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AD with subcortical white matter lesions and vascular dementia: CSF markers for differential diagnosis

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Abstract

We investigated whether the cerebrospinal fluid (CSF) biomarkers beta-amyloid 1–42 (Aβ1–42), total tau (t-tau) protein and tau protein phosphorylated at threonine 181 (p-tau181) could discriminate Alzheimer's disease (AD) from vascular dementia (VD) patients. CSF samples of Aβ1–42, t-tau, and p-tau181 were collected from probable AD ($n=35$), probable AD with white matter changes (WMC) indicative of concomitant cerebrovascular disorder (CVD, $n=31$), VD ($n=20$), and an age-matched subgroup of patients with other neurological disorders (OND) without cognitive impairment ($n=24$).

AD patients showed very low Aβ1–42 levels (median=393 pg/ml). Aβ1–42, but not t-tau, differentiated AD from VD patients. However, the markers did not discriminate AD vs. AD plus WMC. In particular, both subgroups showed similar CSF biomarkers but they were significantly different from VD. ROC analysis showed that Aβ1–42 could discriminate AD from VD (AUC=0.85). The cutoff of 493 pg/ml gave sensitivity and specificity values of 77% and 80%, respectively. Similar results were obtained when Aβ1–42 was employed to discriminate AD with WMC from VD (95% specificity and 60% sensitivity, but with cutoff of 750 pg/ml). T-tau increased aspecifically in all cognitively impaired patients. P-tau181 performed better than t-tau in discriminating AD (with or without WMC) vs. VD.

In conclusion, Aβ1–42 proved to be a valuable tool to discriminate AD vs. VD patients and possibly to improve diagnostic accuracy in clinical forms, improperly classified as "mixed dementia" based on radiological vascular lesions.

Keywords: Dementia; Biomarkers; Diagnosis; Cerebro-vascular disorder; White Matter Changes

1. Introduction

Recent developments in therapeutic strategies require a clear assessment of a differential diagnosis in primary dementias [1]. Although prospective clinical observation usually provides an accurate diagnosis, it may require a rather long-lasting and costly follow-up. In the early stage of Alzheimer's disease (AD) the use of specific cerebrospinal fluid (CSF) biomarkers may speed up the diagnosis based on clinical and radiological approaches [2–5]. Recently, Sunderland and co-authors performed a meta-analysis on 3133 AD patients [6] and showed that CSF beta-amyloid 1–42 (Aβ1–42) level greater than 444 pg/ml and total tau protein (t-tau) greater than 195 pg/ml provide sensitivity and specificity of 92% and 89%, comparable to clinical criteria.

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However, AD patients are not a homogeneous population. Many cognitively impaired patients, with a progressive history of classical cortical dementia, show different degrees of concomitant vascular lesions, thus hindering diagnosis accuracy.

The long-standing debate on the importance of distinguishing AD from VD [7–9] remains relevant. Some reviews have suggested a misleading role of the amyloidogenic cascade in the pathogenesis of AD and proposed AD as a primary vascular disorder [9,10]. Yet, a clear distinction between "pure AD" and "pure VD" is possible when the latter is clinically defined by step-by-step progression, prominent impairment of executive functions, Hachinsky scale >4, and focal neurological signs implying extensive cortical and subcortical lesions [11,12]. Diagnostic distinction becomes less clear in case of apparent co-morbidity, because widespread cerebral amyloid angiopathy occurs in late onset AD, and most elderly AD patients have incomplete white-matter infarctions.

