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Clinical Findings and Management of Acute Optic Neuritis as the Initial Manifestation of Multiple Sclerosis

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Abstract:

Multiple sclerosis (MS) is the most common cause of neurological disability among young adults. In some individuals, MS first manifests as an acute attack on the optic nerve. This case report follows the initial clinical diagnosis of optic neuritis suspicious of a clinically isolated syndrome (CIS), followed by final diagnosis of multiple sclerosis via neural imaging studies. This case highlights the importance of understanding the disease process, manifestations, prognosis, and treatment options of MS as an eye care provider.

Keywords:

Optic Neuritis, Multiple Sclerosis, MRI, IV Methylprednisolone, Disease Modifying Drugs, Gilenya, Tecfidera, Fingolimod, Dimethyl Fumarate

Introduction

Optic neuritis is an acute inflammatory demyelinating condition that is marked by a sudden, painful, loss of vision.[1] In North America, the prevalence is approximately 115/100,000 with 1 to 6.4 new cases per 100,000 population being reported each year.[1,2] The most common cause of optic neuritis is multiple sclerosis (MS). Other etiologies for optic neuritis include neuromyelitis optica (NMO), idiopathic inflammatory demyelination, and infectious etiologies such as Lyme disease and neurosyphilis.[3] Optic neuritis is the initial manifestation of MS in 20% of patients with multiple sclerosis.[4] In those cases, the patient not only suffers from frightening symptoms, but must also bear the news of having a chronic, debilitating disease.

Case Report

A 21-year-old female of Mediterranean descent presented to sick call at the family health clinic at 7:45AM on August 25, 2016 with complaints of headaches for 6 days, and a 4 out of 10, constant, sharp pain mostly in the right eye with movement. Her history was negative for any inciting events. Neurological work-up including cranial nerve (CN) testing of nerve numbers 2-12 was normal, Romberg's test was negative, strength and mobility of upper and lower extremities were balanced on both sides without any restrictions. The family health doctor found a superonasal defect in the right eye (OD) approximately 5-degrees from fixation on Amsler grid (**Appendix A**) around 8:10AM, and brought her to optometry for further evaluation.

The patient presented to the optometry clinic complaining of a dark film in her vision since the day prior around 4:30PM. Initially, she suspected she had gotten something in her right eye, but she was unable to spot anything in the mirror. The patient denied flashes and floaters. She reported the area of darkness in her vision had not gotten bigger, but had gotten darker. She also reported light sensitivity and a constant, sharp pain at a level of 4 out of 10 in her right eye, worsening when she looked up and to the right. The patient also reported a dull headache since Friday afternoon, 6 days prior to the visit. She confirmed a history of migraine headaches. She had taken Aspirin, Motrin, and Tylenol, none of which helped to lessen the headache. The patient denied trauma and prior history of similar occurrence.

The patient denied personal and familial eye history of blindness, glaucoma, and macular degeneration. The patient's personal medical history was unremarkable. However, her father had hypertension, and both maternal grandparents had diabetes. The patient was taking Alyacen 1/35 birth control in addition to the over the counter pain medications.

The patient did not wear glasses, and had never had a complete eye exam. Her entering visual acuity (VA) was 20/20 right eye and 20/15-1 left eye (OS), uncorrected. Autorefraction revealed a minimal refractive error of OD: plano-0.25x178 and OS: plano-0.50x174. Her intraocular pressure (IOP) measured 16mmHg OD and 15mmHg OS at 08:21AM with a non-contact tonometer (NCT). Extraocular motilities (EOMs) were restricted in up-gazes due to pain in the right eye. Pupillary testing revealed a 3+ afferent pupillary defect (APD) of immediate redilation in the right eye. A red desaturation test, however, was normal. The patient reported the red medicine bottle cap appeared the same to each eye. Color vision testing with the HRR pseudoisochromatic plate test #4 (HRR#4) was normal with 6/6 correct in the right eye and the left eye. No abnormalities in the red-green or blue-yellow color screening. A brightness comparison test did, however, confirm a dimmer perception of the binocular indirect ophthalmoscope (BIO) light in the right eye compared to the left.

Anterior segment evaluation was normal for both eyes (OU) without conjunctival hyperemia or evidence of cells or flare in the anterior chamber in either eye. An undilated view of the posterior pole with the 90 diopter (D) lens revealed small nerves with mild elevation in both eyes. The cup-to-disk ratio (C/D) was estimated to be 0.10x0.10, round for the right eye, and 0.15x0.15, round for the left eye. Both nerves appeared pink, with no edema, hemorrhage, obscuration of vessels, or pallor. The nerves were assessed to be normal in appearance for both eyes.

Differential diagnoses considered at this point include:

Optic Neuritis
Neuromyelitis Optica
Idiopathic Intracranial Hypertension
Optic Nerve Head Drusen
Migraine with Aura
Transient Ischemic Attack
Anterior Ischemic Optic Neuropathy
Branch Retinal Artery Occlusion
Retinal Detachment

- Optic Neuritis (ON) is an inflammatory demyelination of the optic nerve. If disc edema is present, it called papillitis; if the inflammation is behind the lamina cribrosa, it is called retrobulbar optic neuritis.[4] The patient presents with sudden, painful, unilateral vision loss. Typical demographic is young, white, female. The optic disc may appear normal for up to 4 weeks from the initial attack. Multiple sclerosis is the most common cause, while Lyme and syphilis are common infectious causes. Eye pain is present in 63% of cases.[3] Visual field defect is generally a large, central-type visual field loss in the affected eye at the initial presentation, and 75% of the fellow eye also showed some visual field abnormalities.[5]
- Neuromyelitis Optica, also known as Devic’s syndrome, is a demyelinating condition affecting the optic nerves and spinal cord. Clinical attacks are often severe resulting in residual visual and neurologic deficits. NMO generally affects females in their late 30’s, presenting with bilateral optic neuritis. The diagnostic criteria for NMO include optic neuritis with myelitis, followed by at least 2 of the following conditions: Spinal cord MRI with longitudinally extensive lesion in 3 or more segments, early brain MRI not fulfilling criteria for MS, and/or positive NMO-IgG antibody.[1,2]
- Idiopathic Intracranial Hypertension (IIH), is a condition of elevated intracranial pressure in the absence of anatomical abnormalities or abnormalities in cerebrospinal fluid composition. The patient typically complains of headaches, transient visual obscurations, tinnitus, and less frequently, diplopia, dizziness, and nausea. The patient is typically female, between 20-45 years of age, and has a history of obesity. Bilateral disc edema, enlarged blind spot, and/or inferior-nasal steps on visual fields are common signs.[4]
- Optic Nerve Head Drusen involves retention of hyaline bodies in the optic nerve anterior to the lamina cribrosa. The nerves may appear elevated with irregular margins and minimal

cupping. Refractile bodies may be visible with red-free light. Patients are usually asymptomatic, but report recurrent, transient visual obscurations.[3] Visual field defects, if present, are typically enlarged blindspot (60%), arcuate defects, or irregular peripheral contractions.[3]

