Oxidative stress as a biomarker for Alzheimer's disease

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“In the search for oxidative stress biomarkers, should the specificity include both AD and oxidative stress?”

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It is estimated that Alzheimer's disease (AD) is striking 1 in 20 over age 65, which yielded to 23–35 million people worldwide in 2015. The number of AD victims is expected to almost double every 20 years, thus placing the national healthcare systems under dramatically increasing pressure. This clearly underlines the need to find early biomarkers and efficient medical treatments for AD, both implying a better understanding of the mechanism from the origin of the disease to the death of the neurons. Oxidative damages on neuronal lipids and proteins, in particular, are an important feature of AD and a link with oxidative stress [1]. The latter can have different origins, but the overproduction of reactive oxygen species (ROS) is considered as a major contribution. Loosely bound metal ions (copper and iron), present in the brain and at high concentration in senile plaques of AD patients, may bind to the amyloid beta peptide (A β) thus catalyzing very efficiently the production of ROS (in particular, the oligomeric forms of A β , known as being the most toxic). This represents one of the source for ROS production in brain, a second one being mitochondria dysfunction.

What are the biomarker candidates?

Along with cognitive testing, A β 42, total and phosphorylated tau levels are currently the recommended biomarkers in the cerebrospinal fluid (CSF) for using in clinic to establish a diagnosis of AD [2]. Biomarkers of oxidative stress in AD can either be directly produced after an attack of biomolecules by ROS, result from a reaction between a primary oxidation product – such as 4-hydroxynonenal – and a biomolecule, or be a metabolite that is indirectly upregulated or downregulated by oxidative stress. Thus, usual markers of protein, lipid, DNA and RNA oxidation are associated with AD: carbonylation of proteins, lipid peroxidation, oxidation of nuclear and mitochondrial DNA bases (resulting in 8-oxo-2-dehydroguanine, 8-hydroxyadenine and 5-hydroxyuracil production) and oxidation of mRNA [3]. Lipid peroxidation is involved in disruption of cell membrane integrity and also in the production of 4-hydroxynonenal that is further able to react with proteins (lysine and cysteine residues), as for example, tau or LRP1. Oxidation of the latter would be responsible for the disruption of A β clearance in the brain [4], leading to its accumulation. Oxidation of cholesterol into oxysterols is also reported to play a role in amyloidogenesis, in particular, 24- and 27-hydroxycholesterols [5]. Some of other commonly reported oxidative stress biomarkers of AD are ApoE genotype, malondialdehyde, 8-hydroxy-2'-dehydroguanosine, coenzyme Q10, GSH/GSSG, superoxide dismutase, hydrogen peroxide, glutathione peroxidase and reductase and isoprostanes (see [6] for a review of AD studies). Finally, as metallated A β is one of the significant source of ROS production in the brain, the peptide itself undergoes the ROS attack and the oxidized A β peptide could thus appear as a very specific oxidative stress biomarker for AD.

Which ones would be relevant in the context of *in vivo* sampling procedures?

The relevance of a biomarker for any pathology would lie in three important points: it must be associated as specifically as possible with a particular pathology; it must be easy to detect and quantify, by affordable and robust analytical methodologies; and finally, it must be present in peripheral tissue or fluid – meaning accessible by noninvasive techniques. In the context of AD, a neurodegenerative pathology, the last point is the first to take into account since potential biomarkers specifically present in the brain can only be quantified postmortem in brain tissue. Actually, diagnosis can be made by the use of analytical methodologies based on brain imaging – such as magnetic susceptibility [7] or positron emission tomography [8], for example, used for A β and tau pathologies. However, they usually require sophisticated equipment and are expensive. In clinical and preclinical stages, AD diagnosis is based on the presence of A β and tau in the CSF, which require an invasive sampling procedure. The future of biomarkers discovery for AD thus seems to lie in developing strategies that focus on searching biomarkers in easily available tissues, meaning peripheral biofluids such as blood. Many efforts are currently done by research groups worldwide for finding early AD biomarkers in blood (including plasma, serum, platelets, red blood cells and lymphocytes). The broadly accepted CSF biomarkers are not good for blood since they show either no significant change between AD patient and healthy controls or a considerable variability between studies [9]. Systematic review of AD studies in the literature may help in finding relevant candidates [6], and promising research strategies could focus on lipid peroxidation – in particular, lisophosphatic acid C18:2 [10] – and high levels of isoprostanes and neuroprostanes, found in plasma, but also urine and CSF. However, no consensus has been found yet.

The quest for an early & specific biomarker of AD

Oxidative stress being an early event in AD etiology, one can assume that associated biomarkers could represent an interesting opportunity in terms of early diagnosis of AD. Markers of oxidative stress were suggested as consistent elements of blood-based signatures in AD [10]. Searching for good candidates is often based on AD studies in the literature and/or statistical analysis. To date, none of the suggested biomarkers were validated by large cohort studies at preclinical/clinical stage and associated with AD progression. One reason is because the search for oxidative stress biomarkers for AD is still an emerging field, or actually was not the first way explored by researchers. The major pitfall is that oxidative stress is one of the responses to inflammation and is also commonly induced by various pathologies (such as cancer, atherosclerosis or diabetes), which could share some of the potential biomarkers. For instance, lipid peroxidation and malondialdehyde are also biomarkers of cancer. The current diagnosis of AD is established, biochemically, by A β , total and phosphorylated tau levels, three specific biomarkers. In the search for oxidative stress biomarkers, should the specificity include both AD and oxidative stress? Yes probably, and this reduce the possibilities. In this perspective, one can wonder if oxidation levels of the A β peptide, the AD's closely associated molecule, could be of major interest. Circulating A β has been detected in plasma, along with oligomeric forms that could be considered as potential biomarkers [11]. As the latter are known as the most toxic forms of A β (compared with monomer or fibrils), in particular, because they are associated with ROS production, it can be assumed that oxidized A β species would also be present. The development of antibodies directed against oxidized A β would help in such a quest, although it is challenging since expected levels of circulating oxidized A β should be very low, especially at the beginning of AD progression. However, while continuing to search for other oxidative stress biomarkers, this quest should be very attractive.

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