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Interest of biological biomarkers in the diagnostic approach of neurocognitive disorders in the elderly

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Abstract

Alzheimer's disease (AD) is the most common cause of major neurocognitive disorders in older adults, affecting millions of individuals worldwide and leading to irreversible cognitive decline. The main neuropathological features of AD are brain amyloid deposition and neurofibrillary tangles. The biomarkers of AD are highly accurate in detecting these pathophysiological and neuropathological changes, up to several decades before the onset of cognitive impairment. They specifically reflect the presence of abnormal proteins in the brain, and can be measured reliably in the cerebrospinal fluid of affected individuals and in plasma for research purposes. Their implementation in clinical practice, together with neuropsychological assessment and neuroimaging, strongly increases diagnostic precision. Thus, amyloid and tau biomarkers can help rule out differential diagnoses such as vascular cognitive impairment or frontotemporal lobar degeneration. They also enable earlier diagnosis and are used in research to characterize the preclinical stage of AD.

The new definition of AD has highlighted the usefulness of these biomarkers, shifting the focus from symptoms to biological and brain changes in living patients. Recent longitudinal studies demonstrated the ability of these biomarkers to predict future cognitive decline, regardless of the stage of the disease. Ongoing drug trials against AD systematically require diagnostic confirmation with biomarkers. Apart from clinical research, they have been increasingly used for several years in clinical practice, in secondary and tertiary-referral memory clinics.

Nevertheless, their use has been raising ethical issues, in particular in the oldest old or in patients with multimorbidity. Their interpretation in patients older than 90 years is limited by the lack of evidence. The implications of a misdiagnosis of AD should be taken into account. Besides, there may be discrepancies between the biological diagnosis and the clinical course of the disease. In the absence of clear guidelines for their utilization, we hereby discuss their potential interests and limitations in older individuals.

Keywords: Alzheimer's disease; early diagnosis; biomarkers; lumbar puncture

Introduction: Diagnosis and definition of Alzheimer's disease

Alzheimer's disease (AD) currently affects more than 35 million people worldwide. The clinical and economic burden of AD is comparable to cancer or cardiovascular diseases in terms of morbidity and mortality [1]. The seminal observation reported more than a century ago in a 51-year-old woman described the disease on the basis of post-mortem neuropathological criteria, including cerebral atrophy, "senile" plaques and neurofibrillary tangles (NFT) [2]. Amyloid beta ($A\beta$) and tau proteins, which are constitutive of these lesions, were only described eight decades later. However, AD mostly affects older adults, since its prevalence increases exponentially with age. Thus, only 1% of the population is affected at age 60 whereas AD is common at age 85 (20 to 25%) [1]. In parallel, the first diagnostic criteria for clinical practice were published: those of the Diagnostic and Statistical Manual of Mental Disorders (DSM-3) and those of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [3,4]. Nevertheless, these criteria highlighted that the gold standard for the etiological diagnosis remained the neuropathological assessment. In addition, the publication of an autopsy series of 2661 brains by Braak and Braak in 1997 revealed that $A\beta$ and tau characteristic lesions of AD may precede the onset of clinical symptoms for several decades, suggesting that an exclusive clinical diagnostic approach would be inappropriate [5].

In the 2000s, the development and validation of imaging and cerebrospinal fluid (CSF) biomarkers were consistent with these neuropathological findings. Accordingly, the new diagnostic criteria of the National Institute of Aging-Alzheimer's Association (NIA-AA) in 2011 distinguishing three stages of the disease: preclinical or subjective cognitive impairment (SCI), mild cognitive impairment (MCI) due to AD (i.e. prodromal AD) and AD dementia [6,7]. The DSM-5 renamed the dementia syndrome as "major neurocognitive disorder", a term

considered less pejorative for patients and their relatives. In this classification, the minor neurocognitive disorder stage is defined by an objective cognitive impairment (abnormal test results for age and education level) with no impact on instrumental activities of daily living. This stage of the disease is preceded by a long asymptomatic period, characterized exclusively by brain neuropathological changes and abnormal CSF biomarkers.