- Migraine with Aura, as defined by International Headache Society (IHS), is a primary headache disorder characterized by a reversible visual, sensory, and/or speech symptoms for an hour followed by a headache. Complicated migraines have been reported to include attacks lasting greater than 72 hours or auras persisting for more than 1 week.[6]
- Transient Ischemic Attack (TIA) typically affects older patients at risk for stroke. Symptoms include numbness, visual loss, paralysis, and ataxia. Typical duration is less than one hour and recurrent spells can occur over days, weeks or months. Headaches typically present at the time of the TIA.[7]
- Anterior Ischemic Optic Neuropathy (AION) is a stroke of the optic nerve head. It presents as a sudden, painless, monocular vision loss. It can be caused by temporal arteritis, arteriosclerotic ischemic optic neuropathy, embolism, or cataract surgery. Patients generally present with optic nerve head edema, peripapillary hemorrhage, and optic nerve pallor. The retinal arteries may appear attenuated. Visual field loss is typically inferior altitudinal defect or arcuate scotoma. Visual acuity can be worse than 20/100.[3]
- Branch retinal artery occlusion presents as a superficial, edematous, whitening of an area of the retina supplied by an occluded branch of retinal artery. The occlusion is usually caused by an emboli. Although the retinal artery may appear normalized and the retinal edema resolved, permanent visual field defects persist in the area as evidence of the retinal infarction.[3]
- Retinal Detachment is the separation of sensory retina and the RPE caused by fluids that have extravasated into the subretinal space. The retina will appear gray and opaque, and if the fluid collection is significant, the retina may appear to billow with numerous folds. The loss of central vision is reported if the macula is involved.[3,8]

In the absence of retinal abnormalities on undilated fundus examination, retinal detachment and branch retinal artery occlusion were ruled out. Based on the optic nerve appearances, the absence of disc edema, peripapillary hemorrhage, and optic nerve pallor ruled out the differential diagnoses of anterior ischemic optic neuropathy, idiopathic intracranial hypertension, and optic nerve head drusen. Based on the history of the events, migraine with headache and transient ischemic attacks were ruled out. In a classic textbook presentation of a young, white female complaining of sudden, painful, monocular vision loss, optic neuritis was suspected.

The patient was assessed on the Zeiss Humphrey Field Analyzer Model 750i, and completed a Central 30-2 SITA-Fast Threshold Test (HVF 30-2) for each eye. The patient completed the field for the right eye in 5 minutes and 40 seconds with the fixation monitor turned off, a false positive error rate (FP) of 3%, a false negative error rate (FN) of 11%, mean deviation (MD) of -10.01 decibels, and pattern standard deviation (PSD) of 16.48 decibels. Glaucoma hemifield test (GHT) was outside the normal limits. The right eye revealed a dense superior altitudinal defect that was spreading into the inferonasal quadrant (**Appendix B)**. The patient completed the field for the left eye in 3 minutes and 27 seconds with the fixation monitor turned off, a false positive error rate of 5%, a false negative error rate of 5%, mean deviation of -2.75 decibels, and pattern standard deviation of 2.06 decibels. Glaucoma Hemifield Test was borderline. The left eye revealed a mild superotemporal depression of around 4-8 decibels (**Appendix C**).

The visual field test was completed at 09:10AM, and showed a significant progression compared to the Amsler grid findings from an hour earlier. The patient was diagnosed with acute optic neuritis OD, suspicious of a clinically isolated syndrome (CIS). The patient was educated on the findings. The patient was reassured that vision should recover promptly with treatment. Based on the guidelines from the Optic Neuritis Treatment Trials (ONTT), 250mg of methylprednisolone intravenously (IV) four times a day for 3 days, followed by 60mg of oral prednisone each day for 11 days and a 4-day taper were indicated. The patient was educated that there is a 50% chance of developing multiple sclerosis in 15 years of an optic neuritis attack,[9] and that a prompt magnetic resonance imaging (MRI) was recommended to rule out possible multiple sclerosis and neuromyelitis optica. The family health clinic was enlisted to help coordinate the treatment and the ordering of the MRI scans.

Immediate Follow-up

The patient was sent to the local hospital for a same day MRI scan. The family care doctor initially ordered oral Prednisone, 50mg by mouth daily for 5 days with 5-day taper based on recommendation by a local civilian neurologist. However, upon being presented the findings of the Optic Neuritis Treatment Trials[10] study recommending against oral steroids due to a doubled rate of recurrence of optic neuritis in oral steroid group compared to IV steroid and placebo groups, he consulted with another neurologist at another Air Force Base for a second opinion. The second neurologist recommended a minimum of 3 days of 1g Solu-Medrol intravenously, followed by taper. Thus, the original oral steroid prescription was cancelled. However, the local hospital could not treat the patient with IV steroid due to a lack of neurology support. After extended coordination, the patient was arranged to present to the emergency department at Vidant Medical Center for treatment.

The patient was admitted to Vidant Medical Center on August 25, 2016 at 9:07PM, and started on 1g of IV Solu-Medrol. Lumbar puncture was performed on Aug 26, 2016. On Aug 27, 2016, the patient was discharged after completing 3 days of IV Solu-Medrol with a 6 day taper of 60mg of oral prednisone.

Test Results

The MRI of the brain with and without Gadolinium was performed on Aug 25, 2016 at 1:29PM to include sagittal T1-weighted, axial T1-weighted, T2-weighted, FLAIR, diffusion, and postgadolinium-T1-weighted sagittal, axial and coronal images. The radiologist noted numerous, bilateral cerebral, cerebellar, and brainstem hyperintense T2-weighted foci, several of which enhanced with Gadolinium, and few lesions arranged in typical Dawson's finger appearance. There were no mass effects or midline shifts. The findings were characteristic of multiple sclerosis or other demyelinating disease.

MRI of the orbits with and without Gadolinium was also performed on Aug 25, 2016 including coronal T1-weighted and fat-sat T2-weighted; axial T1-weighted and fat-sat T2-weighted;

postgadolinium, coronal, fat-sat T1-weighted; postgadolinium, axial, T1-weighted; and postgadolinium, axial, fat-sat T1-weighted images. The radiologist did not note any abnormal enhancements with the optic nerves, extraocular muscles, or other structures within either orbit.

Cerebral spinal fluid (CSF) was collected via lumbar puncture (LP) on Aug 26, 2016 at 5:41PM. Analysis of the CSF showed high levels of lymphocytes at 96% and low percentage of monocytes at 4%. VDRL was nonreactive, ruling out syphilis. The IgG to albumin ratio was 0.34 (reference range: 0.02-0.26) indicating an elevated CSF-IgG level, which is elevated in 60-75% of patients with definite MS. Greater than 5 oligoclonal bands, which indicate the abnormal synthesis of gammaglobulins in the central nervous system (CNS), were present in the CSF but not in the serum sample. Myelin Basic Protein (MBP) was <2.0 mcg/L, which was interpreted as negative.

