood of six normal subjects was analyzed; by comparison with a native plasma, a significantly increase in the amount of total Aβ peptide was obtained after guanidine extraction and HPLC detection, with concentrations ranging from 100 to 165pg/ml. These results suggest that there is a pool of Aβ peptides in non-denatured plasma samples that is not accessible for the detection by ELISA assay probably due to their interactions with plasma proteins or to their aggregated state that could mask the epitopes.

Several studies on the detection of tau proteins in blood have been performed but failed to show a clear relationship to dementia diagnosis, thus, the correlation between increased tau brain levels and elevated CSF levels of tau in AD patients is not totally clear (Bitsch et al., 2002; Ingelson et al., 1999). Further research is needed to improve the specificity and the sensitivity of the assay in order to develop a robust method to measure tau protein levels in serum or plasma.

Recently, various plasma signalling proteins were proposed as potential candidates to develop a blood test for AD (Ray et al., 2007). O'Bryant and colleagues developed an algorithm in order to differentiate patients with Alzheimer disease from controls. In this study serum protein-based multiplex biomarker data from a large group of Alzheimer patients and controls were analyzed. Combined with age, sex, years of education and ApoE genotype, their logarithm model reached a diagnostic sensitivity and specificity of 94% and 84% respectively (O'Bryant et al., 2010).

In addition to CSF and blood, several other biological fluids are under investigation for the detection of AD biomarkers. Among these biological fluids, a special attention is accorded to saliva and urine. The study of Bermejo and colleagues (Bermejo-Pareja et al., 2010) found that saliva $A\beta_{42}$ is, in comparison with control subjects, significantly elevated in early stage AD patients while $A\beta_{40}$ levels remain unchanged within all the samples analyzed. Curiously the elevated saliva $A\beta_{42}$ levels were not observed in severe stages of the disease. This augmentation seems to be specific to AD and not to Parkinson disease. These results show that in combination with Aβ levels in brain, the saliva levels of $A\beta_{42}$ could be a potential biomarker for clinical AD.

In addition to the specific markers of AD disease (like Aβ peptides and tau proteins), there are non-specific markers like oxidative stress and neuronal inflammation molecules. An increased expression in AD patients of many inflammatory and pro-inflammatory cytokines has been widely documented. Inflammation in AD brains induces important microglia

activation and consequently production of free radicals responsible of an intense oxidative stress. So these inflammatory and oxidative mechanisms are involved in the aetiology of AD and can contribute to the neurodegeneration. However conflicting results exist about the pertinence of the use of these peripheral biomarkers. Among the inflammatory markers several cytokines have been measured in CSF or blood, such as interleukin 1-α and 1-β, interleukin-6, -10, -11 and -18, and tumor necrosis factor-alpha (for review see Casoli et al., 2010; Olson & Humpel, 2010). But the results are very divergent between the different groups. The same conclusions can be enunciated for chemokines. More studies are needed to clarify and determine the reproducibility of such inflammatory markers.

Oxidative stress parameters have also been investigated as AD biomarker. A biomarker of oxidative stress study (BOSS) coordinated by the NIH was performed in order to determine among 16 commonly studied biochemical products of oxidative stress which ones could been validated as *in vivo* biomarkers (kadiiska et al., 2005). This study was performed on plasma, blood and urine samples. Among these molecules, malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and F2-isopropanes were the most promising biomarkers of oxidative stress. F2-isopropanes, a product of lipid peroxidation, was the most extensively investigated in CSF of AD patients. These clinical studies showed comparatively with control subjects a significant increase of F2-isopropanes in damaged regions of AD brain and in CSF in patients in early stages of mild cognitive dementia (Montine et al., 1999, 2001; Pratico et al., 2000). In plasma and urine samples, the quantification of such marker yield to conflicting results.

5. Which techniques could be applied?

Hyperphosphorylated Tau proteins are currently used for AD diagnostics in CSF, as recently proposed by an international working group on Alzheimer Disease (NINCDS-ADRA working group) (Dubois et al., 2007). Moreover, there are no well-established and accepted biochemical tests available for therapeutic follow-up of these diseases. Their diagnosis requires thus high sensitivity and specificity. Sensitivity is needed for early diagnosis, when the biomarker is present at very low levels to ensure cost-effective therapeutic interventions before the disease has progressed to a stage where damages to the brain are irreversible. Specificity is needed to discriminate first, non-degenerative causes of dementia (e.g. vascular, alcoholic, psychiatric, metabolic, infective etc.) from degenerative forms and, second, to discriminate the different molecular aetiologies in order to propose an appropriate therapeutic treatment: for example, anticholinesterase drugs show certain efficacy in AD, but not in frontotemporal dementia (Musial et al., 2007).

