

Commentary

Amyloid Hypothesis: The Emperor's New Clothes?

Poul F. Høilund-Carlsen^{a,b,*}, Jorge R. Barrio^{c,*}, Tom J. Werner^d,
Andrew Newberg^{e,f} and Abass Alavi^d

^a*Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark*

^b*Department of Clinical Research, University of Southern Denmark, Odense, Denmark*

^c*Department of Molecular and Medical Pharmacology, David Geffen UCLA School of Medicine, Los Angeles, CA, USA*

^d*Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA*

^e*Department of Radiology, Thomas Jefferson University, Philadelphia, PA, USA*

^f*Department of Integrative Medicine and Nutritional Sciences, Marcus Institute of Integrative Health, Thomas Jefferson University, Philadelphia, PA, USA*

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Abstract. The lengthy debate on the validity of the amyloid hypothesis and the usefulness of amyloid imaging and anti-amyloid therapeutic interventions in dementia continues unabated, even though none of them have been able to convince the medical world of their correctness and clinical value. There are huge financial interests associated with promoting both, but in spite of the large sums of money in their support, no effective anti-amyloid treatments or diagnostic use of amyloid imaging have emerged. There are solid scientific reasons that explain these negative results, and it is time to move forward to other promising options for the benefit of the patients.

Keywords: Alzheimer's disease, amyloid hypothesis, amyloid imaging, anti-amyloid therapeutic interventions, clinical usefulness

More than a quarter of century of 'amyloid hypothesis' has not produced any therapeutic outcome or any positive use of 'amyloid imaging' [positron emission tomography (PET) A β imaging] at any time that convinced the larger medical community, and the Centers for Medicare & Medicaid Services (CMS), about its applicability to Alzheimer's disease

(AD) [1]. In spite of the billions of dollars spent in the midst of an unrelenting number of studies and publications based on this hypothesis, disease prognosis and outcome has remained unmodified. Most recently, a large clinical investigation involving 12,648 subjects on the utilization of amyloid imaging in patients with mild cognitive impairment (MCI) and AD, matched by sex and age and compared with controls, was presented at the 2020 Alzheimer's Association International Conference (AAIC) meeting (Rabinovici GD, Gareen IF, Song Y, Gutman R, Apgar C, Carrillo MC, Dilworth-Anderson P, Hanna L, Hillner BE, Romanoff J, Siegel B, Wilkins CH, Whitmer RA, Gatsonis C. Association Between Amyloid PET and Health Outcomes:

*Correspondence to: Poul F. Høilund-Carlsen, MD, DMSc, Prof (Hon), Department of Nuclear Medicine, Odense University Hospital, 29 Sdr. Boulevard, 5000 Odense C, Denmark. Tel.: +45 2521 5445; E-mail: pfhc@rsyd.dk. ORCID ID: 0000-0001-7420-2367 and Jorge R. Barrio, PhD, David Geffen School of Medicine at UCLA, Department of Molecular and Medical Pharmacology, CHS B2-086A, 694817, 10833 Le Conte Avenue, Los Angeles, CA 90095-6948, USA. E-mail: jbarrio@mednet.ucla.edu.

the IDEAS Study. Presentation SO-03-07: <https://alz.confex.com/alz/20amsterdam/meetingapp.cgi/Session/6777>). The trial was financed by CMS, and sponsored by the Alzheimer's Association, the American College of Radiology, and participating pharmaceutical companies, to help Medicare officials decide whether covering 'amyloid imaging' brain scans would help curbing emergency room visits and hospitalizations. The CMS IDEAS study missed its goal, established at curbing hospitalizations by 10% in the year after the amyloid PET scan was performed: Rates were 24% among those scanned versus 25% of the others [2]. This comes at the heels of the 2013 CMS determination negating reimbursement of amyloid imaging because the evidence was 'insufficient to conclude that the use of PET amyloid-beta ($A\beta$) imaging is reasonable and necessary for the diagnosis or treatment of illness . . . for Medicare beneficiaries with dementia or neurodegenerative disease, and thus PET $A\beta$ imaging is not covered under §1862(a)(1)(A) of the Social Security Act ("the Act")' [3].

Proponents indicate that even though hospitalization reduction cannot be realized in the CMS study, patients and families may still benefit from an accurate diagnosis [2], despite the fact that this is not what the study showed, nor what the method can provide. This parallels earlier opinions voiced by these and other authors, the majority of whom were company-sponsored, who have relentlessly stated that amyloid PET imaging can have a major impact on how we diagnose and care for patients with AD and other forms of cognitive decline, and that amyloid PET imaging can be a powerful tool to improve the accuracy of AD diagnosis and lead to better medical management, especially in difficult-to-diagnose cases.

