Editorial

Alzheimer's disease in primary care: new tools for improved and simplified diagnostics

Henrik Zetterberg[1,2,3,4*] & Erik Stomrud[5,6,7]

[1]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*
[2]*Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden*
[3]*Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK*
[4]*UK Dementia Research Institute at UCL, London, UK*
[5]*Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden*
[6]*Memory Clinic Skåne University Hospital, Malmö Sweden*
[7]*Emmaboda Primary Healthcare Central, Region Kalmar County, Emmaboda, Sweden*

*Correspondence: henrik.zetterberg@clinchem.gu.se

In the current issue of *Journal of Internal Medicine*, Liss and colleagues highlight the critical role of primary care clinicians in Alzheimer's disease (AD) prevention, diagnosis and management, and present practical recommendations on how an early diagnosis of AD could be made in primary care using new and accessible diagnostic tools [1]. AD is very common, the progress in diagnostics during the past few years has been enormous, and disease-modifying treatments may be around the corner, making the paper a must-read for any clinician caring for patients in mid- to late-adult life in general practice as well as decision-makers in health care providers.

Why is this important?

We all hope for breakthroughs regarding disease-modifying treatments against AD in the near future. These treatments should stop or slow down the disease process, and not just temporarily reduce the symptoms. We do not know when this will happen, but one amyloid-targeting drug (aducanumab) is currently undergoing evaluation for potential regulatory approval [2]. Additionally, there are large late-phase clinical trials of other drug candidates

underway, with much more data expected during 2021 and 2022. With access to disease-modifying treatments, we will need widespread ability to detect AD pathology before it has caused too much harm to the brain networks and too much neuronal loss. This might even require pre-clinical detection, given the powerful compensatory mechanisms that are defining features of human brain function, and/or the use of refined tools to unveil subtle cognitive changes caused by the disease process before they are clinically overt (*e.g.*, digital monitoring or cognitive stress tests).

The patients will typically first be seen and evaluated in primary care. An effective diagnostic algorithm to identify and determine who should be referred to a memory clinic to be evaluated for potential disease-modifying treatment is needed. Again AD is such a common disease with an immense number of individuals at risk, primarily due to age, that any measures taken need to be precise, cost-effective and wisely chosen . In the future, when more experience on the new treatments (when approved) has been gained, one could imagine treatment initiation and/or evaluation in primary care (much like diabetes and asthma are taken care of by sub-specialised primary care physicians and nurses), with unusual or difficult cases (atypical AD and non-AD neurodegenerative dementias) being referred to hospital specialists for further evaluation.

What if we do not get disease-modifying treatments in the near future?

If a patient seeks medical advice because of cognitive symptoms that have made him or her worry about AD, it is important to give a timely and an as accurate diagnosis as possible, also in the absence of disease-modifying treatments. AD is a serious disease with personal consequences that may be harsh, and the diagnosis is often difficult to make, especially before the symptoms are severe enough for the patient to fulfil dementia criteria. Somatic or non-AD neurologic or psychiatric disease may cause cognitive symptoms mimicking AD [3]. As emphasised by Liss *et al*., such diseases must be identified through a complete diagnostic work-up including clinical examination, blood tests, brain imaging and CSF analysis [1]. In short, a careful medical evaluation is warranted to detect treatable and non-treatable causes of the symptoms, to give the patient the most accurate information possible on his or her condition, and to optimize patient care and management, irrespective of whether or not a disease-modifying treatment is available.

Improved and accessible diagnostic tools are at hand

Imaging (amyloid and tau positron emission tomography) and CSF (the 42 to 40 ratio of amyloid β, total and phosphorylated tau, and neurofilament light) biomarkers allow for detection of amyloid pathology, tau pathology and neurodegeneration, *i.e.*, the pathological hallmarks of AD [4]. The CSF tests have recently been developed into blood-based tests with surprisingly good diagnostic accuracy [5]; some studies even suggest that they can replace the imaging and CSF biomarkers altogether [6, 7]. These blood biomarkers, especially if used in combination with refined cognitive screening tools, will likely make it possible to accurately identify or exclude AD in individual patients in primary care, which would truly revolutionize AD management [8]. However, before clinical implementation, careful evaluation of such a primary care-based, biomarker-supported diagnostic algorithm, in close collaboration with AD specialists, is needed.

Ethical and clinical challenges ahead

If we start to use the blood biomarkers and more sensitive cognitive tests for AD in primary care, we will identify more patients with pre-dementia AD. There is nothing wrong with this. However, it means that we will have to re-think AD as a clinical concept, how the diagnosis is perceived in the society, legal, employment and insurance aspects, and how we communicate with the patient and his or her relatives regarding the diagnosis. Sensitive cognitive tests may expose symptoms that otherwise would have gone unnoticed in everyday life for years. Blood biomarkers will detect pathology, the clinical expression of which may be variable. Irrespective of positive biomarkers, other causes of symptoms still need to be excluded. Linking biomarker values to a clinical presentation will be very important but demanding, especially considering the clinically silent incubation time (decades) of AD pathology; the clinical evaluation and follow-up will thus remain ever so important. We must not make diagnoses based on laboratory tests only. We need to think about the AD biomarkers the way we think about clinical chemistry tests for liver or heart disease. And we should abstain from predicting future disease trajectories for individual patients based on group level data; this can be attempted in research and clinical trials, but the future of an individual patient is hard to predict. It is most probably better to find out and deal with it together with the patient through continuity and careful clinical follow-up.

Putting all this together into a complete medical context, involving the healthcare system and the society as a whole, will need some work. The review and synthesis provided by Liss *et al*. is an excellent start [1].

Acknowledgements

HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C and #ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2019-0228), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), and the UK Dementia Research Institute at UCL. ES…

Conflicts of interest

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies and CogRx, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. ES reports no conflicts of interest.

References

1. Liss JL, Seleri Marques Assuncao S, Cummings J, Atri A, Geldmacher DS, Candela SF, Devanand DP, Fillit HM, Susman J, Mintzer J *et al*: **Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis**. *J Intern Med* 2021, **In press**.
2. Kaplon H, Muralidharan M, Schneider Z, Reichert JM: **Antibodies to watch in 2020**. *MAbs* 2020, **12**(1):1703531.
3. Schott JM, Warren JD: **Alzheimer's disease: mimics and chameleons**. *Pract Neurol* 2012, **12**(6):358-366.
4. Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J *et al*: **NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease**. *Alzheimers Dement* 2018, **14**(4):535-562.
5. Zetterberg H, Bendlin BB: **Biomarkers for Alzheimer's disease-preparing for a new era of disease-modifying therapies**. *Mol Psychiatry* 2020.
6. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, Su Y, Chen Y, Serrano GE, Leuzy A *et al*: **Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders**. *JAMA* 2020, **324**(8):772-781.
7. Barthelemy NR, Horie K, Sato C, Bateman RJ: **Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease**. *J Exp Med* 2020, **217**(11).

8. Cullen NC, Leuzy A, Palmqvist S, Janelidze S, Stomrud E, Pesini P, Sarasa L, Antonio Allué J, Proctor NK, Zetterberg H *et al*: **Individualized prognosis of cognitive decline and dementia in mild cognitive impairment based on plasma biomarker combinations**. *Nat Aging* 2021, **1**:114–123.