Today, AD can be diagnosed with certainty only post-mortem with histopathological evaluation of amyloid plaques and NFTs. Ante-mortem, AD is diagnosed by clinical criteria. Clinical diagnosis included systematically before 2007 December the presence of dementia (McKhann et al., 1984). Before apparition of dementia symptoms, complaining patients suffer from memory trouble without social and professional effects; this clinical phase was usually called "amnestic mild cognitive impairment (MCI)" (Petersen et al., 1999). Many of these patients convert to AD whereas few of them convert to other neurodegenerative dementia or remain stable (Fischer et al., 2007). As recently proposed, using the combination of clinical, neuropsychological, imaging methods and CSF biomarkers, this clinical stage would be nowadays called preclinical AD and, more important, its detection would allow a better care for AD patients. Neuropsychological evaluation permits a more accurately defined diagnosis, but it is time consuming (half a day), is not available for all concerned

people, is still proposed at advanced stages of disease, and is not 100% accurate since there is a risk of overlaps among different aetiologies of dementia as frontotemporal degeneration (FTD), Lewy's body dementia (LBD), and potentially other dementias. Neuroimaging may permit exclusion of vascular pathology, detection of hippocampal atrophy and cerebral hypoperfusion (Tapiola et al., 2008; Xu et al., 2007). It must be noted that first AD lesions may coexist with vascular dementia in at least 50 % of cases. During the past years, great efforts have been made to identify reliable biomarkers for AD in body fluids of patients that are suitable for minimal invasive early diagnosis of AD, mainly cerebrospinal fluid (CSF) and blood. Recently, we've summarized all of the criteria needed to establish convenient technique with the following advantages (Dupiereux et al. (2009):

a. Low-cost
b. Rapid-fast
c. Good level of accuracy

6. Should Alzheimer's detection be associated to biomarkers of other diseases?

Other diseases could be associated with AD resulting in mixed dementias. Furthermore, unique pathologies could mimic others and it is difficult to make differences between given pathological events or to identify all neurodegenerative processes. Effectively, 15 to 50% of AD patients have Lewy bodies (neuropathological hallmark of DLB constituted by α-synuclein) associated with NFT and Aβ deposits after neuropathological examination (Hamilton 2000). Nevertheless, α-synuclein (α-Syn) is not always associated with this clinical phenotype (Parkkinen, Kauppinen et al. 2005). This pathological association seems to make part for cognitive alteration severity with a synergic effect (Clinton, Blurton-Jones et al. 2010). Mixed dementia may be more aggressive than pure AD (Kraybill, Larson et al. 2005). Since a low CSF α-Syn level was detected in CSF of patients with DLB and Parkinson disease comparing to other neurodegenerative diseases, an association of this measurement with typical CSF biomarkers of AD seems interesting (Tokuda, Salem et al. 2006; Kasuga, Tokutake et al. 2010). Moreover, oligomeric forms of α-Syn were detected in CSF and blood of patients with Parkinson disease (El-Agnaf, Salem et al. 2006). Nevertheless, several studies are conflicting since elevated or normal CSF levels were also observed in DLB patients (Mukaetova-Ladinska, Milne et al. 2008; Spies, Melis et al. 2009; Ballard, Jones et al. 2010). In the same way, we can postulate an association of typical CSF biomarkers of AD with prion CSF measurement since neuropathology of CJD is more intricate than we though it several years ago (Kovacs, Seguin et al. 2011).

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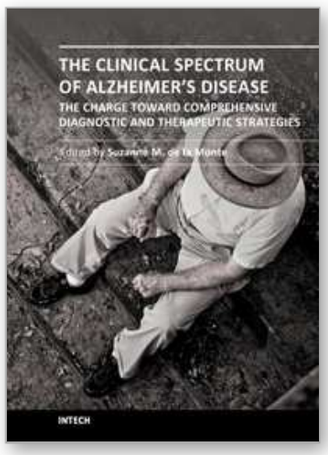
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The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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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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