CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and Alzheimer's disease: a meta-analysis of 51 studies
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CRD summary
The review found cerebrospinal fluid phosphorylated tau protein was a good marker of probable Alzheimer's disease, a satisfactory marker of mild cognitive impairment and its progression, but less useful for distinguishing Alzheimer's disease from other dementias. Overall, given weaknesses in the review methods, analysis and the design of the studies, these conclusions appear optimistic and should be viewed with caution.

Authors' objectives
To assess the accuracy and clinical utility of cerebrospinal fluid phosphorylated tau protein for the diagnosis of Alzheimer's disease and for diagnosis and prognosis of mild cognitive impairment.

Searching
MEDLINE, PsycINFO, ASSIA (Applied Social Sciences Index and Abstracts), EMBASE and Web of Knowledge were searched from inception to February 2009; search terms were reported. Science Direct, Ingenta Select, Ovid Full text and Wiley-Blackwell full text collection were also searched. Dissertation Abstracts (1975 to December 2007) and recent conference proceedings (handsearch) were searched to identify unpublished studies. Experts in the field were contacted for unidentified studies.

Study selection
Studies that assessed cerebrospinal fluid phosphorylated tau for the diagnosis of Alzheimer's disease, the diagnosis or prognosis of mild cognitive impairment, or the differential diagnosis of Alzheimer's disease compared with mild cognitive impairment, were eligible for inclusion. Studies could use any recognised definition of Alzheimer's disease or mild cognitive impairment.

Studies were excluded if they had 'inadequate data', based on an assessment using the STARD criteria for the reporting of diagnostic accuracy studies (i.e. did not adequately describe the study population, the reference standard, the technical specifications of the materials and methods used, or the definition and rationale for the units used).

All included studies were conducted in specialist centres, mostly clinics specialising in neurology or dementia. The reference standard for Alzheimer's disease diagnosis was usually the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. For mild cognitive impairment diagnosis, the Mayo Clinic criteria were most frequently used, with prospective validation over at least one year in the case of progressive versus non-progressive illness.

All studies of diagnosis were case-control studies and studies of mild cognitive impairment prognosis were follow-up cohorts. For studies of Alzheimer's disease the control groups were most frequently patients without dementia but with neurological disease, or patients with non-Alzheimer's dementia. For mild cognitive impairment, the control groups were healthy controls, with or without subjective memory complaints. Tau epitopes measures and the cut-off values for cerebrospinal fluid phosphorylated tau (used to diagnose Alzheimer's disease and mild cognitive impairment) varied across studies.

The author did not state how studies were selected for inclusion, or how many reviewers performed the selection.

Assessment of study quality
The STARD (Standards for Reporting of Diagnostic Accuracy) guideline was used as a basis for assessing study quality. Studies were deemed to have failed quality assessment if they omitted five or more of the 25 items on the STARD checklist.
The author did not state how validity assessment was performed.

Data extraction
Data were extracted to calculate the sensitivity and specificity of cerebrospinal fluid phosphorylated tau, with 95% confidence intervals (CIs), for each study and each differential diagnosis.

The author did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Pooled estimates of sensitivity and specificity, with 95% confidences, were calculated using the DerSimonian-Laird random-effects model, for each differential diagnosis. The main analyses combined data for all tau epitopes (p181, p199 and p231); subgroup analyses, by epitope, were also undertaken.

Between study heterogeneity was assessed using the $I^2$ test.

Clinical utility was assessed using the clinical utility index, where the positive utility index (for ruling-in the diagnosis) was sensitivity x positive predictive value, and the negative utility index (for ruling-out diagnosis) was specificity x negative predictive value. Utility index was classified as at least 0.81 for excellent, at least 0.64 for good, at least 0.49 for satisfactory, 0.49 or lower for poor.

Results of the review
Overall, 30 studies (n=4,597 participants who received cerebrospinal fluid testing) providing 51 comparisons were included in the review.

