ELSEVIER

Alzheimer's & Dementia 6 (2010) 104–109

Alzheimer's & Dementia

Cerebrospinal fluid biomarker results in relation to neuropathological dementia diagnoses

Hans Brunnström[a,*], Nina Rawshani[a], Henrik Zetterberg[b], Kaj Blennow[b], Lennart Minthon[c], Ulla Passant[d], Elisabet Englund[a]

[a]*Department of Pathology, Institution of Clinical Sciences, Lund University, Lund, Sweden*
[b]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden*
[c]*Clinical Memory Research Unit, Institute of Clinical Sciences, Lund University, Malmö, Sweden*
[d]*Department of Geriatric Psychiatry, Institution of Clinical Sciences, Lund University, Lund, Sweden*

Abstract

Background: Clinical dementia diagnoses are not always consistent with neuropathological findings. As correct diagnosis is important for treatment and care, new diagnostic possibilities for dementia are in demand. Cerebrospinal fluid biomarkers should ideally be able to identify ongoing processes in the brain, but need to be further compared with neuropathological findings for evaluation of their diagnostic validity.

Methods: This study included 43 patients with a clinical dementia disorder. All patients were neuropathologically examined at the University Hospital in Lund, Sweden, during the years 2001-2008, and all had a lumbar puncture carried out as part of the clinical investigation during the time of cognitive impairment.

Results: Of eight patients, five with Alzheimer's disease had elevated total tau protein (T-tau) and decreased amyloid beta 1-42 protein (Aβ42), while both values for the other three patients were normal. Slightly elevated T-tau and/or decreased Aβ42 were also seen in several patients with other dementia diagnoses such as Lewy body disease, frontotemporal lobar degeneration and vascular dementia. Furthermore, T-tau levels did not differ markedly between patients with morphologically tau-positive and tau-negative frontotemporal lobar degeneration. Also, seven of nine patients with Creutzfeldt-Jacob disease exhibited pronounced elevation in T-tau concentration.

Conclusion: From this rather limited study, being the first of its kind in Sweden, we may conclude that there is no perfect concordance between cerebrospinal fluid biomarker levels and pathological findings, which should be taken into account in the clinical diagnostic setting.

Keywords: Alzheimer disease; Amyloid; Autopsy; Biochemical markers; Creutzfeldt-Jakob disease; Frontotemporal dementia; Lewy body disease; Neuropathology; Tau; Vascular dementia

1. Introduction

Clinical dementia diagnoses are not always consistent with neuropathological findings post-mortem [1–4]. As correct diagnosis is important for treatment and care, and also for calculating on prognosis and predicting complications, new diagnostic possibilities for dementia are in demand.

Analysis of biochemical markers (biomarkers) in cerebrospinal fluid (CSF) has been part of the diagnostic arsenal for some years. The CSF is continuous with the cerebral extracellular space, and CSF biomarkers are considered to reflect some of the biochemical condition in the brain. Hence, such markers should ideally be able to identify ongoing neuropathological processes.

The most studied CSF biomarkers in dementia are total tau protein (T-tau), phosphorylated tau protein (P-tau), and amyloid beta 1-42 protein (Aβ42). These markers are primarily used to identify Alzheimer's disease (AD), in which T-tau

*Corresponding author. Tel.: 01146-46173510; Fax: 01146-46143307.
E-mail address: hans.brunnstrom@med.lu.se

1552-5260/10/$ – see front matter
doi:10.1016/j.jalz.2009.12.005

and P-tau levels are increased and Aβ42 decreased [5,6]. However, neither amyloid nor tau proteins are specific for AD. Elevated T-tau and/or reduced Aβ42 levels in CSF have been reported in some, though not a majority of, neuropathologically examined patients with vascular dementia (VaD), frontotemporal dementia, dementia with Lewy bodies (LBs), and Creutzfeldt-Jakob disease (CJD) [7–10]. Even P-tau may be elevated in patients with dementia subtypes other than AD, as known from a few cases [8,10].

