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Cerebrospinal fluid biomarkers in diagnosing Alzheimer's Disease in clinical practice; an illustration with three case reports.

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Case Rep Neurol. 2010 Feb 24;2(1):5-11.

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Abstract

Analysis of the brain specific biomarkers amyloid β_{42} ($A\beta_{42}$) and total tau (t-tau) protein in cerebrospinal fluid (CSF) has a sensitivity and specificity of more than 85% for differentiating Alzheimer's Disease (AD) from non-demented controls. The combination of $A\beta_{42}$ and phosphorylated tau (p-tau) proteins in CSF allows a differentiation between AD and VaD with both a sensitivity and a specificity of around 85%. However, when CSF biomarkers are used to differentiate AD from other dementia syndromes, the sensitivity and specificity are modest. International guidelines are contradictory in their advice on the use of CSF biomarkers in AD diagnostics, resulting in a lack of consistency in clinical practice. We present three case-reports that illustrate clinical practice according to the Dutch and European guidelines and portray the value of CSF biomarker analysis as an add-on diagnostic to the standard diagnostic workup for AD.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of extracellular senile plaques and intracellular neurofibrillary tangles. It is becoming increasingly important to accurately diagnose AD at an early stage. An adequate diagnosis allows appropriate education, guidance, care and treatment for patients and their informal caregivers. Occupational therapy and caregiver support improve quality of life for AD patients, while treatment with acetylcholinesterase inhibitors can improve cognitive function [1]. Moreover, potentially neuroprotective therapies for AD, which are currently under development, are probably most beneficial when initiated at an early stage of the disease [2].

According to the current NINCDS-ADRDA diagnostic guidelines [3], definite diagnosis of AD can only be made post-mortem by histopathological examination of the brain. However, by using different diagnostic tools, such as neuropsychological tests and imaging techniques, a probable diagnosis can be achieved with reasonable sensitivity and specificity. Nowadays analysis of cerebrospinal fluid (CSF) biomarkers amyloid β_{42} ($A\beta_{42}$), total tau (t-tau) and phosphorylated tau (p-tau) is increasingly used to differentiate AD from other dementia disorders and non-demented patients. AD patients show a typical pattern of decreased $A\beta_{42}$ and increased p-tau and t-tau. The combination of decreased $A\beta_{42}$ and increased t-tau has a sensitivity and specificity of more than 85% in differentiating AD from healthy controls [4, 5]. The addition of p-tau to $A\beta_{42}$ and t-tau further increases specificity for AD [4]. Moreover, analysis of CSF biomarkers resulted in a correct diagnosis in 82% of neuropathologically confirmed AD and non AD cases [6]. A high NPV of 96% shows that normal CSF results make AD pathology very unlikely [7]. For differentiating AD from VaD, both the ratio of $A\beta_{42}/p\text{-tau}$, and $t\text{-tau} \times p\text{-tau} / A\beta_{42}$ yield sensitivities and specificities of more than 85% [8-10]. When CSF biomarkers are used to differentiate AD from dementia syndromes such as frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB), discrimination is more difficult. FTD can be discriminated from AD with reasonable sensitivity and specificity, using the t-

tau/A β_{42} ratio, and especially using p-tau, which is not elevated in FTD [11-14]. DLB patients show normal p-tau levels and lower tau levels compared to AD patients but overlap of values is still high, probably due to mixed pathology in the DLB group [15, 16].

The prevailing guidelines, NINCDS-ADRDA and the DSM-IV-TR, do not include CSF biomarkers in AD diagnostics, since the criteria were developed before these biomarkers were described [3]. The dementia guidelines from the American Academy of Neurology, which were last revised in 2001, mention CSF biomarkers but state that they are not appropriate for routine use in clinical practice [17]. The more recent European Federation of Neurological Societies (EFNS) dementia guidelines (2006) state that 'CSF A β_{42} , t-tau, and p-tau can be used as an adjunct in cases of diagnostic doubt' [18]. Dutch guidelines state that CSF analysis of these biomarkers are not part of the standard diagnostic work up but can be taken into consideration when a higher diagnostic certainty is desired [19, 20]. More specifically, they state that CSF analysis can be of additional value in patients under 65 years of age whose differential diagnosis is broad, or in patients in whom imaging techniques and neuropsychological tests do not lead to a clear-cut diagnosis. In 2007 a proposition was made for revising the research criteria for the diagnosis of AD [21]. This proposition states that a probable diagnosis of AD should be made using the core diagnostic criteria of early subjective memory impairments which gradually progress over more than 6 months, with objective evidence of significant memory impairment deficits supported by at least one of three abnormal biomarker values; i.e. abnormal CSF biomarkers, abnormal PET/SPECT scanning, or abnormal MRI, the latter two with the hallmarks of mediotemporal lobe hypoperfusion or atrophy. The somewhat contradictory suggestions in the guidelines result in inconsistency of routine diagnostics in clinical practice. We aim to clarify the contribution of CSF biomarkers in clinical practice with three typical case reports, and illustrate the need for an unambiguous guideline.

