



The Effect of Multiple Sclerosis on Nerve Fiber Layer of the Retina

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسببائك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٢٢

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List of Abbreviations

Abb.	Full term
BCVA	Best Corrected Visual Acuity
BL	Bacillary Layer
C/D.....	Cup/Disc
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CRA	Central Retinal Artery
CRV.....	Central Retinal Vein
DIS.....	Dissemination in space
DIT.....	Dissemination in time
DM	Diabetes Milletus
DMT.....	Disease Modifying Therapy
EBV.....	Epstein-Barr Virus
ELM.....	External Limiting Membrane
FD	Fourier Domain
GCIP	Ganglion cell / inner plexiform layer
GCL	Ganglion Cell Layer
HPV	Human Papilloma Virus
IBS.....	Irritable Bowel Syndrome
ILM	Internal Limiting Membrane
INL	Inner Nuclear Layer
IPL	Inner Plexiform Layer
IS	Photoreceptor Inner Segment
IS/OS	Interface between IS and OS
LogMAR.....	Logarithm of Minimum Angle of Resolution
MS.....	Multiple Sclerosis
NFL.....	Nerve Fiber Layer
OCT	Optical Coherence Tomography
ON.....	Optic Neuritis

List of Abbreviations Cont...

Abb.	Full term
<i>ONH</i>	<i>Optic Nerve Head</i>
<i>ONL</i>	<i>Outer Nuclear Layer</i>
<i>OPL</i>	<i>Outer Plexiform Layer</i>
<i>OPR</i>	<i>Outer photoreceptor / RPE complex</i>
<i>OR</i>	<i>Ora Serrata</i>
<i>OS</i>	<i>Photoreceptor Outer segment</i>
<i>PMB</i>	<i>Papillo-Macular Bundle</i>
<i>PPMS</i>	<i>Primary progressive MS</i>
<i>RNFL</i>	<i>Retinal Nerve Fiber Layer</i>
<i>RPE</i>	<i>Retinal Pigment Epithelium</i>
<i>RRMS</i>	<i>Relapsing-remitting Multiple Sclerosis</i>
<i>SD</i>	<i>Spectral Domain</i>
<i>SPMS</i>	<i>Secondary progressive MS</i>
<i>TD</i>	<i>Time Domain</i>
<i>UBM</i>	<i>Ultrasound BioMicroscopy</i>
<i>UCVA</i>	<i>UnCorrected Visual Acuity</i>
<i>VA</i>	<i>Visual Acuity</i>

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INTRODUCTION

Axonal loss is considered to be the predominant cause of enduring disability in multiple sclerosis (MS). This is particularly so in the progressive forms of the disease. Pathologically, axonal loss has been demonstrated within both inflammatory lesions and normal appearing white matter in brain and spinal cord (*Trapp et al., 1998*).

The retinal nerve fiber layer (RNFL) is composed predominantly of unmyelinated axons of retinal ganglion cells. Measurement of the RNFL should, therefore, give relatively direct measures of the number of axons present without the confounding variable of tissue loss due to demyelination (*Lovas et al., 2000*).

Axonal loss has been recognized in the RNFL in MS by appearance of abnormalities on fundoscopy. In many detailed studies, by using indirect ophthalmoscopy and fundus photography, RNFL defects were visible in symptomatic MS eyes. In asymptomatic MS eyes, RNFL defects were also clearly seen (*Elbol and Work, 1990*).

Optical Coherence Tomography (OCT) is a non-invasive technique that allows the quantitative cross-sectional imaging of the RNFL. Its use has been predominantly to investigate retinal axonal loss in glaucoma (*Zaveri et al., 2008*), but demonstrated a significant reduction in the mean RNFL thickness in the eyes of MS patients that were clinically Unaffected by optic neuritis (ON).

AIM OF THE WORK

The purpose of this work is to study the effect of Multiple Sclerosis, with and without optic neuritis, on the thickness of retinal nerve fiber layer using Optical Coherence Tomography (OCT) and correlate this relation to visual function.

Chapter 1

STRUCTURE AND FUNCTION OF THE RETINA

Anatomy

Precise anatomical knowledge of the retina is a prerequisite to understand retinal changes in MS. Retina comes from Latin word *rēte* meaning Net. It is the third innermost delicate coat of the eye which is light sensitive (figure 1). In adults, the entire retina is approximately 72% of a sphere about 22mm in diameter. In section the retina is no more than 0.5mm thick (*Provis et al., 2005*).