Follow Up #1

The patient returned to clinic on August 30, 2016 for a previously scheduled repeat visual field test and OCT scans. However, the patient reported she was not feeling well enough due to neck pains to sit for the tests. She reported her vision felt improved. Visual acuity was measured at 20/15 for the right and left eye, uncorrected.

Follow Up #2

The patient presented to clinic on Sep 28, 2016 for HVF 30-2, optical coherence tomography (OCT) and vision test. She reported she had discontinued her oral steroid taper on Sep 2, 2016. She was seen by neurology and they did not diagnose any new problems. They ordered MRI for her cervical and thoracic spine, but she had not gotten the scans yet. They prescribed 4mg ondansetron (Zofran) for nausea and 20mg baclofen (Lioresal) for muscle spasm. She denied any eye pain and vision loss since she was discharged from the hospital. She had been having a headache since her lumbar puncture on August 26, but it had been improving and was less constant. She reported an increased incidence of memory loss. She recalled prior history of transient visual obscurations during exercise consistent with Uhthoff's phenomenon that she had previously attributed to possible low blood pressure or sugar. She had an appointment scheduled with her neurologist on October 5, 2016.

Her entering VA without correction was 20/20 OD and OS at this visit. Her IOP measured 14mmHg OD and 15mmHg OS at 14:39 with the NCT. Her pupils and EOMS were normal, with no APD, gaze restrictions, or pain, OU. Anterior and posterior segments were unremarkable OU, undilated. C/D of the optic nerves were 0.15x0.15, OU, without hemorrhages or edema.

The HVF 30-2 SITA-Fast for OD (**Appendix D**) showed remarkable recovery of the dense superior altitudinal defect at her initial presentation. There was still a relative nasal scotoma slightly denser superiorly compared to inferiorly. GHT was still outside of normal limits. The test was compromised by a high FP of 20%, so actual field results may be worse. The HVF 30-2 SITA-Fast for OS (**Appendix E**) was also marred by a high FP of 20%, a FN of 12%, and 3/13 fixation losses (FL). The left visual field showed a mild superotemporal defect, with a few points of sensitivity loss; however, GHT was within normal limits this time.

The OCT of the optic nerves (**Appendix F**) showed a mild nasal swelling in the extracted horizontal tomogram of right eye, otherwise, the retinal nerve fiber layer (RNFL) analysis for both eyes were unremarkable. The ganglion cell analysis (GCA) of the maculae (**Appendix G**) showed thinning in the nasal wedges, with borderline thinning in the inferior, superior, and superotemporal wedges in the right eye. The macular scan of the left eye was misaligned, and resulted in artifactual thinning in all 360 degrees.

Follow Up #3

The patient returned to clinic on Oct 6, 2016 for follow up. She denied any new episodes of eye pain, vision loss, or muscle weakness. She saw her neurologist the day before, and he told her she had more lesions in her spinal cord.

The MRI of her cervical and thoracic spine with and without contrast was done on Sep 29, 2016. The radiologist found focal T2-weighted hyperintensities within the lower pontine tegmentum and an irregular diffuse area of hyperintensity from C2 to C6 of spinal cord. The radiologist assessed these abnormal, multilevel, scattered, central and dorsal spinal cord hyperintensities as strongly supportive of the clinical diagnosis of multiple sclerosis.

The patient reported the neurologist wanted to start her on Gilenya, but she was waiting for approval from the Tricare insurance. Her neurologist ordered John Cunningham virus (JCV) antibody ELISA test, and the results came back positive.

The patient reported an increased level of stress due to her health and work. Her entering VA without correction was 20/15 OD and OS. Her IOP measured 15mmHg OD and 17mmHg OS at 13:35 with the NCT. Her pupils and EOMS were normal, with no APD, gaze restrictions, or pain, OU. Anterior and posterior segments were unremarkable OU, undilated. C/D of the optic nerves were 0.10x0.10, OU, without hemorrhages or edema.

The HVF 30-2 SITA-Fast for OD (**Appendix H**) was much more reliable with 2/12 FL, 0%FP, 5%FN. The field further improved upon the recovery shown at the last visit, one week ago, and GHT is now within normal limits. There were only a few scattered points of depressed sensitivity remaining in the superonasal quadrant. The left HVF 30-2 SITA-Fast (**Appendix I**), however, had 3/12FL, 0%FP, 8%FN, and had a mild decrease in sensitivity across the superior half of the field compared to the inferior, resulting in the GHT being flagged as outside normal limits. Overall, the sensitivity seemed stable to the previous field from the last week.

The OCT of the optic nerves (**Appendix J**) were relatively unremarkable OU. The previously suspicious elevation in the right nasal extracted horizontal tomogram had subsided in this scan. The ganglion cell analysis (GCA) of the right eye (**Appendix K**) showed thinning of ganglion cell and innerplexiform layers in the superonasal half, borderline thinning in the infratemporal half of the right macula, and relatively stability to the September 28 scan. The macular scan of the left macula revealed a borderline thinning in the superotemporal and the superior sectors, but overall a normal average and minimum thickness for that eye.

Follow Up #4

The patient presented to clinic on November 16, 2016 with complaints of new sustained headache and eye pain. She was concerned about a relapse. The patient reported she saw her neurologist last week, Nov 8, 2016, and started to keep a headache diary. Her neurologist had started her on Zoloft 25mg for migraine and situational anxiousness. Her neurologist also prescribed Gilenya 0.5mg daily pending evaluation by ophthalmology and cardiology for contraindications. The patient said she saw ophthalmology on Nov 10, and evaluation was normal without signs of any flare-up. She was still waiting for her cardiology and neurology appointments scheduled for next week.

The patient reported her headaches used to last 4-5 hours, but starting two days ago, on Monday, her headache persisted overnight. The pain would travel from her right upper forehead to the left forehead. She also reported a tightness and pain in her left eye when she looks down and to the left. She denied any fading of vision.

The patient entered with 20/15 VA, OD and OS, without correction. Her IOP measured 20mmHg in both eyes at 08:16 AM with the NCT. Pupils were normal with no APD OU. Color vision with HRR#4 was normal with 6/6 correct OD and OS. EOM revealed mild pain on lower left gaze OS only. Undilated anterior and posterior examinations were unremarkable OU. C/D ratio for both eyes were 0.15x0.15 without hemorrhage, edema, or pallor.

The HVF 30-2 SITA-Fast for OD (**Appendix L**) was completed with 2/12 FL, 2%FP, 5%FN. The field showed small cluster of superonasal depression, with trace signs of progression compared to Oct 6, 2016 field. GHT was assessed as outside normal limits. The HVF 30-2 SITA-Fast for OS (**Appendix M**) was completed with 0/13 FL, 3%FP, 1%FN. The field showed a superotemporal wedge defect, with clusters of depression in the superonasal quadrant as well. Slight progression from the Oct 6, 2016 field was evident.

The OCT of the optic nerves (**Appendix N**) remained relatively unremarkable OU. The ganglion cell analysis (GCA) of the right eye (**Appendix O**) showed thinning of ganglion cell and innerplexiform layers in the nasally, mild improvement of superior and superotemporal wedges, and stable elsewhere compared to Oct 10, 2016 scan. The macular scan of the left macula revealed a borderline thinning in the superotemporal wedge, but overall a normal average and minimum thickness for that eye, stable to prior scans. Fundus photos (**Appendix P**) were also taken for documentation.

