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Editorial

Imaging Amyloid

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Proteinopathies, Amyloidoses and Neurodegenerative Diseases

In certain diseases, protein conformation gets changed, either due to mutation or environmental factors or other inherent risk factors, such as metabolic and epigenetic changes. Proteins mis-fold into a state away from native or intrinsically disordered state. The new, very stable state is characterized by an all β-secondary structure and the protein forms prefibrillar oligomers – in range of 6 to 12-mers (prone to bind to membranes) and mature, μm long fibrils. The diseases of this type are called amyloidoses; derived from the word amyloid (to be described) and can be systemic or organ related. Most neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), fall into this category as well as other dementias and prion diseases and show intracellular and/or extracellular inclusions. The intracellular inclusions in AD appear mainly from the phosphorylated protein tau and in PD from the protein α-synuclein. The extracellular deposits/ plaques in AD are composed from fragments of amyloid-β precursor protein, a membrane protein, which is cut by aspartic proteases – secretases α, β and γ into peptides of various lengths. Especially the N-terminal fragments called amyloid-β peptides: A-β (1-40) and A-β (1-42) are prone to aggregate into amyloid state. Amyloid plaque is, in distinction to what initially its name meant (starch colored by iodine), composed of misfolded and fibrillized protein, where usually one type of protein predominates.

Are Amyloid Deposits Dangerous?

10 to 30% of elderly people with normal cognitive abilities show amyloid deposits. No direct relation of amyloid burden and less efficient cognition or memory loss, exists. Therefore, amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease patients [1] is accompanied with some ethical dilemmas. Whether to tell a person that he may be at risk or to keep such information? [2]

New research shows that amyloid burden is to some extent reversible. In accordance, lowering amyloid plaques in model mice improved their cognitive abilities. Vaccination is one such A-beta lowering method [3].

An opinion prevails that neurodegenerative diseases are at a stage as were vascular diseases about 20 years ago, when preventive measures were pursued. So, to follow the stage of vascular disease usually the blood pressure is measured or ultra-sound scan of the veins is made. In a similar way perhaps markers of AD should be followed and life style changes proposed in order to reduce the risk to obtain AD. The in vivo amyloid imaging with positron emission tomography (PET) - as described below - is found correlated to clinical data [4-5].

Imaging Living Brains by Radiometry

Positron emission tomography (PET) has been used to follow amyloid deposition in the living brains of patients with Alzheimer's disease (AD), other dementias and mild cognitive impairment (MCI). Two compounds are being used most frequently, 11C-Pittsburgh compound B (PIB), a thioflavin derivative and florbetapir [6]. Usage of both radioligands is replaceable as Ab status can be reliably transformed from PIB to florbetapir units. A recent study identified the presence of multiple PIB binding sites (high- and low-affinity) in AD patient's brain homogenates. From competition studies they propose a multiple site model where PIB, AV-45 (florbetapir) and AV-1 (florbetaben) share similar binding to high affinity site (site 1) in nanomolar range, thus, these amyloid ligands are comparable and reliable measure of the brain amyloid deposition. A somewhat different binding pattern is observed for compounds BF-227 and FDDNP with preference for sites 3 and 2, respectively [7].

Labels Free Imaging

Structural MR

MR imaging and volumentry allow a comprehensive brain assessment and can be viewed as a structural imaging biomarker of AD. It has been found that hippocampal atrophy is a risk factor for progressing from amnesic MCI to AD in normal aging. Hippocampal and temporal gray matter atrophy can happen in cognitively healthy older people, however, their presence is predictive of later risk for dementia [8].

Functional MRI (fMRI)

Promising seems also fMRI, both task-related, and intrinsic-connectivity network (resting-state) fMRI [8-10]. fMRI studies during memory tasks of patients with clinical AD have shown alterations in the networks of the posteromedial cortices, including the precuneus and posterior cingulate. Similar functional abnormalities have been detected in subjects at-risk for AD, including those with genetic risk and older individuals with mild cognitive impairment. Evidence of functional alterations in these memory related networks was found also among cognitively intact older individuals with increased amyloid pathology, previously detected by PET [11].

In general, potential clinical applications of resting state fMRI include presurgical planning for patients with brain tumors or epilepsy. As this method is not invasive and does not require patient cooperation, it is particularly useful in patients who are not able to

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cooperate, such as patients with AD and various psychiatric diseases [12].

Blood tests

A blood test for AD [13] is viewed as an advantage over more complex tests, such as measuring markers in cerebrospinal fluid or imaging brains by magnetic resonance or PET. So far, the recognized biomarkers of Alzheimer's disease comprise amyloid-β, tau and phosphorylated tau. As a new feature, recently, a test to differentiate an early onset AD from healthy population based on RNAi, isolated from exosomes was reported [14]. The biological markers tests have to be compared to other tests, such as neuropsychological assessment [15].

Special Biophysical Properties of Amyloid – as a Future Sensor and Reporter

Amyloid state of proteins, especially extended-amyloid fibrils exert physico-chemical properties similar to other elongated and asymmetric polymers or crystals. Materials showing some similar properties are peptide nanotubes [16-18]. Together with DNA [19] and graphene [20], amyloid fibrils make very interesting and resistant, stable as steal, composite materials[18].

What of these properties do pathological and functional amyloids have in living organisms? Do they transmit light as in bioluminescence? Do they emit light? Do they interact with magnetic fields? - are the open questions. Some of the answers may bring also possible applications for minuscule diagnostic or therapeutical tools.

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