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EDITORIAL

Proven validity and management impact of amyloid imaging in Alzheimer's disease—repetita juvant

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The Editorial "Suboptimal Validity of Amyloid Imaging-Based Diagnosis and Management of Alzheimer's Disease: Why It Is Time to Abandon the Approach" which appeared online ahead of print on October 31, 2019, in the EJNMMI [1] has come to our attention. From our point of view, the topic of amyloid imaging is discussed in a biased and opinionated form in this Editorial. Some facts generally accepted by imaging experts and neuropathologists are questioned or neglected, which may leave the reader with a misleading impression that does not correspond with the current state of knowledge. The EANM Neuroimaging Committee, thus, feels the need to correct this impression in order to allow the reader to differentiate between commonly accepted scientific facts versus individual opinions and matters still unresolved, regarding the topic discussed. For space reasons, we will discuss here only the issues with the greatest risk for misleading interpretation.

(I) Significant parts of the Editorial by Alavi et al. including Figure 1 are repetitions of another Editorial by the same group, published in 2012 in the EJNMMI [2]. What the authors do not mention is that many of the alleged shortcomings of amyloid imaging raised in their 2012 Editorial were, at that time, already thoroughly refuted in a responding Editorial by a group of amyloid imaging experts [3]. Therefore, it is disturbing to see that, without adding new scientific evidence, some of those invalidated allegations are raised again in the latest Editorial. As an example, now and in 2012, the authors argue that the distribution of amyloid plaques as detected neuropathologically post-mortem would not correspond with uptake patterns observed by amyloid PET (particularly in the frontal cortex). On the contrary, it is a scientifically proven fact that different to this assumption by the authors amyloid plaques are widely distributed throughout the neocortex in Alzheimer's disease (AD) patients, including the frontal part. We will refrain from repeating all the arguments already presented before and refer the interested reader to the previous publication [3].

(II) The authors propose to abandon amyloid imaging and they base this statement primarily on the fact that amyloid imaging is not able to provide the full histopathological picture of AD (amyloid plaques & tau aggregates & neurodegeneration). This is an illogical conclusion. Instead, asking for the addition of tau and neurodegeneration imaging to amyloid imaging would be logical. A tracer that binds to several targets at once would be considered to be non-specific, and it is commonly perceived

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as an advantage rather than a shortcoming that amyloid imaging provides highly specific information. In analogy, nobody would propose abandoning FDG PET in tumor imaging by arguing with the fact that obtaining the glucose readout does not provide the full histopathological picture of the tumor. A unique strength of nuclear medicine is the reliable non-invasive assessment of specific molecular features: when multiple targets have to be measured, multiple tracers have to be used. Our task as specialists is indeed to define an appropriate and efficient sequence/combination of tests, with a systematic validation of markers, including amyloid PET tracers [4]. The requirement that a tracer should answer multiple questions at once to be diagnostically useful cannot be justified.

(III) The Editorial by Alavi et al. argues (specifically in Figure 2) that amyloid images should, in order to qualify as useful, inversely match with FDG PET images. This argument is irrational for several reasons: It seems hard to understand what added value a new diagnostic PET tracer would provide if it just represented an "upside-down" FDG image. Amyloid imaging is supposed to provide specific complementary information to FDG PET. Further, Alavi et al. ignore, in this specific argumentation, the known presence of the other histopathological hallmark in AD, namely, tau aggregates. It is a scientifically proven fact that regional tau, and not amyloid load, is closely linked to regional neurodegeneration in AD. Again, the fact that neurodegeneration and amyloid deposition occur independently without tight regional association is well known, and it does not at all raise any doubt about the value of amyloid imaging as a tool to detect amyloid deposition. Amyloid imaging measures amyloid deposition (proven to be a hallmark of AD) not neuronal dysfunction. Neuronal dysfunction as measured by FDG PET can occur also without amyloid deposition in non-Alzheimer forms of disease. This is one of the reasons why even recently published guidelines on biomarker use require independent information on amyloid status, tau status, and neuronal injury [5] for a comprehensive characterization of AD. Amyloid imaging is able to provide specific information independent and ahead of ongoing neuronal dysfunction, thus complementing rather than replacing FDG PET.