A bilateral retrobulbar optic neuritis was suspected. The patient was advised to keep her appointment with neurology regarding treatment and management of multiple sclerosis and any relapses she may be experiencing. In light of her upcoming appointment on Monday, Nov 21, 2016 with her neurologist and the fact that there were no long term negative visual impacts from withholding treatment, no treatment was intiated at this visit. The patient was advised to follow up in a week for repeat of the field test and to return to clinic if symptoms worsen.

Discussion

Multiple Sclerosis (MS) is a chronic, inflammatory, progressive, demyelinating disease of the central nervous system (CNS). In 2013, an estimated 2.3 million people worldwide had MS, making it a leading cause of neurological disability among young people.[11,12] The exact cause of MS is still under debate; however, many risk factors have been identified to be associated with the development of the disease. Autoimmune factors such as having higher than normal autoreactive T and B cells that target myelin basic proteins (MBP) have been found in MS patients. Genetic factors such as having a monozygotic twin with MS or having different human leukocyte antigens (HLA) have been shown to be either protective against or detrimental towards MS. A history of microbial infection such as the Epstein - Barr virus (EBV) that causes mononucleosis has been found in >99% of MS patients compared to 90-95% of the general population. A low level of vitamin D has been shown in different studies to be associated with increased risk for MS; and inversely, high serum levels of vitamin D was associated with a lower risk for MS. Smoking has also been associated with an increase in risk for MS. Being female of childbearing age has been shown to have a twice or three times the rate of developing relapsing-remitting form of MS compared to males. Environmental factors have been implicated in the fact that certain regions of the world have a higher number of MS cases, such as North America and parts of Europe. Furthermore, migration data have shown that childhood spent living in a region where MS is more prevalent results in a higher risk for developing MS.[11] Although the exact etiology is still unclear, the pathophysiology is slightly better understood.

The signs and symptoms of multiple sclerosis are caused by the demyelination and in some cases, the loss of axons in the central nervous system. In normal physiology, the lipid-rich plasma membranes of oligodendrocytes form insulating sheaths, called myelin, around the axons of the neurons in the CNS. The myelination of the axons allows for rapid propagation of nerve impulses in a saltatory fashion. When the myelin or the oligodendrocytes are damaged, conduction of nerve impulses is either reduced to 5 or 10% of normal speeds or inhibited altogether. This damaged signal conduction manifests in a wide variety of clinical symptoms including: optic neuritis, nystagmus, internuclear ophthalmoplegia (INO), vertigo, numbness and tingling, paraparesis and spasticity, intention tremor, gait imbalance, incontinence, constipation, fatigue, memory loss, and other cognitive, motor, and sensory impairments.[11]

The diagnosis of multiple sclerosis has evolved with the availability of new imaging technologies. Previously, diagnosis has been largely a clinical one based on an idiopathic syndrome consistent with inflammatory demyelination of the optic nerve, brain, and spinal cord.[1]A diagnosis of clinically probable MS was given if there was a new neurological symptom plus clinical evidence of a lesion consistent with the symptoms. A clinically definite MS was diagnosed if there were 2 attacks with evidence of 2 separate lesions.[13] New guidelines have since emerged, such as the McDonald's Criteria 2010 and the magnetic resonance imaging in multiple sclerosis (MAGNIMS) 2015, resulting in earlier diagnosis at a higher sensitivity and specificity.[14] MAGNIMS published the updated diagnostic criteria in 2015 to determine disease dissemination in space (DIS) and dissemination in time (DIT).

DIS is established if involvement is detected in 2 or more of the following areas of the CNS:[15]

- periventricular: ≥3 lesions

- cortical-juxtacortical: ≥1 lesions
- infratentorial: ≥1 lesions
- spinal cord: ≥1 lesions
- optic nerve: ≥1 lesions

DIT is confirmed by either a new T2 hyperintense lesion not present on a previous scan regardless of time between the scans, or the presence of an enhancing and a non-enhancing T2 lesion in a single scan.[15]

The lesions typical of MS are either active or inactive plaques consisting of demyelinated axons. Active plaques appear whitish-yellow or pink with indistinct borders on gross examination, and are filled with T cells, macrophages, and plasma cells in histology studies. Older plaques appear translucent with a greyish-blue hue, and have sharply demarcated margins on gross examination.[11] On MRI, these acute lesions appear with less defined margins. A Gadolinium contrast enhancement of these lesions on T1-weighted scans indicate the inflammation and disruption of the blood-brain barrier (BBB). Chronic lesions, highlighted by T2 or FLAIR sequences, are usually smaller with more distinct borders.[11] On T1 scans, hypointensive lesions, "black holes," are an indicated of irreversible axonal loss or demyelination.[11]

The patient initially presented to clinic with an acute optic neuritis of the right eye, which could have been an isolated, idiopathic event, a manifestation of Devic's disease, or in this case, a manifestation of multiple sclerosis. The prevalence of optic neuritis in North America is approximately 115/100,000, and the incidence has been reported between 1/100,000 and 6.4/100,000 per year.[1] According to the ONTT, 46.9% of patients with acute optic neuritis had an abornmal MRI at presentation, and 26.7% of patients had two or more cerebral white matter lesions.[16] Those who presented with 3 or more lesions at the time of the optic neuritis attack had a 78% chance of developing MS by 15 years.[17]

In this case, the patient's radiology report confirmed both dissemination in space and dissemination in time of multiple sclerosis. There were multiple bilateral cerebral, cerebellar, and brainstem T2-hyperintense foci as well as several lesions that enhanced postgadolinium. A subsequent MRI of her cervical and thoracic spine also found focal T2-weighted hyperintensities within the lower pontine tegmentum and an irregular diffuse area of hyperintensity from C2 to C6 of spinal cord. Such findings of spinal cord lesions are common in over 90% of MS patients.[11] Interestingly, the MRI of the orbit in this case did not reveal any enhancements of the optic nerve. A study by Kupersmith et al found that only 5.6% of acute optic neuritis did not show any abnormal enhancements of the nerve on an MRI performed within 20 days of the visual loss.[18] Although less predictive of MS, the patient also presented with oligoclonal bands in her CSF, which has been associated with 67.5% of clinically defined multiple sclerosis.[19]

There are four subcategories of MS, based on the course of the disease. Relapsing-Remitting MS (RRMS) is the most common, affecting up to 85% of all MS cases. It is characterized by episodic flare-ups (relapses) followed by periods of stability (remissions). Many RRMS sufferers go on to develop a second form of MS known as secondary-progressive MS (SPMS), where initial relapses and remissions are replaced by progressive worsening of conditions with minor relapses, remission, and plateaus. A small percentage, 8%-10%, are affected by a primary progressive form of MS (PPMS). These patients experience a gradual, but continuous decline in neurologic function from the onset. The rarest form of MS, progressive-relapsing MS (PRMS), affects less than 5% of the patients is continuous progression of the disease with clear acute relapses interspersed.[12,11,20]