These biomarkers not only increase diagnostic certainty but also predict the clinical evolution i.e. the future cognitive performance of the individuals. Based on the relevance of biomarkers, the NIA-AA proposed, in May 2018, a biological definition of the disease to better understand and characterize the sequence of events leading to cognitive impairment in AD [8]. This paradigm shift has been driven by the accuracy of the specific biomarkers that allow a better understanding of the spreading of brain lesions, but also by the negative results of recent clinical trials using anti-A β in cognitively impaired participants. Therefore, a reliable and universally accepted definition of preclinical AD would open up new perspectives in therapeutic research.

In clinical practice, biomarkers can help differentiating AD from alternative diagnoses that could meet the clinical criteria for AD, such as major depressive episode, vascular cognitive impairment, frontotemporal lobar degeneration, Lewy body dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus... In the absence of biomarkers, the diagnostic error rate is as high as 25% to 30% [9]. Making an early and accurate diagnosis of AD would provide opportunities to set-up the right care pathway or to participate in clinical trials. European and American guidelines now advocate for an early detection of AD [10-12]. As a consequence, AD biomarkers tend to be increasingly used in clinical practice, including outside of memory clinics and expert neurology departments.

Biomarkers of Alzheimer's disease

A biomarker is a measurable parameter that reflects a physiological or pathological process. It must be reliable, accurate, reproducible, inexpensive, and measurable following a non- (or moderately invasive) action. In AD, a distinction is made between diagnostic biomarkers that indicate the existence of characteristic histological lesions ($A\beta$, tau) and biomarkers of progression that indicate a degree of disease impairment, but are less specific (e.g. cortical atrophy on cerebral magnetic resonance imaging (MRI), hypometabolism on positron emission tomography (18-FDG-PET)). These biomarkers have complementary interests. Currently, plasma biological markers, CSF markers and imaging markers are being considered. Only biological markers will be discussed in this review.

Plasma biomarkers

Plasma markers can be easily measurable, requiring only blood collection, and might be used in the future as screening tools. So far, only $A\beta$ peptides measurements in plasma have been studied leading to discordant results. In the Framingham cohort study, low plasma level of $A\beta_{42}$ in cognitively intact subjects increased the risk of developing major cognitive impairment [13]. Recently, the BALTAZAR study showed an association between plasma $A\beta_{42}$ and $A\beta$ and tau CSF levels in MCI subjects, as well as an association between plasma $A\beta_{42}$ and $A\beta_{42}$ in CSF adjusted for age and ApoE genotype, in subjects with major cognitive impairment [14]. A recent Japanese study also showed a strong association between $A\beta$ plasma and CSF levels and brain amyloid deposition on PET imaging [15]. However, the screening performance and accuracy of these tools has been insufficiently studied so far. The mechanisms explaining the parallel variations of these markers in blood and CSF require further investigation. In addition, the assessment of plasma $A\beta$ alone is not sufficient to diagnose AD and plasmatic tau assessments are not reliable for the moment. Several studies

have also investigated the relationship between plasma inflammatory markers (including interleukin-6) and AD [16]. Nevertheless, the specificity of these markers for AD remains too low for clinical practice.

To date, it remains difficult to validate plasma biomarkers with regards to their limitations. First, a part of the measured biomarker may not come from the central nervous system, second, plasma levels may be influenced by intercurrent disease (e.g. inflammatory markers and infectious episodes) or treatment. Further studies are needed to determine the influence of various factors on plasmatic amyloid levels. Concerning tau proteins, the only feasible plasma measurement is t-tau, which may not reflect the actual NFT burden in the brain. Further studies on this field are ongoing [17].

Cerebrospinal fluid biomarkers

CSF analysis mirrors intracerebral biochemical activity. CSF quantification of three markers – A β 42 peptide, t-tau proteins, phosphorylated tau (p-tau) – is of specific interest for diagnosis purpose. The combination of these three parameters has demonstrated high sensitivity and specificity for the diagnosis of clinical and preclinical AD. CSF collection requires a lumbar puncture (LP). The risk of side effects and especially post-LP headache remains low, especially in older adults. In addition, the use of small-diameter, atraumatic needles has significantly reduced the onset of side effects [18]. Regardless of the patient's age, it should be noted that post-LP bed rest and hyperhydration are unnecessary and that the amount of CSF collected (up to 30 ml) does not influence the occurrence of headache after LP; only the use of a 22g or 24g atraumatic needle significantly reduces the risk of post-LP complications [19]. CSF must be collected in a polypropylene tube to prevent the aggregation of the A β peptide. Several studies have highlighted the variability of biomarkers measures, in particular A β peptide, due to the sampling tube [20,21]. Inter-center variability represents the main

limitation for broader use of these biomarkers, mostly because of pre-analytical differences (including the tube), leading to variability in the standards used [22]. In France, several studies have been performed, leading to the use of a single tube in most centers. An international quality control is also ongoing in some centers [23-25].

