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Retinal Imaging

Retinal oxygen metabolism in patients with mild cognitive impairment

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Abstract

Introduction: We have previously reported that retinal vessel oxygen saturation is increased in mild-to-moderate dementia of Alzheimer's type when compared with healthy individuals. Mild cognitive impairment (MCI) is the predementia stage of the disease. The main purpose was to investigate if these changes are seen in MCI.

Methods: Retinal vessel oxygen saturation was measured in 42 patients with MCI and 42 healthy individuals with a noninvasive retinal oximeter, Oxymap T1. The groups were paired according to age.

Results: Arteriolar and venular oxygen saturation was increased in MCI patients compared to healthy individuals (arterioles: 93.1 ± 3.7% vs. 91.1 ± 3.4%, $P = .01$; venules: 59.6 ± 6.1% vs. 54.9 ± 6.4%, $P = .001$). Arteriovenous difference was decreased in MCI compared to healthy individuals (33.5 ± 4.5% vs. 36.2 ± 5.2%, $P = .01$).

Discussion: Increased retinal vessel oxygen saturation and decreased arteriovenous difference in MCI could reflect less oxygen extraction by retinal tissue. This indicates that retinal oxygen metabolism may be affected in patients with MCI.

Keywords: Mild cognitive impairment; Alzheimer's disease; Oximetry; Retina; Retinal vessels; Oxygen saturation; Spectrophotometry

1. Background

Mild cognitive impairment (MCI) is a broad term that can be defined as an early stage of Alzheimer's disease (AD) as well as of other types of dementias [1]. Some individuals with MCI are however stable and can even recover [2]. Complaints about visual impairment are common in AD patients [3], and retinal vascular abnormalities have been found in patients with AD [4]. There is some evidence of thinning of the retinal nerve fiber layer (RNFL) in MCI [5,6] and AD [7–12] as well as with progression from MCI to severe AD [6]. It has been suggested that this may help in diagnosis and also to evaluate progression [13].

Einarsdottir et al. measured difference in retinal oxygen metabolism in mild-to-moderate Alzheimer's dementia and found increased vessel oxygen saturation compared to healthy individuals [14]. In other retinal oximetry studies in retinal atrophic diseases such as in glaucoma, increased venular oxygen saturation and decreased arteriovenous difference (oxygen uptake) were correlated with worse glaucomatous visual fields [15,16] and thinner RNFLs [17].

Biomarkers for AD have gained increased recognition and include cerebrospinal fluid protein biomarkers (total tau, phospho-tau, and β amyloid-42), amyloid imaging

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positron emission tomography, and magnetic resonance imaging for evaluation of medial temporal lobe atrophy (MTA). These methods are however invasive and/or expensive, and there is still a need for simpler and reliable biomarkers of the disease. The purpose of the study was to test whether retinal oxygen metabolism is abnormal in AD in the stage of MCI when compared with healthy individuals and to examine whether retinal oximetry can serve as a noninvasive biomarker for early AD.

2. Methods

2.1. Study population

This study is a part of a larger study on progression of cognitive impairment in MCI. All participants signed an informed consent which followed the Tenets of the Declaration of Helsinki (www.wma.net/policy). The study is a case-control study.

Patients were diagnosed at the Memory Clinic of the Geriatric Department, Landspitali University Hospital, Reykjavik, Iceland. The diagnosis of MCI for inclusion in the study was made according to the Petersen criteria [18,19] based on information on cognitive impairment compared to earlier abilities from the patients and their relatives but without any change in abilities of daily life. The IQCODE questionnaire [20] was used in evaluating the changes seen by the relatives during the preceding years. An MMSE score [21] of 24 or above and an IQCODE score of 4.0 or less were used for inclusion. All patients went through a standardized procedure with neuropsychological testing and brain magnetic resonance imaging for evaluation of MTA. In some cases, analysis of β amyloid and tau proteins from cerebrospinal fluid was also performed.

All participants underwent comprehensive eye examination and were excluded if they had retinal or optic nerve disease such as glaucoma and age-related macular degeneration or trauma, diabetes mellitus, or other systemic diseases that can affect the eye. The healthy cohort included individuals with no history of cognitive impairment. All participants were of Caucasian origin. Sixty patients were originally recruited for oximetry. Thirteen patients were excluded because of retinal or optic disc disease or because of nonattendance on measurement day. In all, 47 patients went through oximetry. From the group of 47 patients, we were able to pair 44 with a healthy cohort, according to age (where no more than 7 years were between paired individuals). Of those 44, two were excluded because of bad image quality. Therefore, the final number of included participants was 42 in each group; the MCI group and the group of healthy control subjects.

Each participant answered a questionnaire on medical history, medications, and smoking. Blood pressure and heart rate were measured (Omron M6 Comfort [HEM-7000-E]; Omron Healthcare Europe, Hoofddorp, the Netherlands) as well as finger pulse oximetry (healthy cohort: Ohmeda Biox 3700; Ohmeda, Boulder, CO, USA; patient group: Masimo Rad 57, Masimo Corp., CA, USA) and intraocular pressure (iCare Tonometer TAO1; Tiolat Oy, Helsinki, Finland). Pupils were dilated with 1% tropicamide (Mydriacyl; S.A. Alcon-Couvreur N.V., Puurs, Belgium), which was supplemented with 10% phenylephrine hydrochloride (AK-Dilate; Akorn Inc., Lake Forest, IL, USA).

Magnetic resonance imaging of the brain was obtained from every participant with visual evaluation of atrophy of the medial temporal lobes scoring atrophy from 0 (no atrophy) to 4 (maximal atrophy, [22]). For the purpose of this study, the same experienced radiologist scored all the images consecutively.

Optical coherence tomography (OCT) imaging was performed on most MCI patients. Peripapillary scans were obtained with Topcon 3D OCT 2000 (Topcon Inc. Tokyo, Japan).

All the cases were diagnosed in a consensus meeting of at least three geriatricians. Based on all available information, the participants were grouped into one of two groups:

1. Clinical signs and biomarkers consistent with AD (n = 16)
2. Clinical signs of MCI but without clear biomarkers for AD (n = 25).

One patient had clinical signs and biomarkers that were consistent with early Lewy body dementia.

The consensus diagnosis was made according to ICD-10 (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems by the World health organization). Patients that did not fulfill the diagnosis of MCI by neuropsychological testing but still experienced loss of memory were considered to be in very early stage of MCI and were included in the study. Details on participants can be found in Table 1.

2.2. Retinal oximetry

Oximetry was performed with a dual wavelength, noninvasive spectrophotometric oximeter, Oxymap T1 (Oxymap ehf., Reykjavik, Iceland). The oximeter has been described in details elsewhere [23]. In short, the oximeter consists of a conventional fundus camera (Topcon TRC-50DX, Topcon Corporation, Tokyo, Japan) with two attached digital cameras. Two images of the retina at two different wavelengths, 570 nm (insensitive to oxygen saturation) and 600 nm (sensitive to oxygen saturation), are simultaneously acquired, and retinal vessel oxygen saturation is calculated from those two images.

2.2.1. Analysis of oximetry images

For every individual, both eyes were analyzed with a specialized analysis program for Oxymap T1, Oxymap Analyzer (version 2.2.1, revision 10927, Oxymap ehf., Reykjavik, Iceland). Excluded were images with image quality graded below five (according to the Oxymap Analyzer