Is this the Emperor's New Clothes? (Fig. 1). This seems to be the case, as these opinions are not supported by scientific evidence that conclusively indicates that PET $A\beta$ imaging is a valid, accurate, or useful diagnostic tool [4], and its direct impact in patient management has remained questionable for the same reasons. Extensive pathology data obtained in autopsy determinations have earlier demonstrated that brain amyloid pathology, in itself, does not characterize or is specific for AD. We have discussed this previously in great detail in sections (B) and (C) of a critical review presenting the various inconsistencies reported in the literature on their alleged *in vivo* amyloid specificity and potential use in patients [4]. Subsequently, with reference to two



Fig. 1. The kind of arguing in contradiction to the actual results as presented in [2], is a type of spin termed "The Emperor's New Clothes" with reference to the poet Hans Christian Andersen's tale of the same name: The emperor adorns himself with fictional fashion clothes, which people in his pay loudly comment upon and admire, because otherwise they are considered incompetent for their job, until an outsider, a child along the road, where the emperor parades, reveals what everyone knows, but no one dares say aloud, by shouting: "But he hasn't got anything on". Illustration of 'The Emperor's New Clothes' (artist: Vilhelm Pedersen, 1849), via Wikimedia Commons. With regard to the figure, it can be captured from Wikimedia Commons at this link: https://commons.wikimedia.org/wiki/The_Emperor%27s_New_Clothes.

major meta-analyses on amyloid PET positivity in persons without dementia and subjects with a variety of dementia syndromes, we have pointed to the outspoken lack of specificity prevailing with respect to cerebral amyloid deposits in AD patients compared with healthy individuals [5]. How can then 'amyloid imaging' be used as a diagnostic tool?

Even physicians participating in the Medicare study have indicated that in the absence of effective treatments, it is a fair question to ask about the need for an amyloid imaging determination, particularly when the procedure has no diagnostic value. Why would CMS (and private insurance) support payment of \$4,000 – \$5,000 for amyloid PET scans with no diagnostic value, when no changes in hospitalizations or patient prognosis would exist? Particularly, when the FDA-approved, and CMS reimbursed, FDG-PET and even MRI scans approved for AD clinical characterization already exist at much lower cost?

We have earlier argued similar points [5, 6]. In a recent editorial in the *European Journal of Nuclear Medicine and Molecular Imaging* [6], we claimed that "it is time to re-evaluate the validity of the amyloid hypothesis, anti-amyloid therapeutic interventions, and amyloid imaging". There are

additional reasons for our claim, among them, significant questions regarding the ability and specificity of existing ‘amyloid tracers’ to label amyloid-A β plaques *in vivo*. A few examples illustrate this point, some of which have already been discussed in the literature [4]:

- 1) A study by Barthel et al. has provided strong evidence, using [^{18}F]florbetaben, of the large non-specific tracer retention in the white matter observed to be significantly higher than that in the frontal, temporal, and parietal lobes in A β -positive cases [7].
- 2) Similarly, it has remained unexplained based on amyloid PET imaging, why approximately 30% of cognitively normal control subjects have been reported to have an A β load comparable with that found in AD patients, when these claims are far from being supported by neuropathological determinations. Instead, it has been reported in autopsy determinations that A β plaques may be present in the brain of some normal controls, but it is ‘extraordinarily rare for a case with widespread, dense AD-type neocortical lesions to lack documented ante mortem cognitive decline’ [8].
- 3) Most recently, direct evidence was obtained that amyloid agents (e.g., [^{11}C]PiB PET) are able to produce characteristic focal signals in the living human brain in the absence of amyloid-A β plaques. In this case, brain images were obtained as a result of intracranial inflammation, a prevalent condition in patients with Moya-Moya disease [9].

These data alone indicate that amyloid-A β imaging signals may not necessarily be consistent with the presence of brain amyloid aggregates in humans and may not comply with basic requirements for their use in the diagnosis or management of AD patients.

The evidence collected after more than 30 years, in countless number of laboratory studies [1, 4, 10] and clinical trials involving thousands of patients and billions of dollars spent by the funding agencies and pharmaceutical industry is hard to bend. A most recent Biogen request for Aducanumab approval to the FDA was submitted based on a very limited benefit to a patient sub-group following protocol modification, after its clinical trials missed their established primary end-points of slowing dementia progression (<https://www.alzforum.org/news/research-news/biogen-asks-fda-approve-aducanumab>, Tom Fagan, released 8 July 2020). The clinical validity of the data resulting from *in-situ* protocol changes

coupled with the minimum benefits observed, has understandably been questioned, as it is a *post-hoc* analysis of data collected in a design with another primary purpose. FDA approval based on statistical maneuvering may provide economic benefits to the sponsor and associates, but NOT necessarily be of help to AD patients. A discussion can be extended, the facts can be twisted for a favorable perception, but at this juncture, there is little question that the multiple, failed anti-amyloid therapeutic trials with dementia patients have raised not only medical but also ethical concerns.

On the same light, there is not scientific pathological data in support of the use of “amyloid imaging”—initially envisioned as a tool to monitor anti-A β therapeutic interventions—for AD diagnosis, or to modify patient management in light of its failed performance in reducing hospitalizations [2]. Or even as a predictor of patient outcomes as a sole indicator [2], when the specificity of amyloid agents is questionable, and serious questions are raised about the interpretation of the PET signal as an expression of the true presence of brain amyloid in the human brain. As expected, amyloid plasma biomarkers are also equally non-specific to characterize AD [11, 12].

Based on available scientific and clinical data, it would be unwise at the present time for regulatory and financial agencies to accept the proclaimed usefulness of amyloid-based diagnostic and therapeutic approaches considering the lack of scientific evidence in their support, consistent with the poor patient outcomes resulting from these trials.

DISCLOSURE STATEMENT

Authors’ disclosures available online (<https://www.j-alz.com/manuscript-disclosures/20-0990r1>).

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