At the Radboud University Nijmegen Medical Centre (RUNMC) memory clinic we currently use CSF analysis according to the latest Dutch and European guidelines. The reference values for the

age group over 50 years that we established in our own laboratory using the sandwich ELISAs by Innogenetics are: $A\beta_{42} > 500$ ng/L, t-tau < 350 ng/L, p-tau < 85 ng/L [8, 22]. These values are largely in line with the reference values proposed in previous publications [5, 7]. In the last 1.5 years CSF analysis was performed in approximately 30 patients of the 200 patients that we saw at our memory clinic. The following case reports were selected from this patient group to exemplify the value of biomarker analysis in the standard diagnostic workup for AD.

CASE REPORTS

Patient A is a 67 year old woman, who had complaints about short term memory loss. Her relatives noticed her repeatedly asking the same questions. She had become insecure and started to double check her own actions. A friend had to help her with administrative duties. Her complaints developed gradually over the last one and a half year. She had a history of hypertension and osteoporosis. She smoked 20 cigarettes a day from the age of 15.

Neuropsychological tests indicated significant cognitive decline, with a Mini Mental State Examination (MMSE) [23] score of 22 out of 30, and a Cambridge Cognitive Examination (CAMCOG, a section of the CAMDEX) [24] score of 81 out of 104 (a higher score indicates a better performance; cut-off adjusted for age and education is 83). Mainly semantic memory function, both verbal and visually, recognition and orientation in time and place were affected, while visuoconstruction, attention, executive functioning and cognitive speed were normal. Therefore AD was suspected, more than VaD. The subsequent MRI showed extensive white matter lesions (<25% of white matter), probably of vascular-ischemic origin, next to distinct atrophy with broadening of the ventricles, and hippocampal atrophy grade 1 according to Scheltens rating scale [25]. Because of these MRI results and the patient's vascular risk factors, a diagnosis of possible VaD was considered next to AD. A lumbar puncture and further neuropsychological testing was performed to help clarify the diagnosis. The CSF biomarker levels were: $A\beta_{42}$ 424 ng/L, t-tau 634 ng/L and p-tau 117 ng/L. The decreased level of $A\beta_{42}$ with a significantly elevated t-tau and p-tau and, consequently, an $A\beta_{42}/p$ -tau ratio of 3.6, which is far below the cut-off ratio of 11.0 to discriminate VAD from AD, supported the diagnosis of AD over VaD, and therefore we diagnosed probable AD with cerebrovascular morbidity [8]. Treatment with acetylcholinesterase inhibitors was initiated, which she tolerated well. 17 months after diagnosis the patient was stable without further deterioration in cognition, behavior or daily activities and no further vascular disease hallmarks developed, supporting our initial diagnosis.