Treatment and management of MS is motivated by the following goals:[11]

1. To shorten acute relapses and limit their sequelae
2. To reduce the frequency of relapses and the accumulation of disability
3. To provide relief or modification of symptoms
4. To alleviate social and economic effects for the patient and their family

High-dose corticosteroids are the most effective for treatment and management of acute relapses of MS. ONTT recommends 1000mg daily of IV methylprednisolone for 3 to 5 days, with or without a short prednisone taper.[11] For the remaining disease management goals, there are currently 13 disease modifying drugs (DMDs) approved by the United State Food and Drug Administration (FDA).[12]

The first DMDs approved were the interferon β drugs. Interferon β modifies the production of cytokines by the immune cells in favor of a more anti-inflammatory subset, and inhibits the production of proinflammatory cytokines. These DMDs are administered either subcutaneously or intramuscularly via injections on a set schedule. They have been shown to reduce the average number of relapses each year (ARR) by 50% to 80%. Adverse effects of interferon β include flu-like symptoms, depression, thyroid dysfunction, liver enzyme abnormalities, leukopenia, and injection-site reactions. These drugs are all in pregnancy-category C. The currently approved interferon β drugs include: Avonex, Plegridy, Rebif, Betasron, and Extavia.[12]

Glatiramer acetate is another class of DMDs indicated for MS. It is a synthetic peptide that is believed to promote the development of Th2-polarized GA-reactive CD4+ T-cells that are anti-inflammatory. It has been shown to reduce relapse rates by 33% over a 2-year period. Adverse effects include injecion site reactions, immediate post-injection reaction, and lipoatrophy. They are pregnancy-category B drugs. Currently approved glatiramer acetate drugs are Copaxone and Glatopa.[12]

Mitoxantron (Novantrone) is a potent T-cell, B-cell, and macrophage suppressor. It is a pregnancy-category D drug with adverse effects including hair loss, cardiotoxicity, leukemia, infertility, infection, leukopenia, anemia, nausea, vomiting, and thrombocytopenia. Alemtuzumab (Lemtrada) depletes circulating B and T lymphocytes to allow a slow repopulation from the unaffected hematopoietic precursor cells. Lemtrada has been shown to reduce ARR by 50%, and more patients remained in remission compared to those treated with interferon β. However, a serious side effect includes secondary autoimmunity.[12]

Natalizumab (Tysabri) binds to leukocytes and reduces their migration across the BBB.[12] One of the more serious side effect of this drug is its association with progressive multifocal leukoencephalopathy (PML).[21] PML is a fatal disease caused by an opportunistic infection by the John-Cunningham virus (JCV) in immunocompromised individuals.[22] Testing for this viral antibody is available to assess for the risk of PML. The patient in this case tested postive for the Anti-JC virus antibodies.

The first oral DMD, fingolimod (Gilenya) was approved in 2010. Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that prevents T cells from leaving the lymph nodes and reducing peripherally circulating immune cells. In two pivotal studies involving fingolimod, ARR was found to be lower than the interferon β group, and there were fewer T2 and gadolinium-enhancing lesions at 12 months comparatively. The most common side effects include headache, liver function abnormalities, viral infections, diarrhea, backpain, and cough. Macular edema has been found in 0.5% of patients within 3-4 months of taking 0.5mg of fingolimod. The patient in this case experienced a relapse at the start of the Gilenya treatment, and was subsequently switched to Tecfidera.

Tecfidera is dimethyl fumarate (DMF). It works to activate nuclear factor-like 2 (NRF-2) mediated antioxidative response pathways and results in natural anti-inflammatory response of immune cells. In the Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) study, 26% of the patients experienced a relapse compared to 46% of the placebo group. Lymphopenia, a serious side effect possibly associated with PML, can occur in up to 6% of the patients. The last FDA approved DMD is teriflunomide (Augabio), which works to inhibit DNA pyrimidine synthesis in diving T and B cells. Studies show a longer time to first relapse and a reduced ARR compared to placebo groups. Teriflunomide is classified as pregnancy-category X due to signs of developmental toxicity in rodent studies.[12]

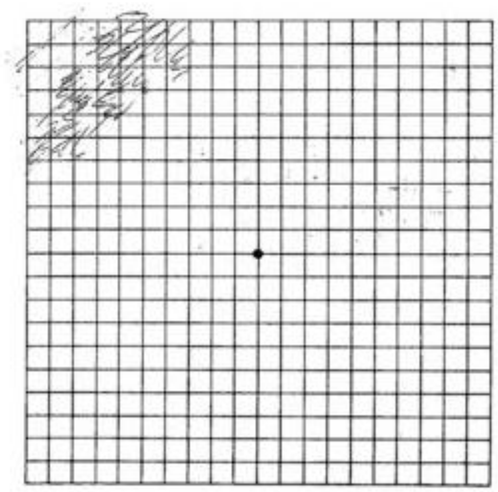
Conclusion

Multiple sclerosis is a progressive disease affecting the central nervous system and the leading cause of neurological disability among young adults. In 20% of multiple sclerosis, the first manifestation is painful vision loss in form of optic neuritis. In those cases, the eye care provider may be the first to discuss the diagnosis of multiple sclerosis with the patient. By understanding the disease process and current treatment modalities, eye care professionals can help the patients understand and manage the anxiety associated with the new diagnosis.

Appendix A

BERNELL M-R-M GRID TEST RECORDING CHART

(Maculopathy-Retinopathy-Metamorphopsia)
USE FOR
M-R-M Grid Test Book, 553M Slide And Amsler Grid Test



Appendix B

SINGLE FIELD ANALYSIS

NAME: [redacted]
ID: [redacted]

EYE: RIGHT
DOB: 02-26-1995

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: OFF
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 0/0
FALSE POS ERRORS: 3 %
FALSE NEG ERRORS: 11 %
TEST DURATION: 05:40

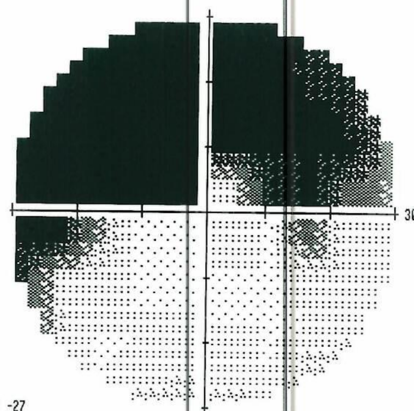
FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER:
VISUAL ACUITY:
RX: DS DC X

DATE: 08-25-2016
TIME: 9:10 AM
AGE: 21

<0 <0 | <0 <0
<0 <0 <0 | <0 <0 2
<0 <0 <0 <0 | <0 <0 <0 2
<0 <0 <0 <0 <0 | <0 <0 <0 0 14
30 <0 <0 <0 <0 <0 | 27 4 <0 12 16
<0 <0 19 31 31 | 30 31 13 27 27
5 26 28 32 32 | 31 32 27 27 27
25 30 30 30 | 31 31 30 28
32 29 27 | 28 31 25
25 24 | 24 28



