JAMDA 17 (2016) 913–920

JAMDA

journal homepage: www.jamda.com

Original Study

Refining Mild-to-Moderate Alzheimer Disease Screening: A Tool for Clinicians

Natalia del Campo PhD [a,b,c,*], Matteo Cesari MD, PhD [a,d], Marco Canevelli MD [e], Emiel O. Hoogendijk PhD [a,f], Matthieu Lilamand MD [a,g], Eirini Kelaiditi PhD [a], Maria E. Soto MD, PhD [a,d], Pierre-Jean Ousset MD [a], Michael W. Weiner MD, PhD [h,i,j,k,l], Sandrine Andrieu MD, PhD [d,m], Bruno Vellas MD, PhD [a,d] the ICTUS and REAL.FR/DSA groups [α,β,γ]

[a] *Gérontopôle, Institute of Ageing, Toulouse University Hospital, Toulouse, France*
[b] *"NeuroToul" Center of Excellence in Neurodegeneration of Toulouse, Toulouse, France*
[c] *Department of Psychiatry, University of Cambridge, Cambridge, England*
[d] *INSERM UMR 1027, Paul Sabatier University of Toulouse, Toulouse, France*
[e] *Memory Clinic, Department of Neurology and Psychiatry, University Sapienza, Rome, Italy*
[f] *Department of Epidemiology & Biostatistics, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands*
[g] *APHP, Department of Geriatrics, Bichat Hospital, Paris, France*
[h] *Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, San Francisco, CA*
[i] *Department of Radiology, University of California, San Francisco, CA*
[j] *Department of Medicine, University of California, San Francisco, CA*
[k] *Department of Psychiatry, University of California, San Francisco, CA*
[l] *Department of Neurology, University of California, San Francisco, CA*
[m] *Department of Epidemiology and Public Health, University Hospital Toulouse, Toulouse, France*

The ICTUS study was partially supported by a grant from the European Commission within the 5th framework program (QLK6-CT-2002-02645) and by an unrestricted equal grant from each of Eisai, Janssen, Lundbeck, and Novartis pharmaceutical companies. The pharmaceutical companies had no role in study design, data collection, data analysis, data interpretation, or writing of this report. REAL.FR was supported by the French Ministry of Health grants (PHRC 98-47 N and PHRC 18-05). Promotion of both studies was supported by the University Hospital Centre of Toulouse. The data sharing activity was supported by the "Association Monegasque pour la recherche sur la maladie d'Alzheimer" (AMPA) and the UMR 1027 Unit INSERM–University of Toulouse III.

Conflicts of interest: NDC, MC, EOH, ML, EK, MES and PJO have no conflicts of interest to declare. M. Cesari reports grants from Pfizer, grants from Innovative Medicines Initiative, personal fees from Nestlé, and personal fees from Novartis. MW has served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, and Eli Lilly. He has provided consulting to Synarc, Pfizer, Janssen, KLJ Associates, Easton Associates, Harvard University, University of California, Los Angeles (UCLA), Alzheimer Drug Discovery Foundation (ADDF), Avid Radiopharmaceuticals, Clearview Healthcare Partners, Perceptive Informatics, Smartfish AS, Decision Resources, Inc., Araclon, Merck, Defined Health, and Genentech. The following entities have provided funding for travel: Pfizer, Paul Sabatier University, MCI Group France, Travel eDreams, Inc., Neuroscience School of Advanced Studies (NSAS), Danone Trading, BV, CTAD Ant Congres, Kenes, Intl., ADRC, UCLA, UCSD, Sanofi-Aventis Groupe, University Center Hospital, Toulouse, Araclon, AC Immune, Eli Lilly, New York Academy of Sciences (NYAS), and National Brain Research Center, India for Johns Hopkins Medicine. He served on the Editorial Boards for Alzheimer & Dementia and MRI. He received honoraria from Pfizer, Tohoku University, and Danone Trading, BV. He received research support from Merck, Avid, the Veterans Administration (VA) and Department of Defense (DOD). SA reports personal fees from Beaufour Ipsen Pharma SAS; Esai Inc.; Pierre Fabre Laboratories; Pfizer; Eli Lilly and Company; Lundbeck Inc.; Nestle S.A; Novartis; Roche; Servier; Janssen; Exhonit; Sanofi; Beaufour Ipsen Pharma SAS; Esai Inc.; Pierre Fabre Laboratories; Pfizer; Lundbeck Inc.; Nestle S.A.; Novartis; Servier; Janssen, grants from Beaufour Ipsen Pharma SAS; Eli Lilly and Company; Lundbeck Inc.; Nestle S.A. BV reports personal fees from Lilly, MSD, Nestlé, Roche, Sanofi, grants from Abbvie, Affiris, Avid, Eisai, Envivo, Exhonit, Genentech, GSK, Lilly, MSD, Nutricia, Otsuka, Pharnext, Pfizer, Pierre-Fabre, Régénéron, Roche, Sanofi, Servier, TauRx Therapeutics, and Wyeth.

