ABSTRACT

Introduction: The use of biomarkers (β-amyloid peptide and Tau protein) in the cerebrospinal fluid (CSF) is useful to identify patients with mild cognitive impairment (MCI) due to Alzheimer’s disease (AD). Other variables, such as a family history of dementia, medial temporal atrophy (MTA) and the ApoE genotype can also help characterize patients with MCI due to AD.

Aim: To identify, using CSF biomarkers for AD in a series of patients with amnestic MCI, those with true prodromal AD and the variables that characterize them.

INTRODUCTION

There is extensive literature characterizing mild cognitive impairment (MCI) as a multisystemic entity that affects one or several cognitive domains and with an annual rate of progression to clinical dementia of around 10%, although the concept encompasses patients in whom the clinical course does not involve clinical progression of impairment, and others who even show cognitive improvement. The misdiagnosis that is MCI affects a wide range of patients with different disorders including systemic diseases, drug-induced cognitive impairment and psychiatric diseases (mainly depression and anxiety), which could explain the variable clinical course [1-3]. Although the diagnosis of MCI is clinical, in this scenario, the detection of both neuroimaging and biochemical biomarkers in the cerebrospinal fluid (CSF), which provide a measure of neuronal damage (hippocampal atrophy on magnetic resonance imaging [MRI] and CSF Tau protein) and cerebral amyloid deposition (Pittsburgh compound B [PiB] on PET scan and CSF β-amyloid peptide) have allowed the characterization of MCI as due to Alzheimer’s disease (AD/MCI) if there is evidence that both pathogenic pathways (β amyloid and Tau protein) are altered in a given patient; so that we appear to be faced with true prodromal Alzheimer’s disease (AD) here [4-6]. This is the stage of disease where the utmost must be done to prevent disease progression by resorting to pharmacological approaches such as cognitive stimulation and promoting clinical trials.

The apparently complex diagnostic procedure can be carried out outside clinics specializing in dementia and tertiary care hospitals; this article thus describes the actions taken in our general neurology unit in a regional hospital, in patients with amnestic MCI using CSF biomarkers of AD to diagnose the prodromal phase of AD, which we believe to constitute an improvement in the quality of care for patients with cognitive impairment.

SUBJECTS AND METHODS

We studied patients with amnestic MCI in a general neurology unit who were diagnosed according to the Petersen criteria [7] and the Spanish Neurology Society criteria for the clinical diagnosis of MCI [8]. The patients were referred from Primary Care due to cognitive symptoms such as short-term memory loss. The first visit involved clinical history-taking to determine the presence of hippocampal amnesia that did not improve with semantic clues and demonstrate that the patient could carry out instrumental activities of daily living independently, and to rule out secondary causes for the cognitive deficits, such as medications that interfere with cognition (tricyclic antidepressants, benzodiazepines, opiate drugs), systemic disease (hepatic, pulmonary or renal chronic diseases) or the presence of persistent depressive disorder. Depression and/or anxiety were discarded through a specific medical interview. They then underwent the Mini Mental State Examination (MMSE) where they had to score ≥26/30 (adjusted for educational level), and episodic memory was assessed using the Memory Alteration Test (MAT) [9]. The patients thus selected underwent brain MRI to assess hippocampal and medial temporal lobe atrophy. The degree of atrophy was quantified by the Radiology Department of our hospital using the Scheltens visual rating scale [10] which classifies it into 5 levels (from 0 to 4) depending on the scores assigned to the width of the Choroid fissure, the radial width of the temporal horn and the length of the hippocampus (Table 1). For the statistical analysis, due to small size of the groups, they were grouped into two categories, one for levels 0-2 (normalminimal temporal atrophy) and the other for levels 3-4 (severe temporal atrophy).

A second visit was scheduled at 3 months to check for the persistence of memory deficit and to tell the patient and caregiver about the possibility of diagnosing AD in the prodromal phase by performing a lumbar puncture and analysing CSF biomarkers, for which written informed consent was requested. In addition, the apolipoprotein E (ApoE) genotype was determined in all patients as a risk marker for the development of AD. Lumbar puncture was performed between 9:00 and 11:00 am in the lateral decubitus position. Three samples of 1 mL of CSF were extracted in polypropylene tubes
for the determination of β-amyloid peptide 1-42, total Tau protein and phosphorylated Tau protein at position 181 (p-Tau). The samples were frozen at -80°C until testing.

The Hulstaert index (HI) was calculated according to the following formula:

\[ HI = \frac{(\text{β-amyloid peptide})}{240 + 1.18 \times \text{total Tau}} + \frac{(\text{p-Tau} - 15)}{285} \]

and the index AD-CSF index (p-Tau) proposed by Molinuevo et al. [12]:

\[ \text{AD-CSF index (p-Tau)} = \left( \frac{(1.200 - \text{β-amyloid peptide})}{1.075} \right) + \frac{(\text{p-Tau} - 15)}{285} \]

The patients were classified under amnestic MCI due to AD if they had a HI ≤ 1.0 and p-Tau ≥ 61 pg/mL (Figure 1).

The statistical analysis was carried out using the SPSS® software platform. Student’s test was used for between-group comparisons of mean basal parameter values, following verification of normality and subsequent logarithmic or square-root transformation when necessary. The results are expressed as median and range.

