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Biomarkers of Alzheimer's disease: The present and the future

Marqueurs biologiques de la maladie d'Alzheimer : présent et futur

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ABSTRACT

A paradigm shift has occurred in the last ten years in the diagnostic field of Alzheimer's disease (AD). Scientific thought has enriched the concept of AD as a pathophysiological continuum and emphasized contribution of biological, morphological and functional brain imaging biomarkers for diagnosis, in particular during the early stages of the disease. We address here the present and the future of these biological biomarkers. Most of them are linked to the pathophysiological lesions of the Alzheimer process: aggregates of hyperphosphorylated tau proteins, also called neurofibrillary tangles (NFT), and extracellular deposit of amyloid-beta peptides (Aβ), also called senile plaques. The detection in the cerebrospinal fluid (CSF) of tau and Aβ represents the current diagnostic practice of AD. Improvement for a more accurate and earlier biological diagnosis is however expected using a new generation of biomarkers, mostly in relation with tau and Aβ metabolism.

RÉSUMÉ

Ces dix dernières années ont été marqués par des changements importants dans notre manière d'appréhender la maladie d'Alzheimer (MA). Il est en effet apparu d'une part, la notion de continuum physiopathologique de la MA, et d'autre part, s'est confirmée l'importance diagnostique des biomarqueurs (biologiques et d'imagerie cérébrale), en particulier durant les premiers stades de la maladie. Nous abordons ici le présent et l'avenir des biomarqueurs biologiques. La plupart d'entre eux sont liés aux lésions physiopathologiques de la MA : les agrégats de protéines tau hyperphosphorylées formant les enchevêtrements neurofibrillaires (NFT) et dépôts extracellulaires de peptides bêta-amyloïdes (Aβ), également appelés plaques séniles. La détection dans le liquide céphalorachidien (LCR) des protéines Tau et des peptides Aβ fait maintenant partie de la pratique

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diagnostique courante. Des améliorations pour un diagnostic biologique plus précis et plus précoce sont cependant attendues grâce à de nouveaux biomarqueurs en rapport principalement avec le métabolisme de Tau et Aβ.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by significant cognitive deficits, behavior changes with a progressive loss of functional autonomy. This devastating neurodegenerative affection is approaching epidemic proportions in the industrialized world mostly due to aging of the population (Ferri et al., 2005). The diagnosis of AD, according to the old NINCDS-ADRDA criteria, was based on clinical exclusion criteria leading to the diagnosis of probable or possible AD (McKhann et al., 1984). Based on these criteria, the diagnosis of probable AD has a mean specificity set at around 70%, meaning that many patients who met the clinical criteria for AD do not have corresponding neuropathological lesions. To optimize patient's therapeutic care, alleviate the burden of caregivers and conduct clinical trials, accurate diagnosis of the disease is becoming mandatory. In addition, the concept of neurodegenerative continuum throughout the time course of AD process (Dubois et al., 2010) is emerging: the brain lesions were present many years before the appearance of the first clinical complaints and beyond a brain damage load' threshold exist the no return point. New disease-modifying drugs will probably be more effective in early AD patients prior to the occurrence of amyloid plaques and neurofibrillary tangles and before neuronal losses become too severe. Consequently with the challenge of new drugs, it is essential to provide early AD diagnosis for the patients (Petersen and Trojanowski, 2009). The newly proposed AD diagnostic criteria for research across the continuum of AD (Dubois et al., 2007; McKhann, 2011) propose to include in vivo AD biomarkers in addition to memory complaint. The core of the diagnostic criteria is the presence of an early and significant episodic memory impairment that includes gradual and progressive change over more than 6 months with recall deficit that does not improve significantly with cueing. The supportive features of the biomarkers include biological (amyloid and Tau CSF biomarkers), morphological (volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI) and functional brain imaging (reduced glucose metabolism in bilateral temporal parietal regions) exams. Initially described only for AD clinical research or clinical trials, these new criteria based on biomarkers are gradually included in the routine clinical practice (Gabelle et al., 2012a).

2. Tau and amyloid peptides biomarkers in the CSF

The two characteristic AD brain lesions are represented by the deposit: of amyloid peptides in the extracellular space, and of hyperphosphorylated Tau proteins in neurons. The amyloid peptide Aβ is normally produced in the brain and results from the processing of a transmembrane precursor protein called APP (amyloid precursor protein). Aβ is generated through two enzymatic cleavages by ß- and γ-secretases. This amyloidogenic processing pathway generates many types of Aβ peptides, the most important ones cleaved at amino acid position 40 (Aß40) or 42 (Aß42). Aβ peptides have a high tendency to aggregate forming toxic oligomers (Klein, 2013). APP is also cleaved by an α-secretase, in a non-amyloidogenic pathway that represents its major metabolic processing. Many questions remained on the presence and concentration of these different Aβ peptide isoforms, on their physiologic role and pathologic impact, as well as on their molecular metabolism (conversion of one form to another, degradation...). Tau is a neuronal protein associated to microtubules. It plays a role in their formation and stabilization. In AD, the phosphorylation of Tau is altered and the protein is hyperphosphorylated with the appearance of new ''pathologic'' phosphorylation sites. Abnormally phosphorylated Tau (p-Tau) loses its microtubule stabilization function and it aggregates in neurons to form toxic neurofibrilary tangles (Buerger et al., 2006; Delacourte et al., 2002). This event occurs also in other neurodegenerative disorders such as fronto-temporal dementia (FTLD), progressive supranuclear palsy, corticobasal degeneration... (Buee et al., 2000; Sergeant et al., 2008).

Unlike the neuroimaging biomarkers which are the indirect reflection of the consequences of the disease, the biological biomarkers reflect directly the brain changes. It is well known that brain biochemical modifications are reflected in the CSF. Numerous studies have evidenced that AD patients display characteristic CSF changes with decreased levels of Aß42 and elevated levels of Tau and p-Tau (Bateman et al., 2012; Blennow et al., 2006). CSF AD biomarkers correlated with the intensity of neuropathological lesions. CSF biomarkers have been validated in research for positive AD diagnosis with good sensitivity and specificity for clinically diagnosed AD versus controls in several mono-centric cohorts (Blennow, 2004; Johansson et al., 2011) and also for differential diagnosis (Bibl et al., 2010; Gabelle et al., 2011; Renard et al., 2012). Recent pathophysiological hypotheses and longitudinal studies have also underlined the major relevance of CSF Aβ42 evaluation at an early stage of the disease (Jack et al., 2011; Mattsson et al., 2009; Shaw et al., 2009).

For the future, the evolution of AD biological diagnosis is first represented by the combination of existing biomarkers. As Aβ42 aggregates before Aβ40 within the brain and has its concentration decreased in the CSF, there is an added value at using the Aβ42/Aβ40 ratio for AD diagnosis (Hansson et al., 2007). This ratio has a higher sensitivity for AD diagnosis and is less affected by variation in endogenous Aβ levels, as well as by pre-analytical biases (Perret-Liaudet et al., 2012). Ratios based on Aβ42 and Tau (Hulstaert et al., 1999) or p-Tau (Hansson et al., 2006) are also of interest especially for the early

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