We are aware that the so-called "mixed dementias", per se, include different entities ranging from bilateral cortical infarction to the small-vessel subcortical lacunar state. In recent studies, patients with definite and widespread vascular lesions were ascribed to the so-called AD with cerebrovascular disorder (CVD). The exact boundaries, if any, between AD+CVD and VD are, however, uncertain. Indeed, this subgroup may include different degrees of vascular damage (see [13,14] as reviews of recent CT and MRI scaling). The present study focuses on the CSF profile of two sub-populations of patients, classified as probable AD due to progressive and diffuse cognitive decline, but distinguished by different MRI findings: the former subgroup did not show significant white matter changes (WMC), while the latter showed "infra-clinical" MRI-positive vascular lesions. Lesions on MRI were described as ill-defined hyper-intensities, 5 mm lesions, both on T2 and PD/FLAIR images, attributable to grade I (focal lesions) and II (beginning confluence of lesions) in Wahlund et al. scale [15]. We tried to assess whether CSF biomarkers correlate or not with clinical diagnostic categories. In particular, we wished to determine if these markers identify a peculiar subtype of AD, namely with or without WMC, and whether they could improve clinical accuracy in discriminating AD (bearing WMC or not) vs. VD.

Preliminary excerpts have been presented at the 9th Alzheimer conference (Philadelphia, July 2004) [16].

2. Materials and methods

2.1. Subjects

Between December 2002 and June 2004, 140 patients suffering from different degrees of cognitive impairment were consecutively evaluated at the Alzheimer Center of the Department of Neuroscience of Tor Vergata University Hospital. All patients provided a medical history and underwent a neurological examination, mini-mental state examination (MMSE), a complete blood screening (including routine exam, thyroid hormones, level of B12), neurophysiologic exams [17], and neuro-imaging (all but 2 had MRI, 39 had additional scintigraphy TC brain scan). The clinical follow-up included a more comprehensive neuropsychological examination, comprising a standardized neuropsychological battery (Mental Deterioration Battery, [18]) and a complete psychiatric evaluation. Hence, it was possible to exclude from the study the following categories: (i) patients with isolated deficits or mostly subjective memory loss and/or stable MMSE $\geq$25/30 on revisit (all together $n=28$); (ii) patients whose neurophychological profile and behavioural symptoms suggested a diagnosis of frontotemporal dementia ($n=13$), according to the diagnostic criteria of Neary et al. [19]; (iii) patients with a suspected diagnosis of dementia with Lewi bodies ($n=7$); (iv) and patients with a clinically manifest acute stroke in the last 6 months ($n=6$), as t-tau could return to normal levels very slowly [20].

Given these premises, the study enrolled 86 patients, affected by mild (MMSE $\geq$18) or moderate (MMSE between 14 and 18) dementia. These 86 patients were further classified, according to clinical criteria, as follows: AD ($n=66$) and VD ($n=20$). All AD patients fulfilled DSM IV [21] and NINCDS-ADRDA [22].

AD group was further divided into two subgroups: 35 "pure" AD (absence of white matter changes at MRI, or grade 0 on Wahlund's scale [15]) and 31 AD with WMC, meeting AD criteria but also showing brain imaging findings suggesting subcortical vascular lesions. In particular, the latter subgroup showed 1 to 4 focal T2-hyperintensities ($\geq$5 mm) sparing cortical regions. Using a formal radiological rating scale, AD and AD+WMC patients could be classified as 0 and 1/2, respectively, in the age-related WMC scale [15]. To discriminate VD from AD+WMC, the following criteria were used: VD included ischemic lesions, clinical history of at least a previous major stroke, subcortical form of dementia with prominent executive dysfunction [11,12], Hachinsky scale $\geq$4 (implying pre-existing clinically manifest ischemic insults and step-by-step clinical decline), presence of specific signs of damage involving pyramidal tracts, and evidence of risk factors such as hypertension. The group of AD plus WMC/CVD, already identified by radiological evidence of subcortical small vessel lesions (with no confluence), showed a progressive cognitive decline in the last 2 years with a significant memory loss, absence of clear neurological deficits, and lack of major risk factors for vascular damage.

The control group consisted of 24 non-demented subjects, affected by other neurological disturbances (OND) (Table 1). The vast majority suffered from lower extremity radiculopathy ($n=16$); 3 presented with signs of polyneuropathy and 5 were diagnosed as proximal myopathy. They were classified as control subjects, since they manifested