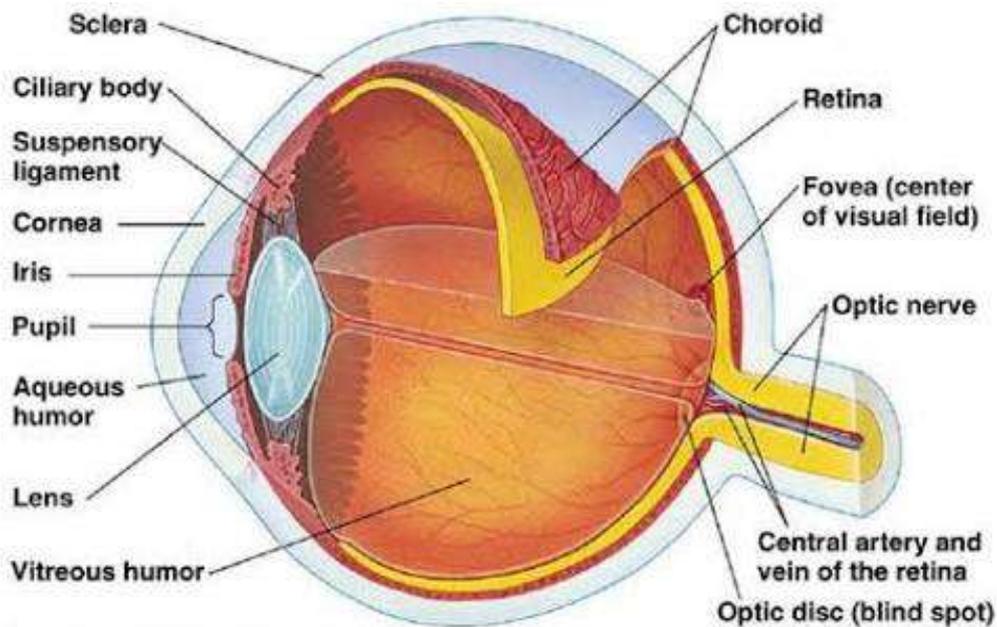


Figure (1): Anatomy of human eye (*Masland, 2001*).

The retina is a layered structure consisting of RPE (retinal pigment epithelium) and the neural retina which contains specific arrangement of neurons interconnected by synapses. The only neurons that are directly sensitive to light are photoreceptor cells of RPE (*Oyster and Nancy, 1999*).

Grossly, the retina is divided into two parts (figure 2)

- *Central retina*: (foveola, fovea, parafovea and macula)

Rich in cones, has more ganglion cells per area than elsewhere and is a relatively small portion of the entire retina

- *Peripheral retina*: (near periphery, mid periphery, far periphery and ora serrata)

Represent most of the retina and is rods dominate (*Fitzgibbon and Taylor, 1990*).

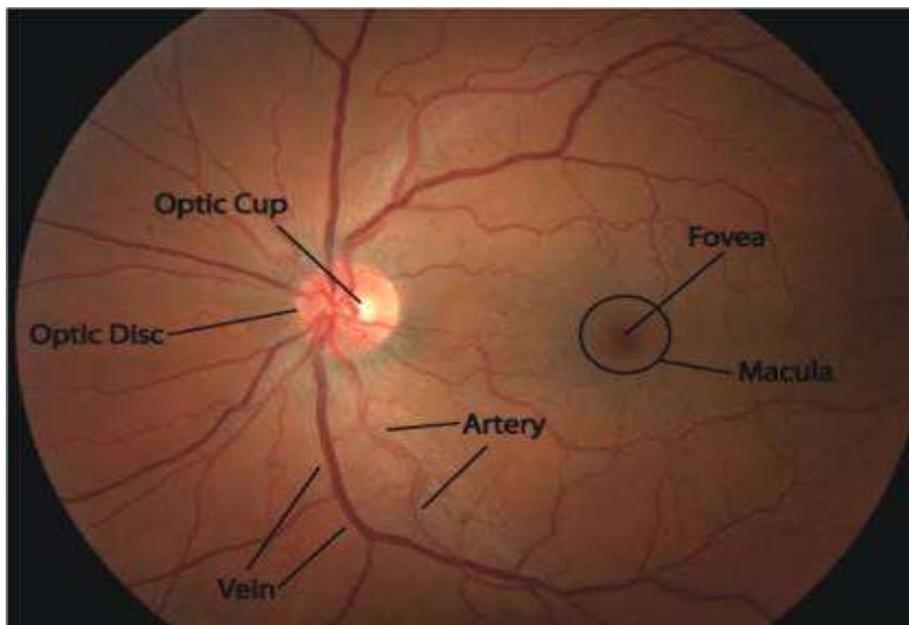


Figure (2): Normal human retina through ophthalmoscope (normal fundus) (*Wang et al., 2016*).

