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Commentary

Examination of a non-invasive biomarker for the diagnosis of prodromal Alzheimer's disease and Alzheimer's disease Dementia

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According to the Alzheimer's Association, in the current year of 2020, there are an estimated 5.8 million Americans aged 65 and older living with Alzheimer's dementia and by 2050 this number is expected to increase to 13.8 million. Although the complex etiology and pathogenesis of Alzheimer's disease (AD) are not fully understood, the disease is characterized by the aggregation of amyloid plaques and neurofibrillary tangles (NFTs) in the brain and the accompanying oxidative stress [1]. It is thought that amyloid-β (Aβ) aggregation may be a result of the presence of microbes, and hence, specific antimicrobial proteins and peptides (APPs) involved in innate immunity may be a potential biomarker for AD diagnosis and treatment [2]. The iron-binding protein lactoferrin (Lf) is a promising biomarker candidate for AD diagnosis and its potential has been examined in an article in *EBioMedicine* by González-Sánchez *et al* this protein is expressed in all body fluids, exhibits early antiviral activity, and has been previously recorded to be downregulated in saliva from patients with AD and mild cognitive impairment (MCI) when compared to normal control subjects [3,4].

For the first time, González-Sánchez and colleagues examined the potential of Lf as a salivary AD biomarker using participants with known amyloid-Positron-Emission Tomography (PET) status [5]. They were successful in demonstrating that reduced salivary Lf levels correlate with positive amyloid PET results and that reduced Lf levels are specific to AD and mild cognitive impairment (MCI) and not to frontotemporal dementia (FTD) patients. This finding successfully shows the relationship between salivary Lf and Aβ plaques in the brain of AD patients, which is a key factor in fully understanding the etiology of this complex disease. The fact that salivary Lf levels were not decreased in FTD patients is interesting and may be because although some hypothalamic regions are affected in FTD, these regions are not the same as those affected in AD [6]. This supports the researcher's hypothesis that the early accumulation of Aβ in a specific region in the hypothalamus disrupts its function, which affects the regulation of the salivary gland and ultimately decreases Lf levels.

The current criteria for diagnosing MCI and AD exists as either 1) the Core Clinical Criteria, which are outlined criteria that can be followed without pricey instrumentation, or 2) the Core Research Criteria, which utilizes biomarkers only in clinical settings, like a research environment or clinical trials. Although accurate, the limitations of the Core Research Criteria are price, lack of research into cut-off points, and limited access to resources in non-specialized settings. PET scans are commonly used to identify Aβ deposition, however, PET scans are expensive and specialized. Cerebrospinal fluid can also be tested for low levels of Aβ and increased total tau or phosphorylated tau proteins. However, obtaining cerebrospinal fluid is considered an invasive procedure [7]. The study by González-Sánchez *et al* successfully revealed a good correlation between decreased salivary Lf and amyloid-PET imaging for AD, but more importantly revealed this same correlation with MCI. The correlation between decreased salivary Lf and amyloid-PET imaging for MCI proposes Lf as a potential biomarker for inexpensive and noninvasive diagnosis of prodromal AD.

One surprising finding in the González-Sánchez *et al* study was that there was no correlation between salivary Lf levels and APOE e4 carriers compared with APOE e2 and e3 carriers. It is widely accepted that carriers of one or more copies of the APOE e4 allele have a higher risk of not only developing AD but developing it at an earlier age. While carriers of at least one of the rare APOE e2 allele have a decreased risk of developing AD [8]. This brings into question the validity of using the APOE genotype as a marker for AD prediction and hints at the multifactorial progression of AD.

The reproducibility of using Lf as a biomarker was demonstrated through the examination of two different cohorts, the first from Central and South of Spain, and the second from the Central Spanish region. Although this begins to scratch the surface on the reproducibility of this biomarker, studies have shown that salivary Lf concentrations can be affected by many environmental and lifestyle factors [9]. Saliva is a variable body fluid that changes in composition over time and even throughout the day, so this variability will need to be taken into consideration in future studies when deciding on a diagnostic limit of Lf. It is also important that more large-scale studies be performed on diverse groups of people both geographically and

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lifestyle-wise to further confirm the hypothesis that salivary Lf can be used as a universal diagnostic biomarker for AD.

The research by González-Sánchez *et al* is promising for the future of AD diagnosis. Many recent research efforts are utilizing Lf to combat AD, including a therapeutic approach using lactoferrin-conjugated linoleic acid micelles to deliver the protein to the brain, which has successfully been shown to lead to reduced oxidative stress and inflammation in the brain tissue [10]. It is clear that the Lf protein will be a key factor in the future of Alzheimer's studies.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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