RESULTS

Thirty of the 41 patients were classified as having MCI due to AD. The differences between the two groups are shown in Table 2. There were no differences between groups in terms of age, sex or family history of dementia. Neither was any differences observed between the two groups in terms of the MAT score.

All CSF biomarkers were significantly altered (decreased β-amyloid, and elevation of total Tau and p-Tau) in patients with MCI-AD. Within the same principle, patients with MCI-AD showed significant elevation of the AD-CSF index (p-Tau).

There were no significant differences between the two groups in terms of the medial temporal atrophy score determined with the Scheltens visual rating scale. Conspicuously, although with a median value of 719 pg/mL, levels of β-amyloid peptide were high, HI was significantly decreased to a range typical of AD. Within the same principle, patients with MCI-AD showed significant elevation of the AD-CSF index (p-Tau).

The MCI-AD group showed a higher prevalence of the ApoE ε4 allele (18.2% vs 63.3%, p=0.012).

DISCUSSION

The clinical-investigative approach to patients with cognitive impairment differs substantially between specialized dementia consultations and general neurology clinics where the clinical approach and the practical application of recommendations from neurologist specializing in dementia prevail. One example in this context is the use of both MRI and CSF biomarkers for the characterization of amnestic MCI as prodromal AD. This approach is likely to provide added value to the quality of care of patients with cognitive impairment.

Although MCI is an entity with multiple aetiologies and an annual rate of progression to clinical dementia of 7-10%, there are currently no approved pharmacological treatments for this progressive phase of dementia. The clinical and therapeutic benefit of using biomarkers in MCI to determine whether it is due to AD is tremendous, as it allows identifying AD in its prodromal phase and justifies the initiation of treatment with acetylcholinesterase inhibitors (ACEI) in these patients in order to try to slow down disease progression.
to neuroimaging studies that use three-dimensional software to assess hippocampal volume, which is decreased in amnestic MCI and AD, but not in multidomain MCI [13]. However, the detection of medial temporal lobe atrophy using the easy-to-apply Scheltens visual rating scale has proved useful for the diagnosis of AD [14], and MTA has been correlated with progression to dementia in MCI [15]. In our daily clinical practice, we use the Scheltens scale to assess the degree of hippocampal and medial temporal lobe atrophy. However, in our series, it proved of little use to identify patients with MCI-AD, in that more severe atrophy was not associated with a decreased MAT score or Hulstaert index. Another approach to assessing neuronal damage which we used in our study relies on CSF biomarkers, specifically elevated levels of total and phosphorylated Tau protein, the latter adding specificity to the diagnosis of AD.

We use imaging techniques such as PiB-PET, which is currently restricted to a few tertiary care/research centres to assess the physiopathological process of cerebral amyloid deposition. Though more accessible, the determination of CSF levels of β-amyloid 1-42 also involves more invasive methods. This biomarker is decreased in patients with AD, which is attributed to its deposition in cerebral amyloid plaques. It is well known that CSF biomarkers are also altered in patients with MCI who progress to dementia during follow-up [16]. In our series, although the behaviour of biomarkers showed the involvement of the two pathogenic pathways involved in AD (amyloid and Tau protein), what was most interesting from a clinical viewpoint was the index that correlates β-amyloid peptide with total Tau protein, known as the Hulstaert index, and p-Tau levels, since both allow to classify amnestic MCI as prodromal AD. In this regard, previous international [16] and national [17] publications have shown that the combination of biomarkers is a highly accurate and specific predictor of progression from MCI to dementia.

Patients with MCI-AD tended to have a more extensive family history of dementia, but the difference was not statistically significant. However, the ApoE genotype was discriminative, in that the ε4 allele was more prevalent in the MCI-AD group. This supports the diagnostic probability of presenting with AD based on the increased relative risk conferred by the presence of this allele in the context of dementia [18] and highlights the predictive value of MCI progression to AD [19].

The diagnostic procedure allowed starting ACEI treatment (which is not approved in MCI) early in about 90% of the patients, in combination with cognitive stimulation therapy. However, current evidence does not support treatment with donepezil, rivastigmine or galantamine to prevent the progression of MCI to clinical dementia [20], although it should be noted that patients in these studies were selected solely on the basis of clinical criteria and not based on biomarkers. Part of the current therapeutic approach focuses on treating aggravating factors of cognitive decline such as depression and cardiovascular risk factors, especially hypotension, which requires more focus and emphasis in patients with MCI-AD. In addition, while donepezil could be effective in the cohort of patients with MCI associated with depression [21], this aspect was not adequately assessed in our study, since we did not make strict enough use of scales validated for the diagnosis of depression to allow conclusions to be drawn in this regard.

Our study, which was conducted under conditions of daily clinical practice, allows concluding the following: 1) amnestic MCI can be classified as prodromal AD based on the use of AD biomarkers in the CSF and the presence of at least one ApoE ε4 allele. 2) the assessment of medial temporal atrophy with a visual rating scale does not allow to differentiate patients with MCI-AD from those who do not have a pathogenesis characteristic of AD, and 3) the identification of prodromal AD allows early initiation of specific ACEI treatment.

REFERENCES