* Address correspondence to Natalia del Campo, PhD, Faculté de Médecine - Institut du Vieillissement, 37 Allées Jules Guesde, Toulouse 31000, France.
E-mail address: nata.delcampo@gmail.com (N.del Campo).

α ICTUS study group: Vellas B., Reynish E., Ousset P.J., Andrieu S. (Toulouse), Burns A. (Manchester), Pasquier F. (Lille), Frisoni G. (Brescia), Salmon E. (Liège), Michel J.P., Zekry D.S. (Geneva), Boada M. (Barcelona), Dartigues J.F. (Bordeaux), Olde-Rikkert M.G.M. (Nijmegen), Rigaud A.S. (Paris), Winblad B. (Huddinge), Malick A., Sinclair A. (Warwick), Frölich L. (Mannheim), Scheltens P. (Amsterdam), Ribera C. (Madrid), Touchon J. (Montpellier), Robert P. (Nice), Salva A. (Barcelona), Waldmar G. (Copenhagen), Bullock R. (Swindon), Costa-Tsolaki M. (Thesaloniki), Rodriguez G. (Genoa), Spiru L. (Bucharest), Jones R.W. (Bath), Stiens G., Stoppe G. (Goettingen), Eriksdotter Jönhagen M. (Stockholm), Cherubini A. (Perugia), Lage P.M., Gomez-Isla T. (Pamplona), Camus V. (Tours), Agüera-Morales E., Lopez F. (Cordoba).

β REAL.FR study group: Vellas B., Ousset PJ., Gillette-Guyonnet S., Nourhashemi F., Andrieu S. (Toulouse); Rainfray M., Richard-Harston S. (Bordeaux); Franco A., Couturier P. (Grenoble); Pasquier F., Mackowiak-Cordoliani M.A. (Lille); Frigard B., Idiri H., Gallouj K. (Wasquehal); Michel B. (Marseille); Jeandel Cl. (Montpellier); Touchon J., Portet F., Lerouge S. (Montpellier); Robert P., Brocker P., Bertogliati C. (Nice); Forette B., Teillet L., Lechowski L. (Paris); Belmin J., Pariel-Madjlelssi S. (Paris); Verny M., Artaz M.A. (Paris); Forette F., Rigaud A.S., Latour F. (Paris); Jouanny P., Belliard S., Michel O. (Rennes); Gonthier G., Girtanner C.,Thomas- Anterion (Saint Etienne).

γ DSA group: Andrieu S., Savy S., Cantet C., Coley N.

http://dx.doi.org/10.1016/j.jamda.2016.06.005

Keywords:
Alzheimer disease
differential diagnosis
cognitive decline
classification and regression tree (CART)

A B S T R A C T

Objectives: Recent evidence suggests that a substantial minority of people clinically diagnosed with probable Alzheimer disease (AD) in fact do not fulfill the neuropathological criteria for the disease. A clinical hallmark of these phenocopies of AD is that these individuals tend to remain cognitively stable for extended periods of time, in contrast to their peers with confirmed AD who show a progressive decline. We aimed to examine the prevalence of patients clinically diagnosed with mild-to-moderate AD who do not experience the expected clinically significant cognitive decline and identify markers easily available in routine medical practice predictive of a stable cognitive prognosis in this population.
Design: Data were obtained from two independent, longitudinal, observational multicenter studies in patients with mild-to-moderate AD.
Setting: The two studies were the European "Impact of Cholinergic Treatment Use" (ICTUS) and the French "REseau sur la maladie d'Alzheimer FRançais" (REAL.FR).
Participants: We used prospective data of 756 patients enrolled in ICTUS and 340 enrolled in REAL.FR.
Measurements: A prediction rule of cognitive decline was derived on ICTUS using classification and regression tree analysis and then cross-validated on REAL.FR. A range of demographic, clinical and cognitive variables were tested as predictor variables.
Results: Overall, 27.9% of patients in ICTUS and 20.9% in REAL.FR did not decline over 2 years. We identified optimized cut-points on the verbal memory items of the Alzheimer Disease Assessment Scale-Cognitive Subscale capable of classifying patients at baseline into those who went on to decline and those who remained stable or improved over the duration of the trial.
Conclusion: The application of this simple rule would allow the identification of dementia cases where a more detailed differential diagnostic examination (eg, with biomarkers) is warranted. These findings are promising toward the refinement of AD screening in the clinic. For a further optimization of our classification rule, we encourage others to use our methodological approach on other episodic memory assessment tools designed to detect even small cognitive changes in patients with AD.