-30 -30 | -29 -29
-32 -32 -32 | -32 -31 -28
-33 -34 -34 -34 | -34 -33 -33 -29
-32 -34 -35 -36 -36 | -35 -35 -34 -31 -18
-32 -34 -35 -36 -37 | -7 -30 -20 -16
-32 -34 -14 -4 -4 | -4 -3 -5 -4
-25 -6 -5 -1 -2 | -3 -1 -6 -5 -4
-5 -2 -2 -3 | -2 -2 -2 -4
2 -2 -4 | -3 -1 -7
-4 -6 | -7 -3

TOTAL DEVIATION

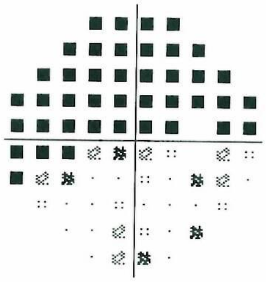
-28 -28 | -27 -27
-30 -30 -30 | -29 -29 -26
-31 -31 -32 -32 | -32 -31 -31 -27
-30 -31 -33 -33 -34 | -33 -33 -32 -29 -16
-30 -32 -33 -34 -35 | -5 -28 -18 -14
-30 -32 -12 -1 -2 | -2 -1 -3 -2
-23 -4 -3 1 0 | -1 1 -4 -3 -2
-3 0 0 -1 | 0 1 0 -2
4 0 -2 | -1 1 -4
-2 -4 | -5 -1

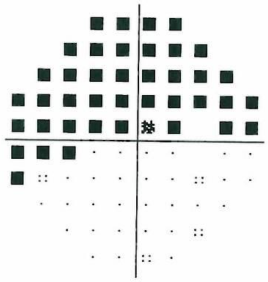
PATTERN DEVIATION

GHT
OUTSIDE NORMAL LIMITS

VFI 52%

MD -18.01 DB P < 0.5%
PSD 16.48 DB P < 0.5%

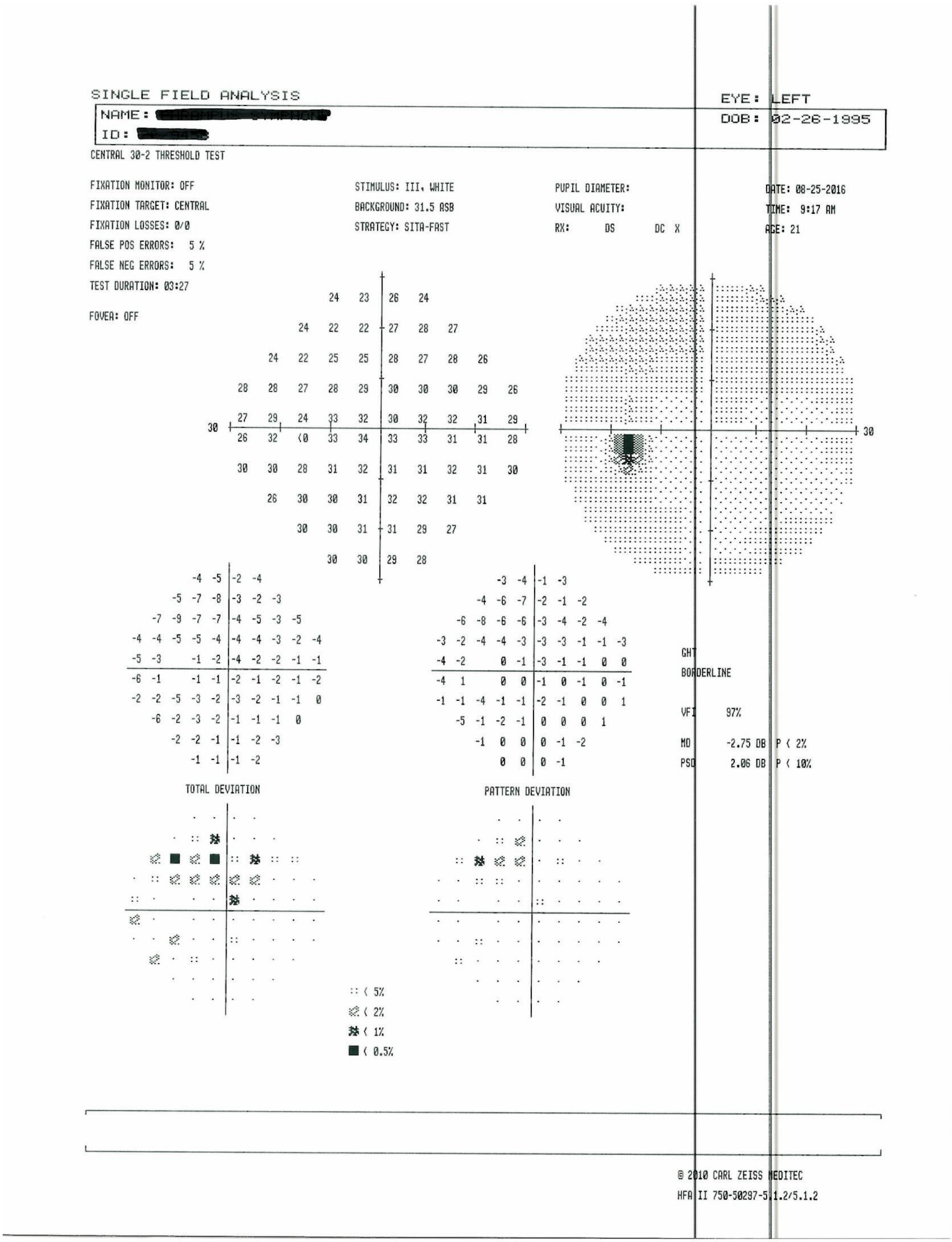




:: < 5%
< 2%
< 1%
< 0.5%

HFA II 750-50297-5.1.2/5.1.2

Appendix C



SINGLE FIELD ANALYSIS

EYE: LEFT

NAME: [redacted]

ID: [redacted]

DOB: 02-26-1995

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: OFF
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 0/0
FALSE POS ERRORS: 5 %
FALSE NEG ERRORS: 5 %
TEST DURATION: 03:27

FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER:
VISUAL ACUITY:
RX: DS DC X

DATE: 08-25-2016
TIME: 9:17 AM
AGE: 21

24 23 | 26 24
24 22 22 | 27 28 27
24 22 25 25 | 28 27 28 26
28 28 27 28 29 | 30 30 30 29 26
27 29 24 33 32 | 30 32 32 31 29
30
26 32 <0 33 34 | 33 33 31 31 28
30 30 28 31 32 | 31 31 32 31 30
26 30 30 31 | 32 32 31 31
30 30 31 | 31 29 27
30 30 | 29 28

