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Neurobiology of Aging 31 (2010) 215–223

NEUROBIOLOGY OF AGING

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Slowing of EEG correlates with CSF biomarkers and reduced cognitive speed in elderly with normal cognition over 4 years

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Received 10 December 2007; received in revised form 17 February 2008; accepted 26 March 2008
Available online 6 May 2008

Abstract

Background: Cerebrospinal fluid (CSF) biomarkers and quantitative EEG show particular patterns of change in Alzheimer's disease (AD) and reflect neuropathologic processes and cerebral function, respectively. The changes precede cognitive decline and should be visible already in preclinical stages. We therefore aimed to investigate their relationship in cognitively healthy individuals.
Method: Thirty-three (33) elderly individuals with repeated normal scores on cognitive tests over 4.5 years underwent EEG recording with quantitative frequency analysis and analysis of CSF total tau (T-tau), phosphorylated tau (P-tau) and β-amyloid$_{1–42}$ (Aβ42).
Results: CSF T-tau and P-tau correlated with relative EEG theta power ($r_s > 0.545$; $p < 0.01$), but not with relative alpha, beta or delta power. The combined P-tau/Aβ42 ratio exhibited an even stronger correlation with relative theta power ($r_s = 0.622$; $p < 0.001$), especially in the right posterior quadrant of the head ($r_s = 0.643$; $p < 10^{-4}$). Slowing of cognitive speed correlated with increased relative theta power, foremost in the posterior quadrants ($r_s > 0.503$; $p < 0.01$), and high P-tau/Aβ42 ratio ($r_s > 0.462$; $p < 0.01$).
Conclusions: Our results suggest that already in cognitively healthy elderly subjects, biochemical changes in CSF, and the possible underlying neuropathologic processes it reflects, have an effect on cerebral function as visualized by the EEG rhythm and cognitive speed. It hereby suggests that CSF biomarkers and EEG theta activity might indicate early abnormal degenerative changes in the brain.

Keywords: Alzheimer disease; Dementia; Mild cognitive impairment; Early diagnosis; Cerebrospinal fluid; Biological markers; Tau protein; Amyloid beta-protein; Electroencephalography; Theta rhythm; Control group; Cognition; AQT

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder where post-mortem studies have suggested disease-onset up to 20–30 years prior to diagnosis (Price and Morris, 1999). AD is believed to evolve in specific patterns (Dubois et al., 2007) and in the last decade mild cognitive impairment (MCI) has gained acceptance as a prodromal state with cognitive impairment and pronounced increased risk of developing AD (Blennow et al., 2006; Gauthier et al., 2006). Diagnostic markers including cerebrospinal fluid (CSF) biomarkers, hippocampal atrophy on MRI, and temporo-parietal abnormalities on functional imaging with PET or SPECT have repeatedly been deviant already in the MCI stage (Gauthier et al., 2006). Therefore, these biological markers have been given the status of supportive features in the newly proposed version of the NINCDS-ADRDA criteria for AD diagnosis (Dubois et al., 2007). It has furthermore been suggested that the biomarkers are affected already in the preMCI state, thus before measurable cognitive deterioration (Fagan et al., 2007; Stomrud et al., 2007). Increased knowledge of potential pre-

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doi:10.1016/j.neurobiolaging.2008.03.025

clinical biomarkers is important since new disease-modifying treatments have already entered into clinical trials and are probably most effective early in disease progression, before irreversible changes are too widespread.

In CSF, the tau protein (T-tau), the phosphorylated tau protein (P-tau) and the β-amyloid$_{(1–42)}$ (Aβ42) are the most validated biomarkers for AD (Blennow, 2004).The tau protein is responsible for axonal stability and transportation and elevated levels in CSF follows neuronal degeneration in AD but also in Creutzfeldt–Jacob's Disease (CJD) and transiently in acute stroke (Blennow, 2004; Hesse et al., 2001). Abnormal hyperphosphorylation of tau protein constitutes a major component of the neurofibrillary tangles observed in AD (Buerger et al., 2006). Hence, elevated P-tau reflects the loss of neurons with a pathologic phosphorylation state seen in AD (Itoh et al., 2001). In contrast to T-tau, normal P-tau levels are seen in CJD and acute stroke (Hesse et al., 2001). Aβ42 is a result of an alternative cleavage of amyloid precursor protein (APP) and it has a high tendency to aggregate and form plaques. Decreased levels are seen in CSF of subjects with AD but also in some other dementias and neurologic diseases (Blennow, 2004). The combination of both elevated T-tau and P-tau together with decreased Aβ42 differentiate and predict AD with good accuracy (Hansson et al., 2006).