Alzheimer’s disease versus healthy or neurological control groups (19 studies, 1,329 patients with probable Alzheimer’s disease, 971 control participants): The pooled estimate of sensitivity was 77.6% (95% CI 70.6 to 83.9) and the pooled estimate of specificity was 87.9% (95% CI 84.3 to 91.1). The $I^2$ test indicated moderate to high heterogeneity. There was no significant difference in sensitivity or specificity between epitopes of cerebrospinal fluid phosphorylated tau. For clinical utility, the positive utility index was 0.70 (good) and negative utility index was 0.64 (good).

Alzheimer’s disease versus other types of dementia (18 studies, 1,304 patients with Alzheimer’s disease, 588 control participants): The pooled estimate of sensitivity was 71.6% (95% CI 63.1 to 79.5) and the pooled estimate of specificity was 77.8% (95% CI 72.3 to 82.7). The $I^2$ test indicated moderate to high heterogeneity. Subgroup analyses of cerebrospinal fluid phosphorylated tau epitopes indicated that p181 may be significantly less sensitive than either p199 or p231, and that p231 may be significantly less specific than either p199 or p181 (both $p=0.01$), but data were limited. For clinical utility, the positive utility index was 0.62 (satisfactory) and negative utility index 0.45 (poor).

Mild cognitive impairment versus healthy control groups (eight studies, 247 patients with mild cognitive impairment, 200 control participants): The pooled estimate of sensitivity was 79.6% (95% CI 64.2 to 91.5) and the pooled estimate of specificity was 83.9% (95% CI 73.1 to 92.4). The $I^2$ test indicated moderate to high heterogeneity. There were insufficient data for subgroup analyses. For clinical utility, the positive utility index was 0.62 (satisfactory) and negative utility index 0.58 (satisfactory).

Progressive mild cognitive impairment versus stable mild cognitive impairment (six studies, 163 patients with progressive mild cognitive impairment, 225 patients with stable mild cognitive impairment): The pooled estimate of sensitivity was 81.1% (95% CI 69.2 to 90.7) and the pooled estimate of specificity was 65.3% (95% CI 49.6 to 79.5). The $I^2$ test indicated moderate heterogeneity. Data were not significantly different for phosphorylated tau epitope p181 alone. For clinical utility, the positive utility index was 0.51 (satisfactory) and negative utility index 0.54 (satisfactory).

There were no data on cerebrospinal fluid phosphorylated tau for the differential diagnosis of Alzheimer's disease versus mild cognitive impairment.
Authors' conclusions
Cerebrospinal fluid phosphorylated tau was a good diagnostic biomarker of probable Alzheimer's disease versus non-dementia, and a satisfactory diagnostic biomarker of mild cognitive impairment. It was also a satisfactory prognostic biomarker for progression of mild cognitive impairment, but was less adequate in separating Alzheimer’s disease from other dementias.

CRD commentary
The objective of the review was clearly stated. However, inclusion criteria were not explicitly stated and appeared to include components of an evaluation of reporting quality, which were not explicitly defined. The search strategy included a wide range of sources, with attempts to identify unpublished studies and no language restrictions reported. The review methods were poorly reported, so it was unclear whether measures to minimise error and/or bias in the review process were applied.

Meta-analyses were used to pool studies with acknowledged heterogeneity and where the diagnostic thresholds varied widely across studies; pooled estimates of sensitivity and specificity generated in this way are of questionable validity. In addition, all of the studies of diagnosis were of case-control type, a design which has been shown to produce over-estimates of test performance.

Overall, given the limitations outlined, the author's conclusions about the clinical utility of cerebrospinal fluid phosphorylated tau testing appear optimistic and should be viewed with caution.

Implications of the review for practice and research
Practice: The author stated that clinicians must decide whether the acceptability of such tests warrants routine use given the available accuracy data.

Research: The author suggested that further work is needed to explore how biomarkers can be combined with other diagnostic tests.

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