30

-4 -5 | -2 -4
-5 -7 -8 | -3 -2 -3
-7 -9 -7 -7 | -4 -5 -3 -5
-4 -4 -5 -5 -4 | -4 -4 -3 -2 -4
-5 -3 -1 -2 | -4 -2 -2 -1 -1
-6 -1 -1 -1 | -2 -1 -2 -1 -2
-2 -2 -5 -3 -2 | -3 -2 -1 -1 0
-6 -2 -3 -2 | -1 -1 -1 0
-2 -2 -1 | -1 -2 -3
-1 -1 | -1 -2

TOTAL DEVIATION

-3 -4 | -1 -3
-4 -6 -7 | -2 -1 -2
-6 -8 -6 -6 | -3 -4 -2 -4
-3 -2 -4 -4 -3 | -3 -3 -1 -1 -3
-4 -2 0 -1 | -3 -1 -1 0 0
-4 1 0 0 | -1 0 -1 0 -1
-1 -1 -4 -1 -1 | -2 -1 0 0 1
-5 -1 -2 -1 | 0 0 0 1
-1 0 0 | 0 -1 -2
0 0 | 0 -1

PATTERN DEVIATION

GHT
BORDERLINE

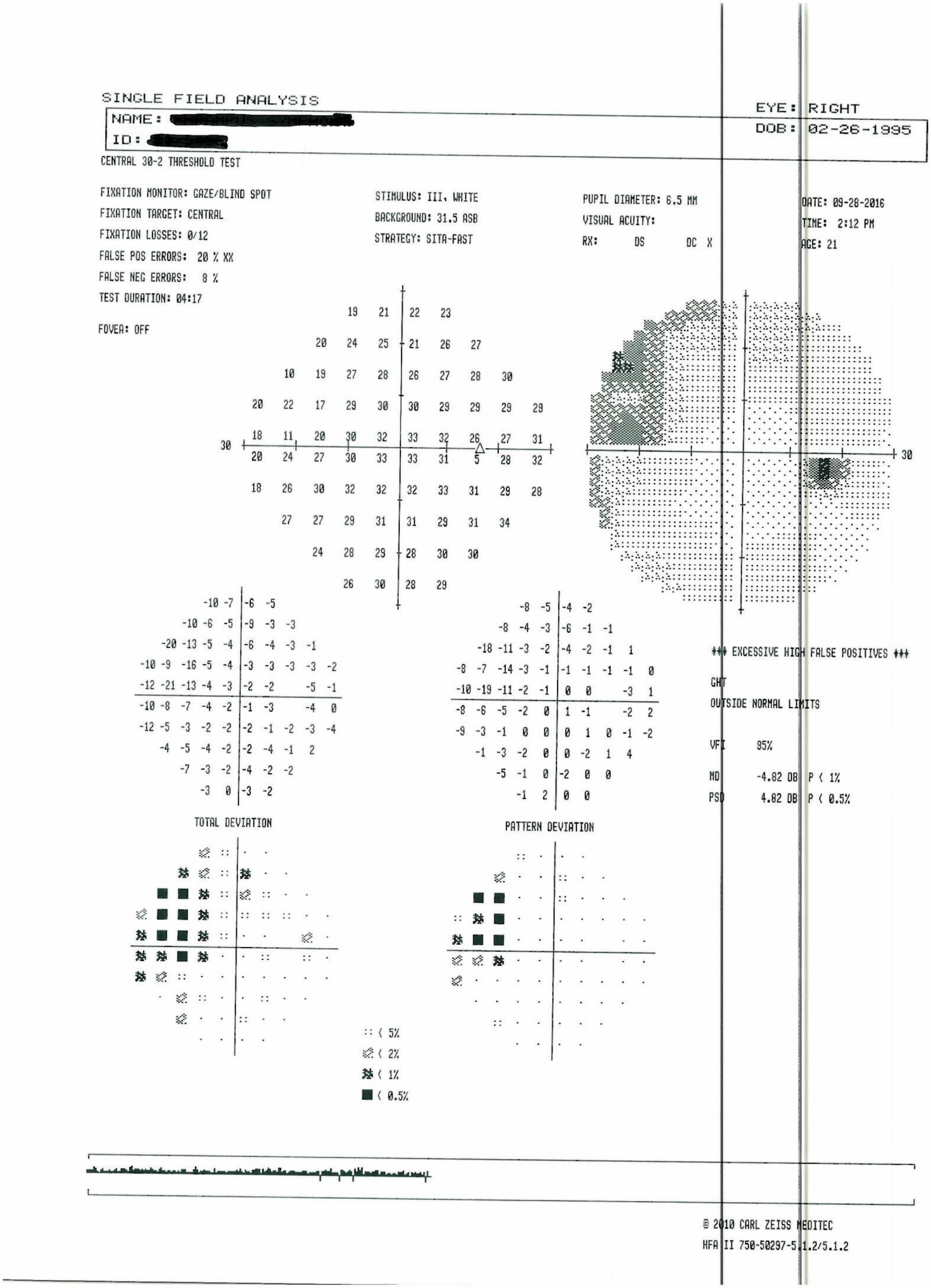
VFI 97%

MD -2.75 DB P < 2%
PSD 2.06 DB P < 10%

:: < 5%
< 2%
< 1%
< 0.5%

HFA II 750-50297-5.1.2/5.1.2

Appendix D


SINGLE FIELD ANALYSIS
NAME: [redacted]
ID: [redacted]
EYE: RIGHT
DOB: 02-26-1995
CENTRAL 30-2 THRESHOLD TEST
FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 0/12
FALSE POS ERRORS: 20 % XX
FALSE NEG ERRORS: 8 %
TEST DURATION: 04:17
FOVEA: OFF
STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST
PUPIL DIAMETER: 6.5 MM
VISUAL ACUITY:
RX: DS DC X
DATE: 09-28-2016
TIME: 2:12 PM
AGE: 21
TOTAL DEVIATION
PATTERN DEVIATION
*** EXCESSIVE HIGH FALSE POSITIVES ***
GHT
OUTSIDE NORMAL LIMITS
VFI 95%
MD -4.82 DB P < 1%
PSD 4.82 DB P < 0.5%
:: < 5%
< 2%
< 1%
< 0.5%
© 2010 CARL ZEISS MEDITEC
HFA II 750-50297-5.1.2/5.1.2

Appendix E

SINGLE FIELD ANALYSIS

NAME: [redacted]
ID: [redacted]

EYE: LEFT
DOB: 02-26-1995

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 3/13 XX
FALSE POS ERRORS: 20 % XX
FALSE NEG ERRORS: 12 %
TEST DURATION: 04:46

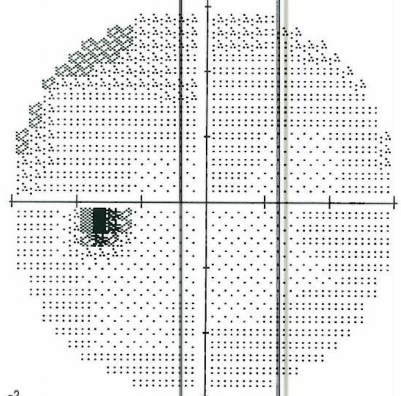
FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 4.3 MM
VISUAL ACUITY:
RX: DS DC X

