Opinion

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The Potential of Infrared Spectroscopy and Multivariate Analysis of Peripheral Blood Components as a Validated Clinical Test for Early Diagnosis of Alzheimer's Disease

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Opinion

Alzheimer's disease (AD) is usually considered as an aging disease as the Greek and Roman physician used to consider, and as the main cause of dementia. AD patients start to do mistakes in language, to lost direction, changes in mood, self-careless until losing their emotional and body functions until death [1]. The symptoms of the disease are getting worse by time. AD was first diagnosed in 1901 by psychiatrist Alois Alzheimer (thus this dementia acquired his name) and till now its causes are not yet known and there is no validated clinical test for diagnosis [2] especially at early stages. According to the statistics in 2015, there is about 48 million persons worldwide diseased with AD [3]. In 2010, 486,000 deaths resulted from dementia. As life expectation increases in developed countries and AD is mainly an aging disease it becomes financially very costly disease [4]. While the death due to other diseases has been decreased, the deaths related to AD are increasing; for example the deaths due to AD in the years 2000 and 2008 have increases by 66%. The economic burden due to AD is very high making it a major medical challenge; the cost of the disease in the USA alone in 2015 was $226 billion and it is in the upward trend [5].

Although there is no medication to treat or reverse the disease, it is important to diagnose AD accurately as early as possible, since there are medications to slow the symptoms and thus to improve the quality of life by preserving daily functioning for more time [3]. These medications are most effective when used at the early stages of AD.

The initiation of the disease is associated with the formation of senile plaques, mitochondrial dysfunction, and hyper phosphorylated tau protein in neurofibrillary tangles in the brain [6].

Today, AD is diagnosed subjectively by a combination of cognitive neurologists, geriatricians, and psychiatrists based on medical files and mental tests such as mini-mental state examination (MMSE). Medical imaging such as positron emission tomography (PET) and magnetic resonance imaging (MRI), computerized tomography (CT) [7] and Cerebrospinal fluid (CSF) [8] are combined to the cognitive tests to enable reliable diagnosis. Actually, it is possible to diagnose AD accurately only just after death [7,9] moreover, 45% of AD patients have not been told about their disease.

Many new techniques were developed for AD diagnosis like, several CSF biomarkers tau, amyloid beta [10], single photon-emission computed tomography (SPECT) [11], spectral method for CSF biomarker analysis (ELISA) [12], mass spectrometry, Raman, polymerase-chain-reaction (PCR)). Different studies used brain tissues for AD diagnosis such as Raman [13] and FTIR microscopy [14] and near infrared fluorescence probes [15].

There are major drawbacks of these new techniques, for example, CSF biomarkers are not well standardized (sample handling, concentration) [16]; the pathognomonic and diagnostic value of the genetic and biochemical markers are not proofed yet (expensive equipments and it is hazardous to extract the CSF [17]). All these drawbacks and the situation of AD early diagnosis empathize the need of objective and reliable technique for clinic diagnosis and follow up of patients which can be used routinely [17]. These features of the diagnostic technique make the blood test as the most promising biomarker [18].

Infrared spectroscopy is known as a cheap, rapid and easy to use technique for objective analysis. It is widely used in the medical fields [19-24] for more than three decades for the detection of cancerous disease based on biomedical changes occurring during the developing of the disease related to the alteration in the chemical composition [25].

Mid-infrared absorption spectra are obtained using infrared spectroscopy by measuring the absorption bands of the functional groups of the molecules that compose the examined sample. These spectra can be used for qualitative and quantitative analysis and is considered as a fingerprint of the biological samples.

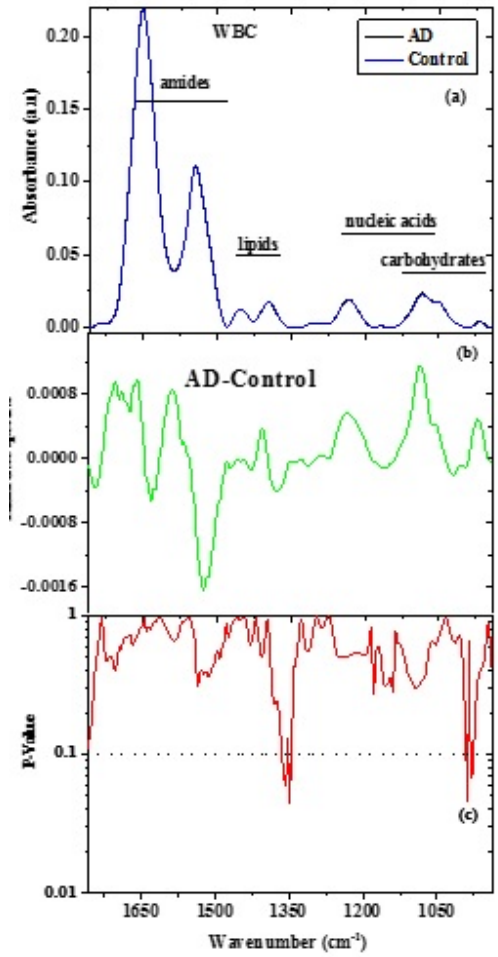

Figure 1 Average infrared absorption spectra (a), difference spectra (b) and p-value spectra (c) of WBC for AD patients and controls in the region 942-1760 cm^{-1}.

