Alzheimer's & Dementia 11 (2015) 561-578

Innovative diagnostic tools for early detection of Alzheimer's disease

Christoph Laske[a,b,*], Hamid R. Sohrabi[c,d], Shaun M. Frost[e,f], Karmele López-de-Ipiña[g], Peter Garrard[h], Massimo Buscema[i,j], Justin Dauwels[k], Surjo R. Soekadar[l], Stephan Mueller[l], Christoph Linnemann[l], Stephanie A. Bridenbaugh[m], Yogesan Kanagasingam[e,f], Ralph N. Martins[c,d], Sid E. O'Bryant[n]

[a]*Section for Dementia Research, Hertie-Institute of Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany*
[b]*German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany*
[c]*Center of Excellence for Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Perth, WA, Australia*
[d]*McCusker Alzheimer's Research Foundation, School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA, Australia*
[e]*Commonwealth Scientific and Industrial Research Organisation (CSIRO), Perth, Australia*
[f]*Australian e-Health Research Centre, Perth, WA, Australia*
[g]*Systems Engineering and Automation Department, University of the Basque Country UPV/EHU, Donostia, Spain*
[h]*Neuroscience Research Center, Cardiovascular and Cell Sciences Research Institute, St George's University of London, London, United Kingdom*
[i]*Semeion Research Centre of Sciences of Communication, Rome, Italy*
[j]*Department of Mathematical and Statistical Sciences, Center for Computational and Mathematical Biology, University of Colorado, Denver, CO, USA*
[k]*School of Electrical and Electronic Engineering, Nanyang Technological University, Singapore*
[l]*Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany*
[m]*Felix Platter Hospital, University Center for Medicine of Aging Basel, Basel Mobility Center, Basel, Switzerland*
[n]*Department of Internal Medicine & Institute for Aging and Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, TX, USA*

Abstract Current state-of-the-art diagnostic measures of Alzheimer's disease (AD) are invasive (cerebrospinal fluid analysis), expensive (neuroimaging) and time-consuming (neuropsychological assessment) and thus have limited accessibility as frontline screening and diagnostic tools for AD. Thus, there is an increasing need for additional noninvasive and/or cost-effective tools, allowing identification of subjects in the preclinical or early clinical stages of AD who could be suitable for further cognitive evaluation and dementia diagnostics. Implementation of such tests may facilitate early and potentially more effective therapeutic and preventative strategies for AD. Before applying them in clinical practice, these tools should be examined in ongoing large clinical trials. This review will summarize and highlight the most promising screening tools including neuropsychometric, clinical, blood, and neurophysiological tests.

Keywords: Alzheimer's disease; Diagnostic tools; Screening tests; Noninvasive tests; Early detection

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, affecting more than 35 million people worldwide [1]. Aging populations in developed countries ensure that AD will reach epidemic proportions unless therapies are developed to cure or prevent it [2]. Unfortunately, to date nearly all "disease-modifying" experimental interventions for AD have failed to demonstrate clinical benefits in individuals with symptomatic AD. The most likely explanation for these failures is that the drugs were administered too late in the course of the AD neuropathological processes [3]. It is plausible to assume that these therapies will be more effective when applied before major brain damage

The authors have no potential conflicts of interest to declare.
*Corresponding author. Tel.: +49-7071-2983444; Fax: +49-7071-294141.
E-mail address: christoph.laske@med.uni-tuebingen.de

1552-5260/$ - see front matter
http://dx.doi.org/10.1016/j.jalz.2014.06.004

has occurred which makes the identification of biomarkers sensitive to preclinical or early clinical stages of AD crucial [4]. Whether an earlier treatment start in the preclinical stage of AD is associated with a better outcome is still unknown and is actually examined in ongoing treatment trials [3]. These trials include the Dominantly Inherited Alzheimer Network Trial (DIAN-TU; ClinicalTrials.gov number, NCT01760005), Alzheimer's Prevention Initiative (NCT01998841), and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study (A4 Study; NCT02008357). Early-stage identification may also help to develop new treatments that are more effective at this stage as it can facilitate monitoring of the response to the intervention. In addition, a positive early diagnosis gives the patients and their family the necessary time to understand the disease, to decide on the life and financial burdens of the disease, and to arrange for the future needs and care of the patients.