Neuropathology is required for a definite dementia diagnosis [11,12]. However, to our knowledge, there are today just a few studies on CSF biomarkers in different dementia subtypes, where all or the majority of the patients have been examined neuropathologically [7,9,10,13–15]. The aim of the present study was to evaluate CSF protein levels in neuropathologically examined demented individuals, for the first time in a Swedish population, to further add to the knowledge on the validity of CSF biomarkers.

2. Methods

2.1. Study population

All patients fulfilling the following three criteria were included in the study:

1. A clinical dementia disorder.
2. A neuropathological examination performed within the Department of Pathology at the University Hospital in Lund, Sweden, during the years 2001–2008.
3. A lumbar puncture (LP) carried out during the time of cognitive impairment as part of the clinical investigation, with subsequent CSF analysis of at least one of T-tau, P-tau, and Aβ42.

A total of 43 patients fulfilled the criteria, and were thus included in the study. There were a few patients during the covered years with analyzed CSF biomarkers and a neuropathologically identified disorder that could have lead to a dementia syndrome (e.g., CJD, amyotrophic lateral sclerosis, multiple system atrophy, or vascular pathology), but where the cognitive status was unknown or not classified as dementia (e.g. mild cognitive impairment or unspecified encephalopathy). In addition, a few patients were identified who fulfilled the criteria except that neither T-tau, P-tau, or Aβ42 were analyzed, and these patients were therefore also excluded (there was no saved CSF for new analyses).

The following data were collected for the included patients: age at time of death, gender, pathological dementia diagnosis, approximate duration of illness, time from LP to death, and the results of CSF biomarker analyses. For four subjects, duration of illness was irretrievable from the medical records. The patients' degree of cognitive impairment at the time of LP was not assessed in this study.

This retrospective cohort study was entirely based on data or samples which had already been collected for purely clinical management purposes. According to Swedish law and ethical guidelines, there is no need for a formal approval from an ethics committee for this kind of descriptive investigations. This has been substantiated by a consultation with the regional ethical review board of the University in Lund (H.B., E.E., 2009).

2.2. Histopathological diagnostics

All cases were previously examined and diagnosed by the same neuropathologist (E.E.). The standard histopathological procedure at the Department of Pathology at the University Hospital in Lund, Sweden, has been previously described in detail [4]. The classification of dementia subtypes was in adherence with the Swedish consensus on dementia [16], generally in accordance with criteria for AD, VaD, and frontotemporal dementia, respectively [17–20]. LB pathology was regarded in accordance with the consensus report on dementia with LBs presented in 2005 [21].

2.3. CSF analysis

CSF samples were collected in the clinical setting, before this study, by LP at the L3/L4 or L4/L5 interspace. The standard procedure was collection of CSF in polypropylene tubes, with aliquoting and freezing of the samples, with subsequent storage at –80°C without further thawing and freezing, before biochemical analyses. All analyses were performed at the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital in Mölndal, Sweden. T-tau was assessed using a sandwich enzyme-linked immunosorbent assay (ELISA) constructed to measure both normal and hyperphosphorylated tau [22]. CSF concentrations of P-tau were determined using a sandwich ELISA constructed to specifically measure tau phosphorylated at Thr181 [23]. Aβ42 was assessed using a sandwich ELISA constructed to specifically measure β-amyloid [24]. CSF concentrations of neurofilament light protein (NFL) were determined using a previously described ELISA method [25]. The detection limit for the NFL ELISA was 250 ng/L. The intra- and interassay coefficients of variation were 5.2% and 16%, respectively.

2.4. Biomarker reference values

The CSF biomarker standard reference values from the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital in Mölndal, Sweden, were applied to determine whether a measured value was normal or pathological. The reference value for T-tau was <300 ng/L at age 18–44 years and <400 ng/L at age >44 years. The reference value for P-tau was <60 ng/L at age 20–59 years and <80 ng/L at age >59 years. The reference value for Aβ42 was >450 ng/L at age >18 years. The reference value for NFL was <250 ng/L at age <60 years, <380 ng/L at age 60–69 years, and <750 ng/L at age >69 years. A study on CSF biomarker reference values has been previously published [26].