Recently infrared spectrometers have benefitted from high spectral and spatial resolution developments making the infrared spectroscopic technique as a reliable in both applied and basic research. In addition, there was a great development of new bioinformatics methods for the analysis of bio-fluid samples from patients with different diseases [26].

Combining bioinformatics methods in tandem with infrared microcopy generate a powerful diagnostic tool for health care using the analysis of bio fluids like serum [27], urine, plasma and white blood cells based on their infrared absorption spectra [28]. There are many advantaged of bio fluids analysis since they are minimal invasive and cheap which makes it ideal for routine and low risk method for clinics [28].

Many studies have been carried out and showed the potential of infrared microscopy of blood components in the medical field [29,30]. For example, detection of different kinds of cancers, detection of AD based on plasma samples and the analyses of the secondary structure due to amyloids beta [31].

Different biochemical changes are associated with AD and just part of them are known like amyloid beta peptides, changes in lymphocytes in AD patients [32], but most of these changes are still not known [32].

Several studies have shown the potential of FTIR microscopy in tandem with multivariate analysis for the early detection of AD [33] and recently our group have shown the potential of this spectroscopy technique for early diagnosis of AD using WBC [34]. There is clear evidence of the ability of multivariate analysis for classification manner even if the changes among the groups are minute [35-39].

Figures 1a and 2a show the examples of mid infrared spectra for two of the blood components WBC and plasma showing the difference between groups. As expected, the spectra are generated as results of the vibrations of the functional groups of the biomolecule that compose the biological samples, such as proteins, lipids carbohydrates and nucleic acid.

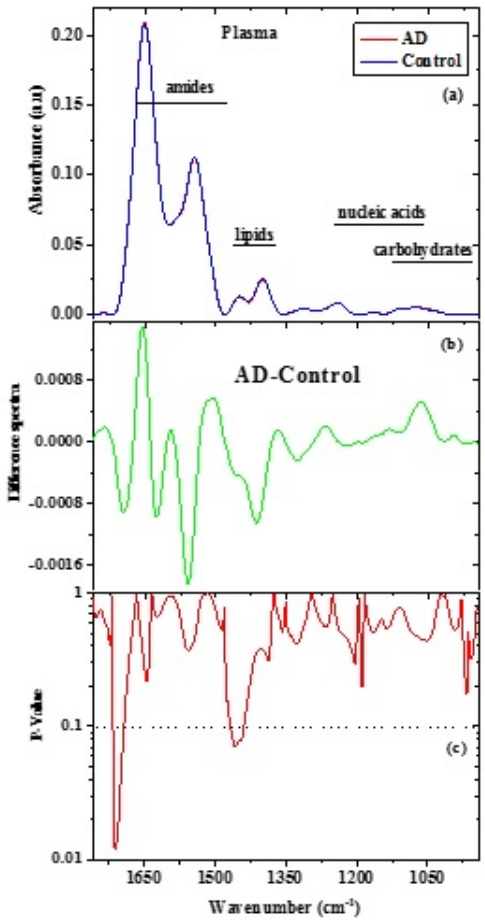

Figure 2 Average infrared absorption spectra (a), difference spectra (b) and p-value spectra (c) of plasma for AD patients and controls in the region 942-1760 cm^{-1}.

The differences between the healthy control and AD patients in both WBC and plasma samples are subtle but they are still sufficiently repeatable to yield the required statistics. The difference spectra calculated as AD minus control for WBC and plasma are plotted in **Figures 1b and 2b** respectively. **Figures 1c and 2c** show the p-values calculated using t-test to

differentiate between the two groups based on WBC and plasma samples respectively. The calculations were performed for each wavenumber separately. As can be seen from the figures there are several sensitive wavenumbers which enable to differentiate significantly (>90%) between AD patients and controls. In the plasma the bands centered at 1713 cm^{-1} attributed to amide I (C=O, thymine), and the wavenumbers in the range 1440-1469 cm^{-1} (due to lipids and proteins) [40]. Both wavenumbers can be considered as biomarkers, which differentiate between AD patients and controls. In WBC, the most sensitive wavenumbers are found in the regions 980-995 cm^{-1} (OCH3 polysaccharides and C-O ribose [41] and C-C) and 1347-1368 cm^{-1}(arising due to C-O stretching C-H and N-H deformations).

Using multivariate analysis PCA followed by LDA it was possible to differentiate between AD regardless of the disease stage and control with more than 90% success rate [34].

Our results indicate that the diagnosis of AD at early stages is plausible based on simple peripheral blood tests. Infrared microscopy combined with machine learning algorithms makes this method more reliable and objective as a diagnostic tool.

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