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Featured Article

Predicting progression to dementia in persons with mild cognitive impairment using cerebrospinal fluid markers

Ron L. H. Handels[a,*], Stephanie J. B. Vos[a], Milica G. Kramberger[b], Vesna Jelic[c], Kaj Blennow[d], Mark van Buchem[e], Wiesje van der Flier[f,g], Yvonne Freund-Levi[c,h], Harald Hampel[i,j], Marcel Olde Rikkert[k], Ania Oleksik[e], Zvezdan Pirtosek[b], Philip Scheltens[f], Hilkka Soininen[l], Charlotte Teunissen[m], Magda Tsolaki[n], Asa K. Wallin[o], Bengt Winblad[c], Frans R. J. Verhey[a], Pieter Jelle Visser[a,f]

[a]*Department of Psychiatry and Neuropsychology, Alzheimer Centre Limburg, School for Mental Health and Neurosciences, Maastricht University, Maastricht, The Netherlands*

[b]*Department of Neurology, Ljubljana University Medical Centre, Ljubljana, Slovenia*

[c]*Division of Clinical Geriatrics, Department of NVS, Karolinska Institutet, Center for Alzheimer Research, Division of Neurogeriatrics, Huddinge, Sweden*

[d]*Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Mölndal, Sweden*

[e]*Department of Radiology, Leiden University Medical Centre, Leiden, The Netherlands*

[f]*Alzheimer Centre and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands*

[g]*Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands*

[h]*Department of Psychiatry, Tiohundra AB Norrtälje Hospital, Stockholm Sweden*

[i]*AXA Research Fund & UPMC Chair, Paris, France*

[j]*Sorbonne Universités Pierre et Marie Curie (UPMC) Paris 06, Inserm, CNRS, Institut du cerveau et de la moelle (ICM), Département de Neurologie, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), Hôpital Pitié-Salpêtrière, Boulevard de l'hôpital, Paris, France*

[k]*Department of Geriatrics, Radboudumc Alzheimer Centre, Donders Institute for Brain Cognition and Behavior, Radboud University Medical Centre, Nijmegen, The Netherlands*

[l]*Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Neurocenter–Neurology, Kuopio University Hospital, Kuopio, Finland*

[m]*Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, VU University Medical Centre, Amsterdam, The Netherlands*

[n]*Memory and Dementia Outpatient Clinic, 3rd Department of Neurology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece*

[o]*Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden*

Abstract

Background: We aimed to determine the added value of cerebrospinal fluid (CSF) to clinical and imaging tests to predict progression from mild cognitive impairment (MCI) to any type of dementia.

Methods: The risk of progression to dementia was estimated using two logistic regression models based on 250 MCI participants: the first included standard clinical measures (demographic, clinical, and imaging test information) without CSF biomarkers, and the second included standard clinical measures with CSF biomarkers.

Results: Adding CSF improved predictive accuracy with 0.11 (scale from 0–1). Of all participants, 136 (54%) had a change in risk score of 0.10 or higher (which was considered clinically relevant), of whom in 101, it was in agreement with their dementia status at follow-up.

Discussion: An individual person's risk of progression from MCI to dementia can be improved by relying on CSF biomarkers in addition to recommended clinical and imaging tests for usual care.

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Keywords: Dementia; Alzheimer's disease; Mild cognitive impairment; Prognosis; Risk; Progression; Predict; Conversion; Reclassification; Risk prediction model

*Corresponding author. Tel.: +31 43 3881036; Fax: ■■■.
E-mail address: ron.handels@maastrichtuniversity.nl

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1. Introduction

Diagnostic research criteria for Alzheimer's disease (AD) have recommended the use of cerebrospinal fluid (CSF) biomarkers to determine etiology and prognosis in persons with mild cognitive impairment (MCI) [1–3]. Because the recommended clinical diagnostic workup already contains much information to identify the risk of dementia progression, it is important to estimate the added value of CSF biomarkers for AD, relative to clinical assessment and brain imaging.

