Austin Journal of Multiple Sclerosis & Neuroimmunology

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Austin Publishing Group

Editorial

Optical Coherence Tomography (OCT) in Multiple Sclerosis: a Good Marker for Neurodegeneration? Not yet

Finkelsztejn A*
Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Brazil

***Corresponding author:** Alessandro Finkelsztejn, Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Rua Mostardeiro 05 sala 1002, Porto Alegre, 90430-001, Brazil, Tel: +55-51-91228605/+55-51-33148590; Email: Alessandro.finkels@gmail.com

Received: January 11, 2015; **Accepted:** January 28, 2015; **Published:** January 30, 2015

Editorial

Several papers have recently highlighted the role and the importance of optical coherence tomography (OCT) in understanding the natural history of multiple sclerosis (MS). Equipment using the "spectral domain" technique allows higher image resolution and better measurement reproducibility, thus decreasing the intrinsic variations of the method and increasing the data reliability when dealing with small variations in retina thickness, as seen in MS [1].

Over the course of recent history and up to the present day, there have been three rather distinct periods regarding knowledge of OCT and its relationship to MS: 1) initial studies in the beginning of the 2000s aimed at understanding the relationship between the thickness of the retinal fiber nerve layer (RFNL) and the visual prognosis in cases of optic neuritis; 2) later on, at the end of the 2000s, studies concentrated on searching for a correlation between the thickness of the RFNL of eyes without optic neuritis and the severity of MS, especially with regard to reduction of the cerebral volume; 3) and finally, from 2011 onwards, studies aimed to understand the relationship between other retinal layers and neurodegeneration in MS. These most recent studies started after the development of new software that enables "segmentation" of the retina, such that the thicknesses of other layers like the ganglion cell layer can be measured.

Several important studies following this historical trend have been published, always trying to answer a given clinical question.

The initial studies using OCT were carried out on patients with MS who had optic neuritis, in an attempt to understand the physiopathology of optic disc inflammation. Costello et al. [2] observed an important correlation between the thickness of the RFNL and the prognosis of optic neuritis.

In 2008, Siger et al. showed that there was a significant correlation between thinning of the RFNL and reduction of brain volume in patients with MS [3].

In 2009, Costello et al. attempted to ascertain whether measurements of the thickness of the RFNL could complement the present methods for determining MS subtypes. They designed a study with 81 patients: 35 patients with optic neuritis as a clinically isolated syndrome (CIS), 39 patients with relapsing-remitting MS and seven patients with secondary progressive MS. Over a two-year follow-up period, no differences were found between measurements that were repeated in the same individual. However, the mean values of RFNL for each group were significantly different: 83.4 micrometers in patients with secondary progressive MS, 101.2 micrometers in patients with CIS and 103.7 micrometers in patients with relapsing-remitting MS. They concluded that patients with secondary progressive MS had lower mean values for the thickness of the RFNL than patients with other MS subtypes [4].

In 2010, Garcia-Martin et al. showed results differing from those of Costello in 2009, in which 25 patients with MS but without optical neuritis were followed for two years. Over this period of time, in which each patient was his own control, there was a decrease in the thickness of the RNFL. It was concluded that there had been neuronal loss even in the absence of optic neuritis [5].

In 2010, Talman et al. published a study with the aim of answering the question "how do changes in RFNL in MS correlate with loss of vision over time?" This study followed 299 patients for 18 months and showed a good correlation between reduction in thickness of the RFNL and reduction of visual acuity [6].

In 2011, Serbecic et al. conducted a study to answer the following question: "can OCT be a marker of neuronal degeneration?" They studied 37 patients with relapsing-remitting MS and 10 with secondary progressive MS. Each patient was his own control and was followed for two years. Their results showed that there were no significant differences in the thickness of the RFNL after two years of follow-up [7].

In 2011, Saidha et al. compared the thickness of the ganglion cells and the inner plexiform layer (GCiP) with RFNL in an attempt to ascertain which of them showed better correlation with MS subtypes, visual function and EDSS score. This study included 132 individuals with MS and 78 control subjects. The results showed that GCiP was thinner in all forms of MS than in controls. Regarding the MS subtypes, GCiP was thinner in secondary progressive than in relapsing-remitting MS. Therefore, it was concluded that GCiP correlated with EDSS and visual function better than did RFNL [8].

