

## EDITORIAL COMMENTARY

## CSF tests for dementia: a potential headache?

In recent years advances have occurred in understanding the fundamental mechanisms associated with Alzheimer's disease.<sup>1</sup> However, despite a torrent of discovery, practical and accurate diagnostic markers have remained elusive. An array of techniques have been tested and most, if not all, have ultimately been deemed to be unsuitable owing either to their impracticality or lack of specificity. Excitement is now mounting that the "holy grail" of Alzheimer's disease diagnosis will be found by quantifying one or more of the metabolic *exhaust* products associated with the pathophysiological mechanisms which cause Alzheimer's disease. An extensive literature has started to emerge and some have gone as far as to commend their use in routine investigation of dementia. What is undisputed is that some CSF indices are abnormal in Alzheimer's disease. For instance, the concentrations of the long form of amyloid  $\beta_{42}$  are paradoxically reduced, presumably as this molecule is preferentially deposited in the brain of patients with Alzheimer's disease.<sup>2</sup> Other markers such as CSF tau protein (CSF-tau) are shown to be significantly increased in the CSF. In this issue Andreasen *et al* (pp 298–305) add to this literature and present CSF-tau assay data from a community population sample of 75 patients clinically diagnosed with Alzheimer's disease. The paper reviews 15 earlier studies and concludes that measurement of CSF-tau may lack specificity, as it sometimes fails to distinguish patients with Alzheimer's disease from those clinically diagnosed as having vascular dementia. Where does this leave the clinician who may wish to confirm the clinical diagnosis of Alzheimer's disease with a CSF test? Despite the convincing evidence which suggests that CSF metabolites such as CSF-tau can consistently be detected in patients with Alzheimer's disease, the clinical utility of these investigations remains uncertain. Important questions remain

unanswered. Firstly, there is no consensus as to the precise cause of the raised CSF-tau and although it may relate to neuronal loss its relation to the phosphorylated form of tau protein is not clear. Secondly, the true sensitivity and specificity of these CSF tests are still unresolved as most current studies have used clinical criteria to diagnose Alzheimer's disease, which means that the diagnoses against which the CSF tests are compared are themselves only 80% to 90% accurate. Finally, data concerning the performance of these markers during the very early or pre-clinical stages of the disease are also not available. While these problems continue to be resolved, I suggest that it is wise to contain our excitement and wait to find a reliable CSF marker that is both specific for definite Alzheimer's disease and not detected in other types of dementia. The major practical headache for research is how to provide more meaningful specificity and sensitivity data for these sorts of study, without waiting for diagnostic confirmation by postmortem examination. I wonder whether there is a need to think the unthinkable and re-evaluate the current clinical diagnostic criteria to see if they can be refined? In the meantime clinicians should continue to reserve CSF examination for those patients suspected of normal pressure hydrocephalus or those with atypical forms of dementia.

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- 1 Hardy J. Amyloid, the presenilins, and Alzheimer's disease. *TINS* 1997;20:154–9.
- 2 Motter R, Vigo-Pelfrey C, Kholodenko D, *et al*. Reduction of beta amyloid peptide 42 in the cerebrospinal fluid of patients with Alzheimer's disease. *Ann Neurol* 1995;38:643–8.