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Abstract of the PhD thesis

Measurement of retinal nerve fibre layer thickness as early diagnosis method in dementia

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The present thesis has analysed the potential of using the thickness of the retinal nerve fibre layer (RNFL) as a potential biomarker for early diagnosis of Alzheimer's disease (AD).

It is well known the fact that dementia is a world-wide epidemic, with Alzheimer's disease being the culprit in about 60-70% of the cases. There have been countless efforts of scientists and researchers around the globe to identify a treatment for this condition, however so far we can only slow down its progression in some cases.

In the absence of an effective treatment, a better approach is identifying the first structural changes of AD that we know can take place years before the first symptoms become evident. Various early diagnosis biomarkers have been studied over time in the hope that they would help diagnose a pre-symptomatic AD hence leading to a slowing in progression of the illness even more.

This research focused on one such early diagnosis biomarker, namely the thickness of the RNFL measured via optical coherence tomography (OCT).

OCT is a non-invasive method of investigating the retina and other structures of the eye. It offers an "in vivo" snapshot of these structures with minimal discomfort for the patient. It has become more intensively used over the past decades in ophthalmology, however researchers have hypothesized it can be used in other areas such as neurology and psychiatry to contribute to the diagnoses of neurodegenerative diseases, such as multiple sclerosis, Parkinson's disease, multiple systemic atrophy and even AD.

The hypothesis of the use of RNFL thickness as early diagnosis for various neurodegenerative diseases stands on the fact that the retina has a very similar structure to the brain as they are both derived from the neural tube and part of the central nervous system. Retina is more accessible for direct investigations, hence the great interest in its study.

We have conducted 3 studies as part of this research and they will be summarized below.

The **first study** represents a systematic review of the literature looking at studies in the past decade which analysed the relationship between RNFL changes and AD. In summary, we have included 31 studies which met the inclusion criteria (out of the 133 studies initially identified). A number of 15 studies compared the RNFL in AD patients with normal controls. Half of them (N=7) showed that there is an overall significant reduction in RNFL thickness in patients with AD as compared to healthy individuals. Moreover, it was shown that the superior quadrant of the RNFL was significantly reduced in AD patients in a number of 13 studies. An interesting finding of 2 studies which looked at individuals with Mild Cognitive Impairment (MCI) as well as patients with AD and healthy controls,

was that they identified an increase of the macular thickness in individuals with MCI. This finding led to the hypothesis of an inflammatory process or a gliosis process which would precede the neuronal loss. Some of the studies also looked at the correlation between the RNFL thickness and the degree of cognitive impairment as shown in cognitive testing. They showed that there is a positive correlation between the level of reduction in RNFL and the level of cognitive impairment. One of the most important findings of this systematic literature review is that we observed a significant variability of the retinal parameters (RNFL, macular thickness) between different populations across the globe. This finding uncovered the need of identifying a normal range of values for retinal parameters of the population in Romania that we conducted our study on.

The **second study** therefore, looked at the retinal parameters of a lot of healthy individuals in a region in Romania with the purpose of identifying what is the normal range of these parameters for our population. We looked at OCT analysis sheets of individuals without retinal pathology (1387 eyes for macular thickness and 1372 eyes for RNFL).

The following mean values were obtained for RNFL in each quadrant: superior quadrant - 115.91 ± 21.86 μm; nasal quadrant - 78.85 ± 14.31μm; inferior quadrant - 128.52 ± 16.6 μm; temporal quadrant - 71.35 ± 9.97 μm. In all four quadrants RNFL was thicker in males than females, but only in the nasal quadrant the difference was statistically different. There is a weak negative correlation between RNFL thickness and age, however this is statistically significant in all four quadrants. When comparing the results in our lot of population with studies conducted in other populations in India, Turkey and Spain, there were significant differences between our results and their results on RNFL in healthy individuals.

The **third study** hypothesised that there might be early changes in the retinal parameters in individuals who are known to have a vulnerability for developing a dementia – namely the first degree relatives of patients who are already diagnosed with AD.

This was an observational, prospective study. We analysed the RNFL thickness and macular thickness in 3 groups: patients with AD, first degree relatives of patients with AD and a lot from the healthy population. We analysed 48 eyes of patients with AD and 68 eyes of first degree relatives.

RNFL thickness is reduced in patients with AD as compared to the relatives group both globally ($p=0.04$), but more specifically in the superior quadrant of the right eye ($p=0.0001$). We would have expected that RNFL thickness would be reduced in the AD group as compared to the normal population, as showed in other studies, however in our study, RNFL was thicker in the AD lot. This finding might mean that, given the fact that all AD patients included suffer from mild-moderate AD, these are still the early stages and an inflammatory process might be still ongoing.

Macular thickness was the second parameter analysed in our study. We have not identified any statistically significant differences between the 3 groups, however it is of note that macular thickness is reduced in patients with AD as compared to the other 2 groups.

This paper represents a starting point for more work to be developed in the area of using retinal parameters as a potential early diagnosis of AD and a close follow-up in time of both patients with AD and first degree relatives would add more valuable information to the actual reliability of these parameters.