Journal of Alzheimer's Disease 83 (2021) 3–4
DOI 10.3233/JAD-215138
IOS Press

Editorial

On the Nomenclature of the Alzheimer's Disease Amyloid and Its Precursor[1]

Nikolaos K. Robakis*
Center for Molecular Biology and Genetics of Neurodegeneration, Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai Medical Center, New York, NY, USA

Accepted 27 July 2021
Pre-press 17 August 2021

Amyloids are insoluble extracellular depositions of protein fibrils with a typical X-ray diffraction pattern. Amyloid fibrils are composed of polypeptide chains arranged in a twisted β-pleated sheet conformation. Amyloids bind Congo red with green, yellow, or orange birefringence when viewed in polarized light [1]. In the last decades, at least 36 distinct human proteins or protein fragments have been identified that, under certain conditions, aggregate to form insoluble amyloid depositions in human organs including the brain [2].

Importantly, the peptide fragments that derive from the AβPP (Aβ protein precursor, also referred to in the literature as APP [3]) and aggregate to form the amyloid found in the brains of Alzheimer's disease (AD) patients, are called "Aβ protein" or "Aβ peptides". Aβ peptides, like all amyloid precursors, are first created as soluble peptides that, depending on conditions, may aggregate to form amyloid precipitation. It is now clear that Aβ peptides are present in soluble form in all humans (most probably since birth) but may precipitate as brain amyloid in aged people and people who suffer from certain disorders including AD and Down syndrome.

Reading the AD scientific literature, however, you often find sentences like "... abnormal levels of amyloid were found in CSF (or serum)..." There are several problems with this terminology:

First, saying that somebody has measured amyloid in human serum or CSF is inaccurate because, by definition, amyloids are insoluble materials precipitated extracellularly and have specific physical and chemical properties [2]. Thus, it is a fallacy to say you measured amyloid in serum or CSF. Actually, what was probably measured in these fluids was soluble Aβ peptides (probably a mixture of monomeric Aβ with low levels of non-amyloid soluble Aβ oligomers) rather than any amyloid.

Second, since there are many amyloid precursor proteins in human serum and CSF, saying that you measured "amyloid" leaves it unclear which specific amyloid you refer to. For example, Immunoglobulin amyloid, Apolipoprotein amyloid, etc., or Aβ amyloid?

Third, for an amyloid to form, soluble oligomeric aggregates of its precursor protein(s) must first form and precipitate in the extracellular space, usually in a non-amyloid form. This is also the case with the Aβ peptides that first aggregate to precipitate in a non-amyloid form called "diffused plaques" that are commonly detected with anti-Aβ antibodies but do not bind amyloid markers like Thioflavin T or Congo red. This "diffused" precipitation of Aβ peptides is

[1]This article has also been posted online as a JAD Editors' Blog: https://www.j-alz.com/editors-blog/posts/nomenclature-alzheimers-disease-amyloid-and-its-precursor

*Correspondence to: Nikolaos K. Robakis, Director, Center for Molecular Biology and Genetics of Neurodegeneration, First A.P. Slaner Professor for Alzheimer disease research, Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai Medical Center, One Gustave Levy Pl. Box 1229, New York, NY 10029, USA. E-mail: nikos.robakis@mssm.edu.

ISSN 1387-2877/$35.00

then slowly (over time) converted to amyloid composed of twisted β-pleated sheet structures able to bind amyloid markers, a property that characterizes the amyloid fibers. Thus, calling "amyloid" anything found soluble in human fluids is clearly wrong.

I propose to call Aβ peptides measured in solutions or human fluids by immunodetection, exactly what they are: "Aβ peptides." This nomenclature accurately identifies the protein species, and any oligomers of it, measured in solution. In addition, we should call extracellular amyloid precipitates composed of Aβ peptides "Aβ amyloid" or "AD amyloid". This clearly identifies the precursor protein that makes up the specific amyloid deposition being studied.

DISCLOSURE STATEMENT

The author's disclosure is available online (https://www.j-alz.com/manuscript-disclosures/21-5138).

REFERENCES

[1] Cooper JH (1974) Selective amyloid staining as a function of amyloid composition and structure. Histochemical analysis of the alkaline Congo red, standardized toluidine blue, and iodine methods. *Lab Invest* **31**, 232-238.

[2] Sipe JD, Benson MD, Buxbaum JN, Ikeda SI, Merlini G, Saraiva MJ, Westermark P (2016) Amyloid fibril proteins and amyloidosis: Chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. *Amyloid* **23**, 209-213.

[3] Robakis NK, Ramakrishna N, Wolfe G, Wisniewski HM (1987) Molecular cloning and characterization of a cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides. *Proc Natl Acad Sci U S A* **84**, 4190-4194. Erratum in: Proc Natl Acad Sci U S A 1987 Oct;84(20):7221.