In 2012, Herrero et al. published the results from a three-year longitudinal study on 94 individuals with MS and 50 control subjects. Their aim was to identify whether, beyond the difference in RFNL thickness, there might be a difference if the patient with MS was not undergoing treatment. They concluded that there was a very small, but significant difference in the annual reduction in mean thickness of the RFNL between individuals with MS and controls. They also demonstrated that there was a significant difference between patients who were treated and those who were not treated, such that the RFNL was thinner among those who were not receiving treatment [9].

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In 2013, Oberwahrenbrock et al. published a study carried out with the objective of determining the stage of MS in which neurodegeneration starts, using OCT as the assessment method. The study included 45 patients with MS and 45 control subjects, and the most important result from it was the observation that the reduction in GCiP thickness was similar between patients with and without a previous history of optic neuritis [10].

In 2013, Saidha et al. published the results from a cross-sectional study that aimed to confirming the relationship between the thicknesses of the RFNL and other retinal layers and neurodegeneration in MS using a new approach: 3-tesla magnetic resonance imaging. They concluded that there was a well-defined relationship between the thicknesses of the retinal layers, the total brain volume and the volume of brain structures in MS [11].

In 2014, Narayanan et al. published the results from a longitudinal study on 131 patients with MS, some with previous optic neuritis and some with no episodes of neuritis. The objective of the study was to assess the rate of thickness reduction per year, comparing the RFNL with the GCiP. They concluded that the GCiP layer was abnormal in a larger number of individuals than was the RFNL, and defined the mean rate of thickness reduction of the RFNL as 1.49 μm, versus 1.27 μm for the GCiP [12].

Despite the various studies cited above, there are still many unanswered questions. Among these are the following: 1) Which layer of the retina correlates best with neurodegeneration in MS? 2) What are the rates of thickness reduction in the various subtypes of MS? 3) What is the rate of thickness reduction in the RNFL in relation to the other layers in individuals with CIS, treated MS and untreated MS? 4) Can the mean thickness or the rate of thickness reduction in any layer of the retina identify patients with primary progressive MS, relapsing-remitting MS or secondary progressive MS? 5) Is there any difference in the mean thickness or in the rate of thickness reduction in any layer of the retina, among the various treatments for MS? and 6) Can OCT be a prognostic marker for MS?

After analyzing the published studies on OCT for MS, it is clear that there are technical and methodological needs for improvement, in order to establish OCT as a monitoring method for patients with MS. Among these needs are: 1) greater knowledge of the physiological and circadian variations of retinal layers, initially showed by Balk et al. in 2013 [13]; 2) greater knowledge of the physiological and circadian variations of brain volume; 3) establishment of normal values for the different retinal layers in normal subjects in different countries, to take into account the ethnic diversity of populations; 4) wider usage of criteria defined by the OSCAR-IB Consensus [14] and its recent validation [15], with the aim of standardizing the techniques and methods for retinal OCT; 5) definition of standard radiological criteria for assessment of demyelinating lesions and brain volume; and 6) more long-term cohort studies among patients with MS and also among individuals with the so-called clinically isolated syndrome (CIS), which corresponds to the first bout of MS but still lacks all the diagnostic criteria.

Based upon what has been presented in this editorial, the following are recommended: further studies on the physiological and circadian variations of retina layers and brain volume; studies for establishing standard values for retinal layer thickness in normal individuals in different countries; and further long-term studies (2 to 10 years), also including subjects with CIS. An important collaborative study group on OCT in MS was recently formed in order to publish the paper on the OSCAR-IB criteria validation, including North American and European researchers. We suggest that researchers from other regions should also be included in such taskforces, for example those from Latin America, in order to increase the territorial and ethnic coverage of forthcoming studies. To reinforce this idea, a recent elegant paper from Kimbrough et al. showed that the thickness of the RFNL in Afro-American descendants was less than in Caucasians in the USA [16]. Through these approaches, OCT will find its place as an important diagnostic and prognostic tool for MS.

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