Next generation brain health depends on early Alzheimer disease diagnosis : from a timely diagnosis to future population screening

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Next generation brain health depends on early Alzheimer's disease diagnosis: from a timely diagnosis to future population screening.

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Recent advances in neuroimaging, cerebrospinal fluid (CSF) assays, and other biomarkers now provide the ability to detect evidence of Alzheimer's disease (AD) pathophysiological process in vivo[1]. This stirs the debate about how and when AD is best detected. Recently the international Association of Gerontology and Geriatrics formed a consensus group (IAGC) [2] to deal with these questions. When discussing the recommendations of the consensus group, in our view, it is important to bear in mind that (1) nowadays disease-modifying drugs are still not available and (2) there might be differences between the interests and needs for individual patients, for wider society and for research purposes. From the perspective of an *individual patient*, in a situation with no effective treatment for AD, **an accurate timely diagnosis** is preferable. Some researches[3] argue that timely means in the prodromal (MCI) phase when mild cognitive or behavioral changes are present. Others[4] consider that a timely diagnosis is not tied to any particular disease stage but that it is established at the "right" moment for each individual case. From a *broader society perspective* one of the options to detect AD in an early phase is by population screening. This can be defined as **screening** of the general population in order to identify undiagnosed AD in individuals without AD symptoms or cognitive complaints[2]. In agreement with our opinion the consensus group decided that in the absence of disease modifying drugs, population screening is not recommended. Another option to identify patients in an early phase is **case finding**, which can be defined as the screening of a subgroup of the general population based on the presence of certain risk factors (e.g. age, genetic risks, …)[2]. The IAGC group concluded, based on age as risk factor, that all individuals from 70 and older should be screened every year with a short neuropsychological screening instrument by their primary health care provider. This recommendation raised a lot of critical questions, especially from primary health care providers[5]. We fully understand the criticism, particularly because the predictive values of current cognitive screening instruments for diagnosing AD have not been studied thoroughly. Therefore screening of this population

can result in large numbers of either missed cases or many false-positively diagnosed people, which is even when a disease-modifying treatment would be available, not beneficial. Moreover AD is a process that starts many years before the first symptoms occur. So starting with "preventive" actions in the early symptomatic phase is certainly too late. For (clinical) research purposes, it is from utmost important to identify (asymptomatic) subjects who are at risk to develop AD, which can be performed through amyloid biomarkers of known genetic risk factors (e.g. pathogenic gene mutation carriers). Through follow-up from first amyloid deposits in the brain, through the symptomatic MCI and dementia stages till death (and brain autopsy), it is possible to gain more insight in the biological, cognitive and behavioral processes of AD. Next to that, such longitudinal observational studies allow the testing from new screening techniques which should ultimately lead to a sensitive and non-invasive screening instrument.

The *research perspective* was underexposed by the current consensus group (IAGC). We are convinced that in the future, when disease modifying medication are available, one should seek to **diagnose AD in its pre-symptomatic phase**. Therefore, minimally invasive (or preferably: non-invasive) and affordable techniques to detect AD in the pre-symptomatic phase should be optimized through (clinical) research. In other words, at this moment, research should focus on the development/optimization of cost efficient screening tools to identify people in the asymptomatic phase. Besides, it is important to underline that drug development can profit from the improvement of detection techniques. Partly due to the advance in detection techniques, research for potential disease-modifying treatments has changed its focus from the dementia phase to the MCI phase and currently also to the pre-symptomatic phase of AD. Both positron emission tomography (PET) with Aβ ligands and analysis of Aβ in the cerebrospinal fluid (CSF) are used as an enrichment strategy for clinical trials in the field of AD[6].

Next to the improvement of screening techniques, more attention is needed for population based research. There is a lack of population based studies for cognitive screening instruments as well as for biomarkers. Like Woo (2015)[7] correctly pointed out, little is known about how cognitive functions change with age. Population based research could result in more insight in how cognitive functions and biomarkers change with age.

In summary, for individual persons and the community, a diagnosis in the pre-symptomatic phase of AD is not preferable at this moment. This in contrast with a (clinical) research context where the development of cost-efficient screening tools to identify people in the pre-symptomatic AD phase and population based studies are needed.

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