Patient B is a 63 year old woman who was referred to our clinic for a second opinion. The past two years she had become increasingly anxious about new situations. She was having difficulty finding words and engaging in conversations. In 2007 a neurologist could not identify a cognitive disorder. At that time, she was diagnosed as having a dysthymic disorder and post-traumatic stress disorder by a psychiatrist and treated with venlafaxine 75 mg, once daily. However, when she came to our memory clinic 9 months later, her complaints had not disappeared. She still had difficulty engaging in conversations and could not finish her chores because she kept forgetting what she was doing. Due to anxiety she stopped driving, internet banking and using the phone and video recorder, and there was a severe loss of initiative. She had a MMSE score of 21 out of 30, a CAMCOG score of 68 out of 104 (cut-off adjusted for age and education is 83) and a geriatric depression scale (GDS) score of 2 out of 15 (a score above 7 indicates depression) [26]. These results suggested cognitive decline, possibly AD, since no other underlying disease was apparent, and history taking and GDS score showed that her depressive mood was in remission. The MRI, already made in 2007, was re-evaluated and showed asymmetrical frontotemporal atrophy without medial temporal lobe atrophy (figure 1). A lumbar puncture was performed, because the neuropsychological assessment and the MRI were not fully conclusive and still left the possibility of AD diagnosis. CSF analysis showed normal levels of all biomarkers ($A\beta_{42}$ 560 ng/L, t-tau 335 ng/L and p-tau 77 ng/L). These results made an AD diagnosis less likely and could be compatible with a diagnosis of FTD. Further specific neuropsychological testing was done, which showed below average learning curves with unimpaired delayed recall and recognition, decline in attention and executive functions with reduced information processing speed and apathy. Apart from a below average word fluency there were no language disorders. The combination of MRI, CSF biomarker results and neuropsychological examination added to the likelihood of FTD. 15 months later the patient had deteriorated mildly with an MMSE now of 18 out of 30. No behavioral problems had occurred and her mood was stable. This clinical follow up still leaves room for AD.

Patient C is a 65 year old woman who visited our memory clinic with gradually increasing memory problems over the past three years. Her medical history revealed a subarachnoidal hemorrhage at the age of 33 due to an aneurysm of the anterior communicating artery, and excision of a frontal meningioma at the age of 54. After examination we objectified both verbal and visual memory dysfunctioning and disturbances in language, attention, visuoconstruction and executive functions ,which influenced her daily activities. Her MMSE score was 21 out of 30 with a CAMCOG score of 80 out of 104 (cut-off adjusted for age and education is 83). We suspected a diagnosis of AD, but because of complicated history and young age, we wanted to support this diagnosis with biomarker evidence. An MRI could not be performed because the patient had a metal clip on the cerebral aneurysm. A CT scan showed leftsided frontal atrophy and frontobasal atrophy of both hemispheres. CSF analysis was done, showing an $A\beta_{42}$ concentration of 431 ng/L, a t-tau concentration of 545 ng/L and a p-tau concentration of 118 ng/L. The decreased level of $A\beta_{42}$ and elevated t-tau and p-tau confirmed our notion of the diagnosis possible AD. Treatment with cholinesterase inhibitors was initiated. After 16 months mild deterioration in memory function was seen, compatible with the diagnosis of AD.

DISCUSSION

These case reports illustrate that CSF analysis may be a valuable addition to the standard workup for AD, when used according to the latest Dutch Diagnostic guidelines and the Dubois criteria for Alzheimer type pathology, although the latter are proposed as research criteria and await further validation [19, 21]. These cases underline that in current clinical practice we already frequently refer to these Alzheimer Disease research criteria, relying on positive AD-hallmarks, instead of the classical NINCDS-ADRDA criteria that only warrant AD diagnosis by exclusion of other systemic or brain diseases.

The first case shows the affirmative value of CSF biomarkers, when the combination of $A\beta_{42}$ and p-tau indicates that a diagnosis of AD with vascular disease is more likely than VaD. The second case report displays the use of CSF biomarkers when the differential diagnosis is broader. In addition, more diagnostic certainty was desired because the patient came for re-evaluation, and MRI had not led to a clear-cut diagnosis. The third case shows an example of a patient group in which MRI cannot be performed. Other conditions that exclude MRI scanning include having a cardiac pacemaker or claustrophobia. As an alternative a CT-scan can be performed to search for white matter lesions and to exclude a tumor, but the diagnostic value of CT images is limited by the lower resolution and lower sensitivity for vascular lesions. Moreover, visualization of the temporal horn requires additional reconstruction and CT more often leads to scatter artifacts. Therefore CSF analysis is regarded as a better alternative, when a lumbar puncture is not contra-indicated, e.g. in case of structural lesions.

The latest guidelines state that CSF analysis can be valuable in AD diagnostic work-up, only as an add-on diagnostic tool [21]. In certain cases the CSF biomarkers can be of help in the differential diagnosis, both for confirming and excluding a diagnosis of AD. Due to practical and occasionally medical circumstances, CSF analysis is not suitable to be used as primary diagnostic tool for all patients investigated at a memory clinic. However, neither the invasiveness of lumbar puncture nor post-puncture complaints are, any longer a serious concern with modern techniques, especially in

older patients. In large series with over 2000 patients zero complications have occurred, and the percentage of older patients suffering from post lumbar puncture pain is low, ranging from 0.9% to 4.1% [27-29].

