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Fundus autofluorescence changes in multiple sclerosis

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Abstract

Visual dysfunction caused by optic neuritis represent the most common ocular manifestation in the multiple sclerosis. Other ocular findings in multiple sclerosis include vasculitis, retinitis and ocular motility dysfunction. An increased interest in the use of non-invasive retinal imaging modalities has been seen in neurodegenerative diseases. In this case report, the fundus autofluorescence findings suggesting changes related to multiple sclerosis is described. A 75 year-old female patient with multiple sclerosis referred for vision impairment in both eyes demonstrated hypoautofluorescence fundus changes suggesting advanced stage of multiple sclerosis and less compromised area with hyperautofluorescence. Fundus autofluorescence findings in multiple sclerosis have not been described previously.

Keywords: Fundus autofluorescence; Neurodegenerative diseases; Ocular manifestations in multiple sclerosis; Wide-field fundus imaging.

Introduction

The retina, an extension of the Central Nervous System (CNS), share a common embryological origin with the CNS. The neurosensory retina and CNS develop from neuroectoderm [1]. There has been growing interest for diagnosing and monitoring neurodegenerative diseases using non-invasive retinal imaging modalities. Multiple Sclerosis (MS), an autoimmune disease, characterized by inflammation, demyelination and neuronal and axonal degeneration of the CNS, may present with visual symptoms. Retinal changes may also reflect neurodegenerative diseases [2-6]. Studies have demonstrated affection of different retinal neural layers in multiple sclerosis. Green et al have analyzed retinal tissues in MS and described extensive retinal involvement with nuclear loss in both ganglion and inner nuclear cell layers in multiple sclerosis [7]. Although MS is a demyelinating disease and human retina is devoid of myelin, inflammatory cell infiltrates prominently close to retinal veins of retinal nerve fiber layer and ganglion cell layer were described [7,8]. Burkholder et al analyzed macular volume and Retinal Nerve Fiber Layer (RNFL) thickness in 1058 eyes of 530 multiple sclerosis patients. They demonstrated lower macular volume associated with RNFL thinning in MS patients with or without a history of optic neuritis [9]. Petzold et al reported particularly thinning of macular retinal nerve fiber and atrophy of ganglion cell layer and inner plexiform layer of the retina using Optical Coherence Tomography (OCT) in a meta-analysis of 110 eligible articles of 40 reported data with a total number of 5776 eyes [10]. Histological evaluation of eyes from 82 patients with multiple sclerosis at autopsy revealed inner retinal atrophy (retinal nerve fiber layer and ganglion cell layer) in 79% of the eyes [7]. They report odds of retinal atrophy in multiple sclerosis patients to be 17 times greater in comparison to controls. About 40% of

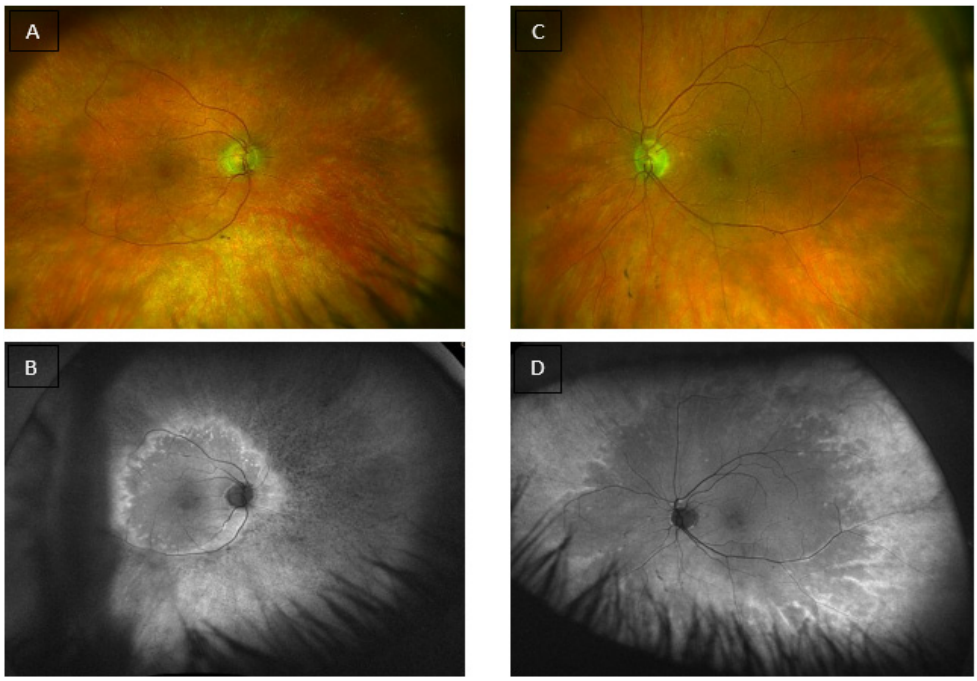

Figure 1: Wide-field fundus images (Optos®, Silverstone, Dunfermline, Scotland).
(A) Color fundus image of right eye reveals thinner retinal vessels outside the temporal vessel arches.
(B) Fundus autofluorescence image of right eye demonstrates hypoautofluorescence outside the temporal vessel arches, and hyperautofluorescence in the area dividing hypoautofluorescence and normal autofluorescence.
(C) The color fundus image of left eye shows thin retinal vessels in the periphery.
(D) Fundus autofluorescence image of left eye reveals hyperautofluorescence of periphery and mid-periphery areas (particularly near proximity of few of the vessels).