Diffuse low frequent activity on quantitative EEG is seen in AD and correlates with disease stage (Babiloni et al., 2006; Coben et al., 1985; Prichep et al., 1994). Increase of relative theta power by itself or in combination with changes in other frequencies has differentiated early forms of AD from controls in several studies, and has showed intermediate characteristics in MCI (Coben et al., 1985; Jelic et al., 2000; Jeong, 2004; Lehmann et al., 2007; Prichep et al., 1994; Rossini et al., 2006). A suggested sequence of changes in EEG frequencies during AD development could be extrapolated from current published data on MCI samples. First an increase of theta power is seen, followed by a decrease of beta power, decrease of alpha power and at last increase of delta power (Jeong, 2004; Prichep et al., 1994). Furthermore administration of anti-cholinergic substances (Osipova et al., 2003) or acetylcholinesterase inhibitors (Brassen and Adler, 2003; Kogan et al., 2001) leads to enhancement and reduction, respectively, of the AD-related changes in EEG frequencies as described above. Moreover, the changes have in some studies been restricted to theta power alone (Brassen and Adler, 2003; Kogan et al., 2001).

Several biomarkers and diagnostic tools correlate with changes in EEG frequencies predominantly in AD cohorts. Hippocampal atrophy on MRI (Grunwald et al., 2007), abnormal cerebral blood flow (Mattia et al., 2003; Rodriguez et al., 1998), autopsy-confirmed neuron loss (Rae-Grant et al., 1987), activity of daily living functions (Onishi et al., 2005) and memory function (Prichep et al., 1994; van der Hiele et al., 2007) have all correlated with slowing of EEG rhythm. Furthermore, a previous study reported a correlation between tau protein and slowing of EEG global field power in a healthy control group (Jelic et al., 1998). The authors requested further studies investigating the relationship between CSF biomarkers and EEG rhythm, however no other study has to our knowledge been published. We therefore aim to investigate whether the levels of cerebrospinal fluid biomarkers are associated with EEG frequency in cognitively healthy elderly.

2. Methods and material

2.1. Subjects

The included subjects are cognitively normal, elderly subjects recruited by the memory clinic at Malmö University Hospital, Sweden to constitute a normal control group in dementia studies and they have been followed over a period of 4.5 years. They were recruited in 2002 through advertisements 3.5 years prior to baseline of this study and they were examined thoroughly, including medical history, somatic and psychiatric examination, and cognitive testing. Inclusion criteria for this control group in 2002 were intact ADL functions, no memory complaints and cognitive tests results within expected normal range. Exclusion criteria were active physical or mental disease, which could affect the cognitive status, including pathology on CT, fulfilment of criteria for AD (McKhann et al., 1984) or other dementia types and fulfilment of criteria for MCI (Petersen et al., 2001). Remaining individuals at baseline of this study in 2005 underwent an EEG followed by CSF collection, which was performed within a year after the EEG. Cognitive testing was made at baseline prior to the EEG investigation and at the time of the CSF collection. The same cognitive test battery and assessments have been used throughout the 4.5 years and include mini-mental state examination (MMSE) (Folstein et al., 1975), Alzheimer's disease assessment scale (ADAS-cog) (Rosen et al., 1984), clock-drawing, cube-drawing and a quick test for cognitive speed (AQT) (Jacobson et al., 2004). Individuals were excluded if they performed subnormal results on MMSE (score of 26 or lower) at any of the cognitive test occasions, since the cognitive status of these could be questioned. Fulfilment of criteria for dementia disorder or MCI during the study period also led to exclusion. The study was approved by the regional ethics committee at Lund University, Lund, Sweden. The subjects gave their written consent to participate.

2.2. EEG procedure

EEG was recorded for 20 min with a Nervus (Viasys Healthcare Inc, Madison WI) equipment from 19 electrodes, according to the 10–20 system and a sampling frequency of 256 Hz, high pass filter 0.16 Hz and low pass filter at 500 Hz. In order to certify that the analysis was performed on EEG recorded with the patient fully awake, 10 s epochs of artefact free EEG were selected in the eyes-closed situation within 5–20 s after interaction with the patient either by verbal communication, or following eye closure on com-