The retina is firmly attached to the underlying RPE at margins of the optic disc and ora serrata.

Thickness of the retina:

Healthy retina is about $280\mu\text{m}$ thick but thickness differs according to site:

- Optic disc → $560\mu\text{m}$
- Around the macula → $350\text{-}400\mu\text{m}$
- Equator → $180\mu\text{m}$
- Ora serrata → $80\text{-}100\mu\text{m}$
- Fovea → $100\text{-}150\mu\text{m}$ (*Provis et al., 2005*).

Microscopic structure of the retina

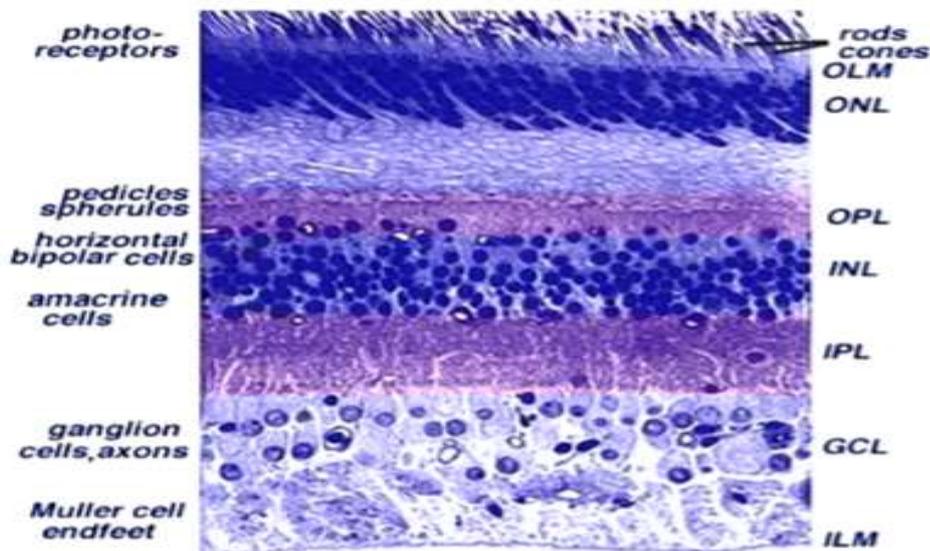


Figure (3): Light micrograph of a vertical section through the human retina (*Sharma & Johnson, 2000*).

The retina has ten distinct layers. From closest to farthest from the vitreous body (*Robert et al., 2007*), that is, from closest to front exterior of the head towards the interior and back of the head:

1. ***Inner limiting membrane (ILM)***: basement membrane elaborated by Muller cells. It represents the boundary between the retina and vitreous body.
2. ***Nerve fiber layer (NFL)***: axons of the ganglion cell nuclei (note that a thin layer of Muller cell footplates exists between this layer and the ILM)
3. ***Ganglion cell layer (GCL)***: contains nuclei of ganglion cells, the axons of which become the optic nerve fibers, and some displaced amacrine cells.
4. ***Inner plexiform layer (IPL)***: contain synapse between the bipolar cell axons and the dendrites of ganglion cells and amacrine cells. It contains nuclei of horizontal, bipolar and amacrine cells.
5. ***Inner nuclear layer (INL)***: contains nuclei and surrounding cell bodies (perikarya) of the amacrine cells, bipolar cells and horizontal cells. (*Bringmann et al. 2006*)
6. ***Outer plexiform layer (OPL)***: projections of rods and cones ending in the rod spherule and cone pedicle, respectively. These make synapses with dendrites of bipolar cells. *In the macular region, this is known as the Fiber layer of Henle.*
7. ***Outer nuclear layer (ONL)***: cell bodies of rods and cones.