Previous research [4–10] has indicated the increased accuracy when using CSF measures in addition to neuropsychological tests or magnetic resonance imaging (MRI) atrophy scores to predict progression to AD-type dementia in persons with MCI. However, their generalizability to clinical practice was limited for three reasons. First, most relied on odds ratios, receiver operating characteristic (ROC) curves, and sensitivity and specificity outcome measures. These measures typically reflect the performance of a model to test if improvements are significant and valuable for research purposes [11]. However, it is difficult to determine whether significant improvements in such performance indicators are clinically relevant. Therefore, alternative outcomes measures have been developed such as the reclassification table or the reclassification index. These measures distinguish between false-positive and false-negative outcomes, which likely are differently weighted in clinical practice [11]. Second, the previous research limitedly reflected the test information that is available from the standard usual care diagnostic workup. Some of the previous research [3,7] did not consider the degree of cognitive performance on neuropsychological test results reflecting the degree of cognitive performance and did not focus on the added value or were mainly for methodological purposes, respectively. Other previous research [4,5,9] selected the best model based on statistical significance omitting information available in standard practice (such as demographics and neuropsychological tests). Other previous research [6,8] only analyzed CSF in addition to neuropsychological test or CSF in addition to MRI. Omitting information from the standard diagnostic workup reduces the generalizability to practice and possibly overestimated the added value of CSF because nonsignificant measures could still contribute as covariates to the overall predictive value of a model when applied in practice. Third, all previous research focused on progression to AD-type dementia while progression to other dementia subtypes is also relevant in clinical practice.

To enable the translation of findings on CSF biomarkers in the research setting to clinical practice, we approached CSF biomarkers as a risk factor to predict individual risks of progression from MCI to any-type dementia in addition to measures available in usual care diagnostic workup. We aimed to determine the added clinical value of CSF biomarkers relative to clinical and imaging tests that are recommended in usual care, to predict progression to dementia.

2. Methods

2.1. Study participants

We selected participants with MCI who consecutively attended a memory clinic from a range of cohorts in various European countries: the DESCRIPA multicenter study [12] (inclusion between 2003 and 2005, with an additional sample of participants seen outside the DESCRIPA inclusion period at one of the sites VUmc center, inclusion between 1998 and 2007 [13]), LEARN multicenter study [14] (inclusion between 2009 and 2011), Ljubljana University Medical Centre [15] (inclusion between 2011 and 2014), and Karolinska University Hospital Huddinge memory clinic [16] (inclusion between 2007 and 2011). Q3

Eligibility criteria for each cohort separately are described elsewhere [4,12,14,15,17]. Inclusion criteria for the present study were new referral to a memory clinic because of cognitive complaint; age 50 years or older; baseline diagnosis of MCI; baseline data of CSF markers of amyloid-β 1–42 ($A\beta_{1-42}$), total tau (t-tau), and phosphorylated tau (p-tau) levels; and at least one follow-up measurement with information on progression to dementia; no diagnosis of a somatic psychiatric or neurological disorder that might have caused the cognitive impairment at baseline. We excluded two participants with CSF t-tau values more than five times the absolute deviation to the median t-tau in the sample, leaving 250 participants for the analyses.

Local ethical committees approved the studies, and all participants provided informed consent to use their data.

MCI was either diagnosed by a clinician according to the criteria as applied in usual practice (Petersen [18] for LEARN and Ljubljana, and Winblad [19] for Karolinska) or by a researcher using the criteria by Petersen [18] operationalized as a score lower than −1.5 standard deviation on standardized neuropsychological examination results (DESCRIPA and VUmc sample). Not all persons who assessed the diagnosis were blind for the CSF analyses as part of the CSF results were used for clinical purposes.

2.2. Clinical measures

Clinical measures were selected when recommended in clinical guidelines [20] and when available to the authors. Demographic information included age, gender, and years of education. Overall cognition was measured by the Mini–Mental State Examination (MMSE). Memory performance was measured by delayed recall of a Word Learning Test (WLT) (Rey Auditory Verbal Learning Test [RAVLT] [21] for the Karolinska, LEARN, and VUmc samples; the California Verbal Learning Test [22] for the Ljubljana sample; and for the DESCRIPA sample, the RAVLT and CERAD [23] were key tests). Raw scores were transformed to a

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