tau Protein in Cerebrospinal Fluid

A Biochemical Marker for Axonal Degeneration in Alzheimer Disease?

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ABSTRACT

Cerebrospinal fluid (CSF) biochemical markers for Alzheimer disease (AD) would be of great value to improve the clinical diagnostic accuracy of the disorder. As abnormally phosphorylated forms of the microtubule-associated protein tau have been consistently found in the brains of AD patients, and since tau can be detected in CSF, two assays based on several well-defined monoclonal tau antibodies were used to study these proteins in CSF. One assay detects most normal and abnormal forms of tau (CSF-tau), while the other is highly specific for phosphorylated tau (CSF-PHFtau). A marked increase in CSF-PHFtau was found in AD (2230 ± 930 pg/mL), as compared with controls (640 ± 230 pg/mL; \( p < 0.0001 \)), vascular dementia, VAD (1610 ± 840 pg/mL; \( p < 0.05 \)), frontal lobe dementia, FLD (1530 ± 1000 pg/mL; \( p < 0.05 \)), Parkinson disease, PD (720 ± 590 pg/mL; \( p < 0.0001 \)), and patients with major depression (230 ± 130 pg/mL; \( p < 0.0001 \)). Parallel results were obtained for CSF-tau. No less than 35/40 (88%) of AD patients had a CSF-PHFtau value higher than the cutoff level of 1140 pg/mL in controls. The present study demonstrates that elevated tau/PHFtau levels are consistently found in CSF of AD patients.

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However, a considerable overlap is still present with other forms of dementia, both VAD and FLD. CSF-tau and CSF-PHFTau may therefore be useful as a positive biochemical marker, to discriminate AD from normal aging, PD, and depressive pseudodementia. Further studies are needed to clarify the sensitivity and specificity of these assays, including follow-up studies with neuropathological examinations.

Index Entries: Alzheimer disease (AD); biochemical markers; cerebrospinal fluid (CSF); tau protein.

INTRODUCTION

Alzheimer disease (AD) is the most common form of dementia. Some relatively rare genetic forms of AD do exist, but the majority of patients have no obvious family history and are classified as suffering from sporadic AD. Although new research criteria for the clinical diagnosis of pure AD have been proposed (Wallin et al., 1994), the clinical diagnosis of sporadic AD continues to be made by way of exclusion (McKhann et al., 1984), without the support of any positive diagnostic criteria. Therefore, biochemical markers for AD would be of great use, both to improve the clinical diagnostic accuracy in scientific studies and treatment trials, and to increase our knowledge concerning the underlying pathogenesis of the disorder. These markers should reflect the pathological changes in the brain, i.e., the degeneration of neurones and their synapses (Coleman and Flood, 1987; Davies et al., 1987; Hamos et al., 1989), as well as the increased number of senile plaques (SPs) and neurofibrillary tangles (NFTs) compared with those found in nondemented individuals of similar age (Tomlinson and Corsellis, 1984).

The normal tau protein is a human brain phosphoprotein with six isoforms ranging in size from 352-441 amino acids (Goedert et al., 1988; Harrington et al., 1991), which binds to tubulin in the microtubules, thereby promoting microtubule assembly and stability (for a review, see Goedert, 1993). In AD, however, the principal component of the paired helical filaments (PHFs), which make up the characteristic NFTs, neuropil threads, and senile plaque neurites, is probably an abnormally hyperphosphorylated form of tau protein (PHFtau) (Grundke-Iqbal et al., 1986; Ihara et al., 1986). PHFtau is also called A68 (Wolozin and Davies, 1987), Alzheimer disease associated proteins (ADAP) (Ghanbari et al., 1990), and tau 64/69 (Delacourte et al., 1990).

The concentration of PHF-tau, is increased in cortical AD brain homogenates (Wolozin and Davies, 1987; Bissette et al., 1991; Harrington et al., 1991; Mukaeovatra-Ladinska et al., 1992; Bramblett et al., 1992; Khatoon et al., 1992; Mercken et al., 1992; Harrington et al., 1994), whereas the concentration of normal tau is reduced (Bramblett et al., 1992; Mukaeovatra-Ladinska et al., 1992; Harrington et al., 1994). These findings are consistent with studies reporting that the tau mRNA level is unchanged in