Recent evidence from in vivo neuroimaging research and postmortem examinations revealed that a higher than expected proportion of subjects clinically diagnosed with mild-to-moderate probable Alzheimer disease (AD) does not meet established neuropathological guidelines for AD[1,2] The misdiagnosis of non–amyloid-dependent dementia, estimated to be approximately 14% 16%, has a detrimental impact both for the clinical management of affected patients and for clinical trials in AD testing the amyloid hypothesis.[3,4] Therefore, it is imperative to improve the identification of these clinical phenocopies of AD. Insofar as amyloid biomarker measurements are not available in routine medical practice, a better understanding of the cognitive and behavioral signatures characteristic of this subset of patients with dementia would empower clinicians to refine the screening of AD.

Subjects with a probable AD dementia diagnosis who do not present with neuropathological criteria for the disease have been observed to have slightly but significantly better cognitive performance at baseline compared to subjects who do have AD pathology.[1,2] They also tend to show no clinically significant decline over 3 years on a range of neuropsychological tests, in contrast with their peers with neuropathologically confirmed AD.[2,5] Therefore, identifying predictors of a stable cognitive prognosis in patients suspected to have mild-to-moderate AD would enable clinicians to detect cases where more detailed differential diagnostic examinations are warranted, possibly involving biomarkers.

Extensive research has been carried out to predict cognitive progression in mild cognitive impairment (MCI) and AD using neuropsychological tests.[6–10] A common approach thus far has been to combine information from neuropsychological tests in sophisticated ways, for example, using multivariate methods to derive latent factors or composite measures predictive of conversion.[11,12] Although these techniques have been proven useful in predicting rates of decline, they are arguably too complex to be implemented in clinical routine. Moreover, to date, most of the literature on cognitive prediction models of decline has focused on conversion from MCI to AD[13,14] and on slow versus rapid decline in patients with AD, with an emphasis on the latter group.[15] Comparatively little is known regarding the predictive factors of a stable prognosis in patients with dementia.

The present study sought to (1) determine the prevalence of a stable cognitive prognosis over 2 years in patients clinically diagnosed with mild-to-moderate AD, (2) identify cognitive and behavioral markers predictive of a stable prognosis, and (3) operationalize these into a quick and straightforward decision rule to be easily implemented in clinical practice. Differentiating our work from previous research, we focused on the prediction of "non-decline" rather than rate of decline, as a targeted approach to identify dementia cases requiring a more detailed etiological enquiry. Data were obtained from two separate, observational, longitudinal, multicenter cohort studies: Impact of Cholinergic Treatment USe (ICTUS) and REseau sur la maladie d'Alzheimer FRançais (REAL.FR). We hypothesized that a relatively preserved episodic memory as measured by the verbal memory items of the Mini-Mental State Examination (MMSE) or the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) would be predictive of a stable prognosis.

Methods

Study Design and Subjects

ICTUS and REAL.FR have been described elsewhere and were carried out with ethical approval.[16,17] In short, ICTUS is a 2-year, prospective, multicenter study, which aimed to investigate the history of AD, its treatment outcomes and its socioeconomic impact on patients and their caregivers. The study enrolled 1376 patients with a clinical diagnosis of mild-to-moderate probable AD recruited at 29 European specialist outpatient memory clinics. REAL.FR is a 4-year, prospective, multicenter study targeting ambulatory community-dwelling patients with probable AD. It was carried out on 686 volunteers recruited in 16 specialized memory clinics across France. Patients in both ICTUS and REAL.FR were diagnosed with probable AD according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition[18] and the