It might be argued that CSF analysis is limited by the high inter-laboratory coefficient of variation [30, 31]. Even though processing and storage conditions have been standardized, inter-laboratory and intra-laboratory variation is still considerable [32]. However, once reference values have been established within the same laboratory, test results can be compared and reproduced. In a previously performed retrospective diagnostic validation study of $A\beta_{42}$, t-tau and p-tau in dementia we calculated optimal cut-offs for our population [33], because applying previously published criteria resulted in less optimal test results; e.g. for the Hansson criteria a sensitivity of 69% and specificity of 61% [7]. Using these reference values we can reliably generate CSF biomarker values with a sensitivity of 96% and a specificity of 97%, and draw firm conclusions from them [22].

So far, all CSF biomarkers studies have been carried out in selected patient cohorts as part of retrospective case control studies or in expert referral clinics, and predetermined cut-off values were usually not applied. Prospective studies should further demonstrate the discriminative value of CSF analysis in clinical practice. An example is a recent study showing the prognostic value of CSF biomarkers in patients with mild cognitive impairment [34]. We feel that, in spite of its limitations, CSF analysis already is a valuable add-on diagnostic measure, as illustrated by these case reports, in which predetermined cut-offs were used. The prevailing guidelines, therefore, should be updated to ensure consensus on the CSF application in clinical practice.

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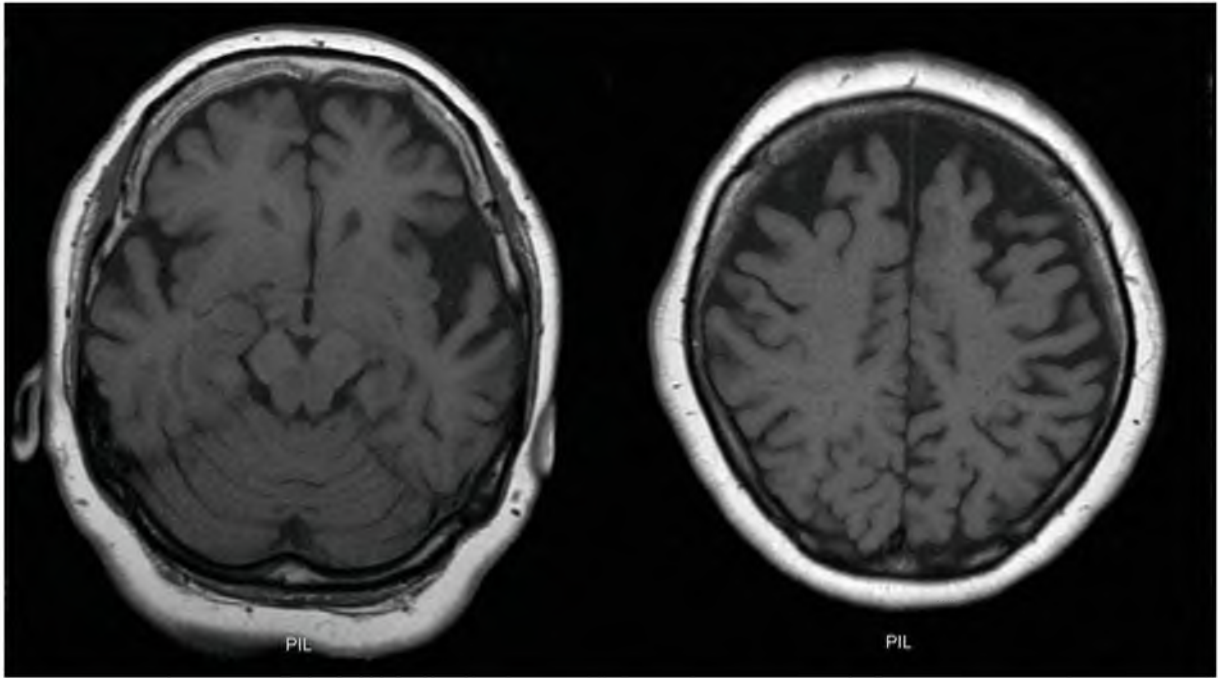


Figure 1. MRI of case 2. Transversal T2-FLAIR showing frontal cortical and asymmetrical left temporal lobe atrophy.