The typical profile of these three CSF biomarkers, A β 42, t-tau and p-tau, is well-validated to characterize the profile of AD, combining a decrease in A β 42 and an increase in total t-tau and p-tau. Neuropathological and in vivo studies using A β imaging showed good correlations between CSF A β 42 and tau concentration and brain neuropathological burden. Thus, when all three markers are abnormal, the sensitivity and specificity for the diagnosis of AD are 90-95% and 90% respectively [26,27]. The "PLM scale" is rated between 0 to 3 and allows to evaluate the risk of having AD according to the number of markers with pathological values (0 = no abnormal marker: risk of developing AD from 6% to 13.2%; 1 = a single abnormal marker: risk from 18% to 31.3%; 2 = two abnormal markers: risk from 67.8% to 86.5%; 3 = all three abnormal markers have a risk from 90.7% to 97.7%) [28]. This scale avoids threshold issues, specific to each laboratory. The additional CSF measure of A β 40 can be useful especially when A β 42 is "falsely" normal, while the tau markers are high. Indeed, the level of A β synthesis shows high interindividual variability. Thus, a decreased A β 42/40 ratio with normal A β 42 suggests brain amyloid deposition, despite high physiological production of A β peptides [29,30]. The implementation of this A β 42/40 in the PLM scale refined the biological diagnosis and reduced by 20% the number of non-conclusive profiles [31,32]. An increase in CSF t-tau and p-tau protein levels reflects NFT but also neuronal death [33]. Finally, an isolated major increase (>1200 pg/ml) in the t-tau levels should suggest an alternative etiology such as Creutzfeldt-Jakob disease, stroke or recent epileptic seizure [34]. However, t-tau may also be individually increased in AD [35]. In all cases, a time period of several weeks after these neurological events is required to perform a reliable CSF measure.

When should biomarkers be used?

The European working group established recent recommendations to move CSF biomarkers toward clinical implementation as indicators of the presence or absence of AD pathological features in major neurocognitive impairment and MCI [11,36]. Similar guidelines have been endorsed by the French health authorities (*Haute Autorité de Santé*), which underlined the importance of early etiological diagnosis, despite the absence of curative treatment for AD today [10]. Preclinical diagnosis is therefore not recommended in clinical practice and remains dedicated to research. In addition, the use of CSF biomarkers is suggested in atypical cases or in young patients [37]. However, there is no clear definition of an “atypical case” or an established threshold to define a “young” patient.

Accordingly, the use of biomarkers depends on the physician’s experience and of the hospital or memory clinic setting. In University Hospitals or memory clinics, they have been increasingly used [38]. In addition, most ongoing therapeutic trials target subjects with MCI due to biomarker-confirmed AD, since many recent longitudinal studies have demonstrated the ability of biomarkers to predict the progression of cognitive impairment and the development of overt dementia [39, 40]. As demonstrated by Mouton-Liger et al. in a large multicentric population, the use of CSF AD biomarkers may change the diagnosis and the management practices [41]. When facing a discrepancy between the clinical symptoms and the CSF analysis, the clinicians trusted the biomarkers results rather than their prior clinical judgment. In a subgroup of this large sample, Paquet et al. showed that CSF AD biomarkers could be useful in atypical psychiatric symptoms [25]. Finally, in a longitudinal study,

Vercruysse et al. demonstrated that patients with clinical AD but without a CSF AD profile, experienced different clinical evolutions [23]. In MCI, identifying AD lesions helps to predict the progression towards AD dementia. Finally, CSF AD biomarkers may help to provide the most appropriate symptomatic treatment and are now mandatory to be enrolled in a drug trial against AD.