MS eyes demonstrated inner nuclear layer atrophy, but none of the control eyes. The MS patients with long-standing and/or progressive disease developed particular retinal atrophy. In addition, localized inflammatory cellular infiltrates surrounding retinal veins in the connective tissue of inner retinal layers (retinal nerve fiber and ganglion cell layer) was demonstrated independent of disease duration. Prominent mononuclear cells with foamy appearance suggesting phagocytic activity were scattered mainly throughout the inner retinal layers. However, these cells did not obey the cell layer boundaries and extended into the inner plexiform and inner nuclear layers. Microglia migrate into the CNS including retina and become resident macrophages. They play a major role in phagocytosis. These immune cells primary respond to pathological conditions including neurodegenerative diseases. These cells migrate throughout different layers of retina and move to the area of degeneration, become activated and proliferate [11-13]. The CD68- positive and-negative cells, collected from subretinal fluid in patients with rhegmatogenous retinal detachment and Coats' disease demonstrate autofluorescence [14]. The CD68 is a marker for macrophages. The possessed autofluorescence of macrophages is spectroscopically similar to lipofuscin [14]. The use of wide-field fundus autofluorescence imaging of the retina in mice expressing fluorescent protein in microglia has been studied. The retinal autofluorescence imaging to quantify retinal microglia correspond to the ex vivo counts on the retinal flat mounts and were equally distributed between the central and peripheral retina (102° widefield lens) [13]. Atrophy of retinal cell layers and microglia may be accountable for fundus autofluorescence changes in multiple sclerosis.

Case presentation

A 75-year-old female with MS presented with bilateral vision impairment that developed gradually over past years. MS was deteriorating over the past 10 years and classified into secondary progressive phase. She had a cerebral insult at the age of 66 with permanent left-sided hemiparesis, hemiplegia and facial nerve palsy. Her past medical history revealed also trigeminal neuropathy and recurrent urinary tract infection. She had best corrected visual acuity of 0.63 in each eye and normal intraocular pressures of 14 mmHg in the right eye and 13 mmHg in the left eye. The anterior segment examination demonstrated well-placed intraocular lens in the bag. The posterior segment examination revealed thin retinal vessels outside temporal vessel arches in the right eye and in the periphery in left eye, normal colored and sharply limited optic discs. She underwent color vision test using Ishihara 38 Plates book and scored 32/38 in the right eye and 33/38 in the left eye. The fundus autofluorescence revealed normal autofluorescence within temporal arches in right eye with hypoautofluorescence outside this area, and the bordering area between this demonstrated hyperautofluorescent dots (Figures 1A,1B). In the left eye, fundus hyperautofluorescent was observed peripherally and mid-peripherally and particularly along few retinal vessels (Figures 1C,1D). The OCT of macula and optic disc revealed normal findings in both eyes. The Electroretinography (ERG) did not demonstrate any scotopic response and showed reduced photopic response with normal implicit time in the right eye. Less prominent ERG changes were demonstrated in the left eye. The findings in this patient did not give any suspicion of hereditary retinal dystrophies or cancer associated retinopathy/melanoma associated retinopathy due to asymmetrical affection.

Discussion/conclusion

Multiple sclerosis, an inflammatory demyelinating disease of CNS, can present with optic neuritis in 20% of patients. The neurosensory retina, a developmental outgrowth of the brain, is accessible to non-invasive imaging with OCT and fundus imaging. A longitudinal study of 107 MS patients followed with serial OCT and magnetic resonance imaging over two years demonstrated ganglion cell and inner plexiform layer atrophy that mirrored whole brain, particularly cortical gray matter atrophy [6]. Fundus autofluorescence detects accumulation of endogenous fluorophores like lipofuscin, melanin or melanolipofuscin at the level of retinal pigment epithelium/photoreceptor complex. In contrast, loss of retinal pigment epithelium or photoreceptor decrease fundus autofluorescence. In this patient hypoautofluorescence area on fundus imaging may suggest an advanced stage of disease with atrophy. The hyperautofluorescent dots may be areas containing more fluorophores or active microglia where retina is less compromised and not atrophic. Likewise, hyperautofluorescent area in close proximity of retinal vessels could represent affinity for vessels in MS. This patient's history of vision deterioration over many years and the asymmetrical fundus autofluorescence findings indicate less likely causes such as cancer associated retinopathy/melanoma associated retinopathy. The ERG findings did not reveal any hereditary retinal dystrophies.

Fundus autofluorescence imaging may detect early stages of MS or progression of MS. Further studies may be warranted to identify and validate image findings and to describe fundus autofluorescence changes in MS at different disease stages. Studies in the future may identify the cellular source responsible for fundus autofluorescence abnormalities in MS patients. Fundus imaging, including fundus autofluorescence, is a widely available and probably cost-effective clinical tool that may be used for diagnosis and follow up of neurodegenerative diseases in the future. But this warrants further studies.

Conflicts of interest: The authors declare that there is no conflict of interest regarding the publication of this case report.

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