Some Notes on Visinin-Like Protein 1 and Alzheimer Disease

To the Editor:

We wish to comment and add some potentially useful information on certain aspects of the report of Lee and collaborators, which was recently published in Clinical Chemistry (1). In an earlier study, the authors had proposed visinin-like protein 1 [VILIP-1(1) or VSNL1; VSNL1 gene (visinin-like 1)] as a potential biomarker for stroke because they had detected this intracellular calcium-binding protein in cerebrospinal fluid (CSF) in a rat model of stroke and in the plasma of patients after stroke (2). The group extended these findings to Alzheimer disease (AD) in a second publication (1). VILIP-1 concentrations were significantly altered in the CSF of AD patients; hence, the authors concluded that VILIP-1 might also be a useful novel biomarker for AD-related brain injury. Lee et al. put forward the hypothesis that measures of VILIP-1 might reflect neuronal injury with subsequent release of the intracellular protein VILIP-1 into the CSF. The authors stated that both Aβ and τ reflect different pathologic features of AD, whereas VILIP-1 may reflect the end result of the disease, namely neuronal cell death. We would like to add important information concerning the hypothesized relationship between the calcium sensor protein VILIP-1 and AD (3–5). Owing to the limited space, we cannot discuss here the findings on the production of VILIP-1 in rat brain (1); instead, we would like to emphasize that VILIP-1 immunoactivity is also abundantly present in the nondemented human brain with a regional and cellular distribution of the protein similar to that in rat brain (3). With a knowledge of the topochemistry of VILIP-1 in human brain, we have addressed 3 questions about VILIP-1 in the brains of AD patients: (a) Is the cellular expression of the protein altered in AD; (b) is the protein content altered in AD brains; and (c) is there any anatomical association of the neuropathologic hallmarks of the disease (plaques, tangles) with VILIP-1? We found that the number of VILIP-1–immunoreactive neurons was significantly reduced in the temporal cortex of AD patients, whereas the total number of neurons was unchanged (4). These data point to a disease-related loss of VILIP-1–producing neurons. Moreover, western blot analyses of brain tissue extracts of AD patients revealed that VILIP-1 is less concentrated in AD brains (5). Importantly, other groups have confirmed the reported changes in VILIP-1 protein production in AD brains by means of gene microarray analysis (6). Both the reduced number of VILIP-1–immunoreactive cortical neurons and the decreased tissue content in AD fit with the CSF data presented by Lee and colleagues. Furthermore, extracellularly located VILIP-1 was detected in close association with typical pathologic hallmarks of AD, such as dystrophic nerve cell processes, amorphous and neuritic plaques, and extracellular tangles, pointing to an involvement of this calcium sensor protein in the pathophysiology of changed calcium homeostasis in AD (4, 5). Moreover, these data provide reason to suppose that VILIP-1 may not only be a CSF marker of cell injury in AD (1) but may also be causally related to AD. Because VILIP-1 is associated with fibrillar tangles in AD brains, we tested whether VILIP-1 has an influence on τ hyperphosphorylation. VILIP-1 production enhanced hyperphosphorylation of τ protein and enhanced calcium-mediated cell death in transfected neuronal cell lines. These findings suggest that this calcium sensor protein may indeed influence τ phosphorylation and have a role in calcium-mediated neurotoxicity in AD. The observed reduction in VILIP-1–producing cells in AD thus may indicate selective vulnerability (5). The close association of VILIP-1 with τ pathology is of special interest because it is in good agreement with the findings of Lee et al. (1) that VILIP-1 values correlate highly with phosphorylated τ in patients, but not with Aβ values.

We hope that our added information on VILIP-1 will enable the readers of Clinical Chemistry to put these highly interesting data on the potential biomarker VILIP-1 in perspective with respect to a possible pathophysiological relationship between VILIP-1 and AD.

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