(IV) In arguing that amyloid imaging has no utility because there is currently no evidence for the efficacy of anti-amyloid therapy, Alavi et al. do not consider the fact that diagnostic utility of a biomarker does not require pathogenetic causality for the biomarker employed. It has been known since the discovery of the disease by Alois Alzheimer that amyloid plaques are indeed present in the AD brain. This presence (regardless of whether amyloid aggregates cause the disease) is what is visualized by amyloid imaging in vivo to support the clinical AD diagnosis, no more, no less. There is still obvious controversy with regard to the causal role of amyloid aggregates in generating AD and also with regard to the prospect of anti-amyloid therapies. However, any attempt to exploit this ongoing debate with regard to the value of amyloid imaging as a diagnostic tool is futile and based on opinions rather than facts. The role of amyloid aggregates as a diagnostic biomarker and landmark of AD on the other hand is uncontroversial among experts in the field and cannot be seriously doubted. It may be noted that CSF amyloid biomarkers are also part of clinical routine work-up of dementia at many memory clinics. The authors of the Editorial, however, appear to repeatedly confuse the established value of amyloid pathology as a diagnostic biomarker of AD with the totally independent questions (or rather opinions) on the causal role of amyloid in the process of AD generation or the meaningfulness of anti-amyloid therapies. Again, in analogy, nobody would propose abandoning FDG PET in tumor imaging by arguing with the fact that oncological diseases are not curable by drugs lowering tumor glucose levels.

(V) By stating "… there is no clear-cut data to support the use of these approaches [amyloid tracers] for either diagnosis or management of AD," the authors are incorrect. There is a wealth of data available with regard to validity and utility of amyloid imaging. Very high standards were applied for approval of the available amyloid PET tracers [6–8] by the US American, European, and other drug-approving authorities. Hardly, any other PET tracers currently in use have undergone similar evaluation procedures. The presence of amyloid pathology clearly is diagnostic, as it is required for the current gold standard neuropathological diagnosis of AD, and amyloid imaging verifiably provides this information in vivo. Interestingly, this is even acknowledged by Alavi and colleagues when they are erroneously trying to convey the specificity of the tracers for amyloid pathology as a weakness rather than a strength (as already discussed above at point (II)). For the impact of amyloid imaging on AD patient management, readers are referred to respective review and meta-analysis publications and to the first results of the IDEAS (an excessively large clinical trial included more than 16.000 patients) study, which concordantly reported a change in management in at least 60% of patients investigated by amyloid imaging [9–11].

(VI) The statement in the Editorial "Reports of patients pondering assisted suicides based on the PET "amyloid imaging" results…" is a grossly misleading interpretation on what indeed was reported in the referring

ALZFORUM news story [12]. Instead, it was clearly stated in this news story that "…the revelation of amyloid positivity [by PET imaging] did not change attitudes toward physician-assisted dying—if someone hadn't considered it a possibility before, learning their amyloid status did not make them think it was now." [12]. We are convinced that the nonbiased reader is aware of the fact that disclosing results of any diagnostic test can have psychological consequences for patients. It is, thus, important to provide careful guidance on how this disclosure should be carried out. For amyloid imaging, the development level for the respective recommendations which can be found in the joint publication by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association on the Appropriate Use Criteria for Amyloid PET [13] is relatively high (in relation to that of other imaging procedures). In addition, research on the effect of disclosing the result of amyloid imaging on patients is relatively advanced showing that the disclosure of the amyloid PET result is safe—providing the consideration of the above-mentioned rules [8]. In general, potential psychological implications of the results of a diagnostic test are not suitable to disprove the diagnostic value of the corresponding test per se. Again, in analogy, nobody would question the value of FDG PET imaging in oncology because of the negative psychological impact the disclosures of the scan results has every day of our clinical work on a relevant number of patients.

(VII) By stating "Diagnostic and therapeutic approaches rooted in the "amyloid hypothesis" have permeated every fiber of AD research for decades…," the authors again ignore the relevant work by numerous research groups and pharmaceutical companies carried out over the last years towards alternative diagnostic and therapeutic targets in AD, like tau, cholinergic neurotransmission, and neuroinflammation. Even if the therapeutic efforts directed against amyloid aggregation remain futile, other therapies targeting different disease mechanisms may require evidence of amyloid pathology for specific and early diagnosis of ongoing disease ahead of irreversible neuronal damage.

Taken together, a critical discussion of the value, the strengths and limitations of amyloid imaging, and its place in the diagnostic cascade is certainly justified. It is a duty of renowned journals such as the EJNMMI to provide a forum for such a discussion of experts, free from personal motives or individual bias. This discussion needs to be based on facts accepted by the scientific community rather than on opinions, believes, or unresolved questions. With regard to amyloid imaging of AD patients, the scientific evidence available clearly proves that it is valid and has relevant patient management impact. The objective discussion of the diagnostic value of this biomarker should not be diluted by neglecting or misinterpreting available evidence, and it should not be confused with the debate about disease pathogenesis or examples of therapeutic success or failure.

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Compliance with ethical standards

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