The current state-of-the-art clinical diagnosis of AD requires a specialty clinic and includes a medical examination, neuropsychological testing, neuroimaging, cerebrospinal fluid (CSF) analysis and blood examination. This process is neither time nor cost-effective. Additionally, given the rapidly aging global population with an expected dramatic increase of AD cases, there are insufficient numbers of specialty clinics to meet the growing needs. While CSF and neuroimaging markers are gold standards for the *in vivo* assessment of the patients, they are invasive and expensive and, therefore, have limited utility as frontline screening and diagnostic tools. In addition, prior work has shown that nonspecialist clinicians are inaccurate at identifying early AD and mild cognitive impairment (MCI) [5], which is a major impetus to the search for clinically-useful screening and diagnostic tools.

Thus, there is an increasing need for additional noninvasive and/or cost-effective tools, allowing frontline identification of subjects in the preclinical or early clinical stages of AD. Further examination of patients with conspicuous noninvasive cognitive and noncognitive measures could be performed in a next step by established clinical, CSF and/or neuroimaging analyses in a specialty clinic. The identification of methods to predict the risk for developing AD would be of great value for healthcare systems. Identification of AD risk markers could help to identify individuals who might benefit from early intensive lifestyle consultations and pharmacological interventions. The relevance of early diagnosis of AD is supported by recent neuropathological, biochemical and neuroimaging findings showing that biomarkers of AD can be detected in the brains and CSF of approximately 20% to 30% of cognitively healthy elderly individuals [6–8].

This review will summarize and highlight the most promising novel noninvasive and/or inexpensive screening and diagnostic tools such as neuropsychometric, clinical, blood, and neurophysiological tests for early detection of AD beyond the established clinical, CSF and neuroimaging dementia diagnostics.

2. Socioeconomic aspects of dementia diagnostics

While many have argued the need for screening methods that are accessible and time- and cost-effective, few have empirically demonstrated this point. To empirically illustrate the need for noninvasive and inexpensive screening/diagnostic tools, we use the U.S. numbers of geriatrician, neurology, and psychiatry physician providers and available magnetic resonance imaging (MRI) machines below. In the United States there were an estimated 7162 physicians certified in geriatrics in 2011 [9]. This translates to 5585 patients aged 65 years old and above to be seen per specialist per year based on 2009 census estimates if all geriatrics were to receive an annual screening that included cognitive examination. This is particularly problematic when geriatric specialists are becoming less and less available [9]. Table 1 outlines the situation for the fields of neurology and psychiatry as well.

The situation is worse considering that not all geriatricians, neurologists or psychiatrists are dementia specialists. Furthermore, psychiatrists and neurologists are aging and working fewer hours than in the past [10,11], therefore this is likely a significant overestimation of capacity in that field. If one considers MRI as frontline screening tool, the situation does not improve. There are an estimated 11,000 MRI machines within the United States currently [12]. This would mean that each MRI machine should be used for 3636 US elders with current estimates and for over 6000 US elders by the year 2030, based on projected age estimates. These numbers assume that all MRI machines

Table 1
US estimates of population age 65 and above for 2009 and 2030 along with estimates of physician availability

Physicians by specialty and MRI machines in the United States	Number of physicians by specialty and of MRI machines	Population age >65 years in 2009, n = 40 million	Population age >65 years in 2030, n = 70 million
		Patients per physician	Patients per physician
Physicians certified in geriatrics [8]	7162	5585	9773
Neurologists [10]	10,154	3939	6893
Psychiatrists [9]	39,457	1014	1774
MRI machines in the United States [11]	10,000	3636	6364

Abbreviation: MRI, magnetic resonance imaging.