Biomarkers of AD in the elderly

Several studies have demonstrated that pathological values of CSF and amyloid PET scan biomarkers were associated with the progression of cognitive impairment in the elderly [33]. Two cohort studies specifically highlighted the link between decreased CSF A β 42 levels and progression to major neurocognitive disorder, in cognitively intact elderly individuals at baseline [42-44]. Conversely, elevated A β 42 levels appeared to be protective against cognitive decline. Nevertheless, the use of CSF biomarkers in elderly subjects raises the issues of pathological thresholds and practical interpretation of a biological AD profile, especially in individuals with life-threatening comorbidities or disability. Furthermore, aging is a risk factor for cognitive decline, independent from brain amyloid pathology. Aging also increases the risk of cerebrovascular damage [45]. In addition, regardless of the evolution of cognitive functions, the prevalence of brain amyloid deposition increases over time. Biomarkers of amyloid pathology are positive in about 30% of cognitively normal elderly subjects and amyloid deposition is found in neuropathological analyses in the same proportion [46,47]. This prevalence reaches 44% among cognitively normal nonagenarians, compared to 71% among those with MCI. In 90-year-old subjects with at least one ApoE- ϵ 4 allele, the prevalence of a positive A β biomarker in cognitively normal subjects is 80%. On the other hand, in older subjects with major cognitive impairment, postmortem neuropathological studies did not find any association between the pathology A β and tau and the severity of cognitive impairment [48]. This result can be explained by the coexistence of specific AD

lesions with other brain lesions (especially vascular lesions) that cause cognitive disorders. In addition, there is a significant relationship between age and NFT. Nevertheless, this relationship seems to be modulated and amplified by the presence of amyloid brain deposition [49].

Thus, in the oldest old subjects (over 85 years of age), very few situations of cognitive impairment are likely to be due only to a single etiological mechanism. Clinical expression of cognitive symptoms can be interpreted as the sum of brain biological lesions ($A\beta$ and tau), cerebrovascular lesions, chronic pathologies or iatrogenic factors, mitigated by the individual's cognitive reserve, which itself depends on genetic, environmental, socio-cultural factors, etc. Accordingly, the results of CSF AD biomarkers may provide explanatory evidence for neurocognitive symptoms and predict the type of evolution, especially when there are no other obvious causes of cognitive impairment. From a technical point of view, LP performed in accordance with good practices, is better accepted in elderly people compared to younger patients, with a rate of post-LP headache of less than 5% [18]. The training to LP using atraumatic needles (including in difficult rachis) was highly recommended by the last French guidelines [19]. This training is available in several medical schools using simulation-based teaching [50].

Ethics and tailored decision in the elderly

The use of AD biomarkers may help the clinician, regardless of the patient's age or comorbidity: it enables more accurate and earlier diagnosis, explanations about the cognitive symptoms, and possibility of anticipating their evolution (e.g. writing advance directives, applying for financial and human assistance, prescribing appropriate symptomatic treatment, or avoiding iatrogenesis). On the other hand, some limitations must be acknowledged:

absence of disease-modifying treatment available, psychological burden of the diagnosis, especially in patients with anosognosia. In the diagnostic work-up for suspected AD, the evidence that CSF biomarkers could identify or exclude AD is strong in patients with mild dementia, but weaker in ambiguous cases. Besides, there are still uncertainties regarding the individual course of cognitive decline, even though the biomarkers show typical AD profile. There is no proof that their use could improve well-being or reduce health-care costs in these patients [51]. They could also generate additional costs, lead to invasive tests (LP), technical issues (CSF analysis). It should also be noted that these biomarkers only reflect the presence of AD lesions and cannot invalidate or confirm the existence of a mixed pathology, a very common situation in elderly subjects. CSF biomarkers for Lewy-body dementia, fronto-temporal dementia and limbic-predominant age-related TDP-43 encephalopathy (LATE) are under development and should highlight the combination of these pathologies in elderly.

So far, systematic screening for cognitive disorders is not currently recommended. On the other hand, an individual diagnosis, as soon as the first cognitive symptoms are identified, is encouraged by the French health authorities (*Haute Autorité de Santé*), without age limit [10, 37]. Patient care is known to be more effective when the etiological diagnosis is established and explained early. Last but not least, establishing the diagnosis of AD is more a source of relief for patients and their families than a psychological trauma [52].

In elderly subjects, three issues should be addressed to allow the best individualized benefit/risk ratio of biomarker use: the stage of cognitive impairment, the physiological age of the patient and the patient's willingness to know his or her diagnosis.

Cognitive Impairment Stage

Recent publications shed light on the preclinical stage of the disease, only characterized by biological changes in the brain. However, there is no recommendation for the use of biomarkers in cognitively intact, asymptomatic subjects. Besides, the overall progression rate of elderly individuals with positive biomarkers followed for an average of three years remains low (12%) [40]. On the other hand, knowledge of the etiological diagnosis in severe dementia would have no practical consequence on patient management. The American Amyloid Task Force consensus addressed the issue of the "proper use" of amyloid PET scans, which could provide insights into the right use of CSF AD biomarkers [12]. This consensus paper insisted on the presence of three criteria: *i*) there is an objectively confirmed memory complaint; *ii*) diagnosis of AD is possible but uncertain after thorough assessment by an expert physician; *iii*) knowledge of the amyloid status will increase the diagnostic certainty and modify management practices. The same article highlighted the potential inappropriate uses of this examination: quantification of amyloid lesions (which is not individually related to symptom severity), asymptomatic lesion search, in case of a family history of AD, non-medical use (e.g., insurance medical examination). As a result, the use of these diagnostic biomarkers may be considered for disorders ranging from MCI to moderately severe major neurocognitive disorders, in the absence of other contraindications.

Physiological age

The average life expectancy for an individual with major neurocognitive disorder and aged 75 to 85 is close to 5 years. After 85, it is close to 4 years on average [1]. Thus, despite their advanced age, some elderly people only complain about cognitive symptoms and request the most precise diagnosis to live out their remaining years. A comprehensive geriatric assessment of daily living activities, locomotor skills, sensory disorders, multimorbidity, and iatrogenesis is mandatory, since the latter conditions could influence the consequences of cognitive disorders. In practice, there is no point in making an etiological diagnosis in a

subject who cannot attend a cognitive rehabilitation session, who has severe presbycusis making verbal communication very difficult or who is repeatedly hospitalized for unstable heart failure. Similarly, making a precise diagnosis in an elderly subject whose life expectancy is less than one year, because of critical health condition (e.g. stage V chronic kidney disease, severe heart failure, metastatic cancer...) has no real impact on the patient's care.

Willingness to know the diagnosis

Since the measurement of CSF biomarkers requires LP, it is crucial to balance the additional value of these results against the disadvantages of the diagnostic procedure (although the risks are very low). It does not seem acceptable to recommend this assessment to someone who does not want to know their diagnosis. Conversely, patients who accept the procedure and demand a precise diagnosis should be informed of the limited scientific evidence in the oldest old. Furthermore, a "normal" CSF assessment should not be regarded as the absence of neurocognitive disease or discourage the patient for medical follow-up. Finally, the large majority of ongoing therapeutic trials targeting AD include participants whose diagnosis is based on biomarkers. The willingness to participate in this type of study should be taken into consideration when discussing the CSF assessment in elderly subjects. As a matter of fact, old age alone should not be an exclusion criterion for prescribing CSF biomarkers.

Conclusion

AD biomarkers can be used to identify specific biological features of the disease. In clinical practice, they enable a precise and early diagnosis; in research, they allow to study the preclinical stage of the disease. Disease-modifying treatments targeting the etiological mechanisms have been shown to be ineffective when prescribed at the stage of major neurocognitive disorders. Ongoing therapeutic trials are targeting the prodromal stage of the disease, which can only be understood using these diagnostic tools. Beyond clinical research, CSF biomarkers are being used more and more widely, to increase the diagnostic certainty, provide comprehensive patient information and optimize management, from the beginning of clinical symptoms. However, there is no precise framework for the use of biomarkers with regards to the age and general health status of the patient. The multiple causes of cognitive impairment in elderly and very elderly subjects make their interpretation difficult and ethical and clinical reflection must be systematically conducted.

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