DATE: 09-28-2016
TIME: 2:19 PM
AGE: 21

```
            22  22 | 25  26
        19  24  26 | 26  28  25
    26  27  26  24 | 28  30  29  28
19  27  26  29  30 | 29  31  31  29  24
23  28  26  32  32 | 30  32  32  30  26
30 ----------------+---------------------
28  32  <0  31  32 | 35  33  30  28  28
30  30  32  31  33 | 33  35  32  29  28
    26  32  32  30 | 31  31  28  29
        31  31  31 | 29  28  27
            28  28 | 27  30
```




```
            -6  -6 | -2  -3
       -10  -5  -3 | -4  -2  -5
    -5  -4  -5  -8 | -4  -2  -2  -3
-13 -5  -6  -4  -4 | -5  -3  -2  -2  -5
-8  -4      -2  -2 | -4  -2  -2  -2  -4
-------------------+-------------------
-3   0      -3  -3 |  0  -1  -3  -4  -2
-2  -2  -1  -2  -1 | -1   1  -1  -2  -2
    -6  -1  -1  -3 | -2  -2  -4  -2
        -1  -1  -1 | -3  -3  -3
            -3  -2 | -3   0
```

TOTAL DEVIATION

```
            -5  -5 | -2  -2
        -9  -4  -2 | -3  -1  -4
    -4  -4  -4  -7 | -3  -1  -1  -2
-12 -4  -5  -3  -3 | -4  -2  -1  -1  -4
-8  -3      -1  -2 | -4  -1  -1  -1  -3
-------------------+-------------------
-2   0      -3  -2 |  0   0  -2  -3  -2
-1  -1   0  -2  -1 |  0   2   0  -1  -1
    -5   0   0  -2 | -1  -1  -3  -1
         0   0   0 | -2  -2  -3
            -2  -2 | -2   1
```

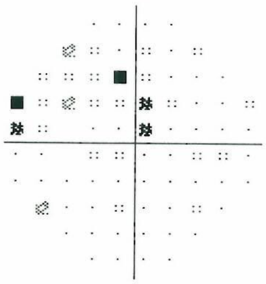
PATTERN DEVIATION

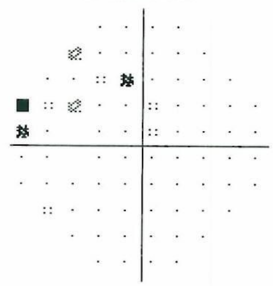
*** EXCESSIVE HIGH FALSE POSITIVES ***

GHT
WITHIN NORMAL LIMITS

VFI 98%

MD -2.81 DB P < 2%
PSD 2.22 DB P < 10%





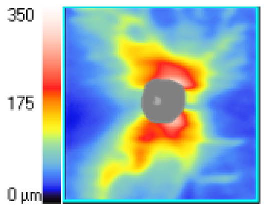
:: < 5%
▒ < 2%
▓ < 1%
■ < 0.5%

Appendix F

Name:	[redacted]		**OD**	**OS**	
ID:	[redacted]	Exam Date:	9/28/2016	9/28/2016	CZMI
DOB:	2/26/1995	Exam Time:	3:43 PM	3:44 PM	
Gender:	Female	Serial Number:	4000-11118	4000-11118	
Technician:	Operator, Cirrus	Signal Strength:	7/10	9/10	

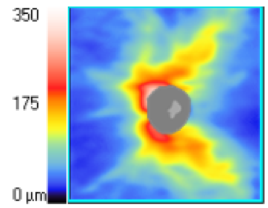
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD ● ● OS

RNFL Thickness Map

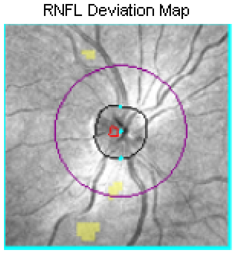


⚠	OD	OS
Average RNFL Thickness	98 µm	95 µm
RNFL Symmetry	90%	
Rim Area	1.52 mm²	1.53 mm²
Disc Area	1.58 mm²	1.67 mm²
Average C/D Ratio	0.19	0.29
Vertical C/D Ratio	0.21	0.33
Cup Volume	0.013 mm³	0.014 mm³

RNFL Thickness Map

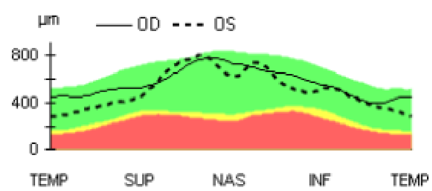


RNFL Deviation Map

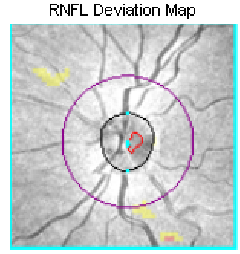


Disc Center(0.06,0.15)mm

Neuro-retinal Rim Thickness

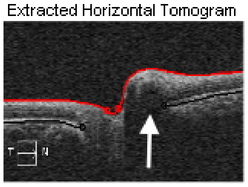


RNFL Deviation Map

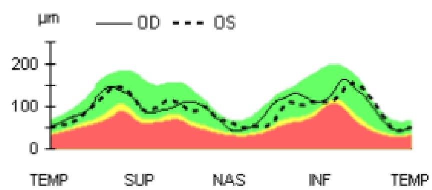


Disc Center(0.09,-0.12)mm

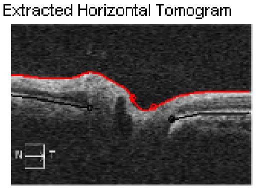
Extracted Horizontal Tomogram



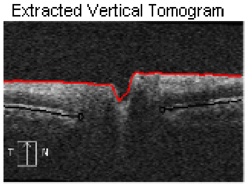
RNFL Thickness

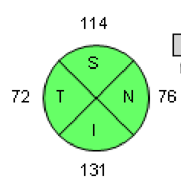


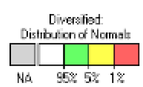
Extracted Horizontal Tomogram



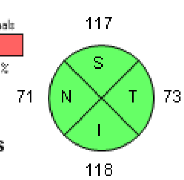
Extracted Vertical Tomogram



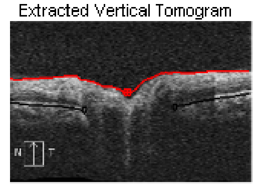




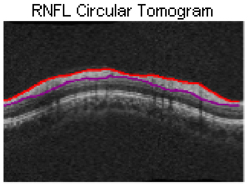
RNFL Quadrants

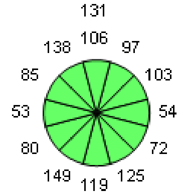


Extracted Vertical Tomogram

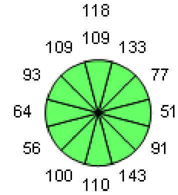


RNFL Circular Tomogram

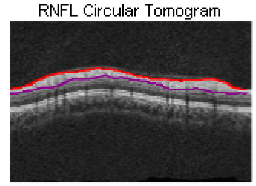




RNFL Clock Hours



RNFL Circular Tomogram



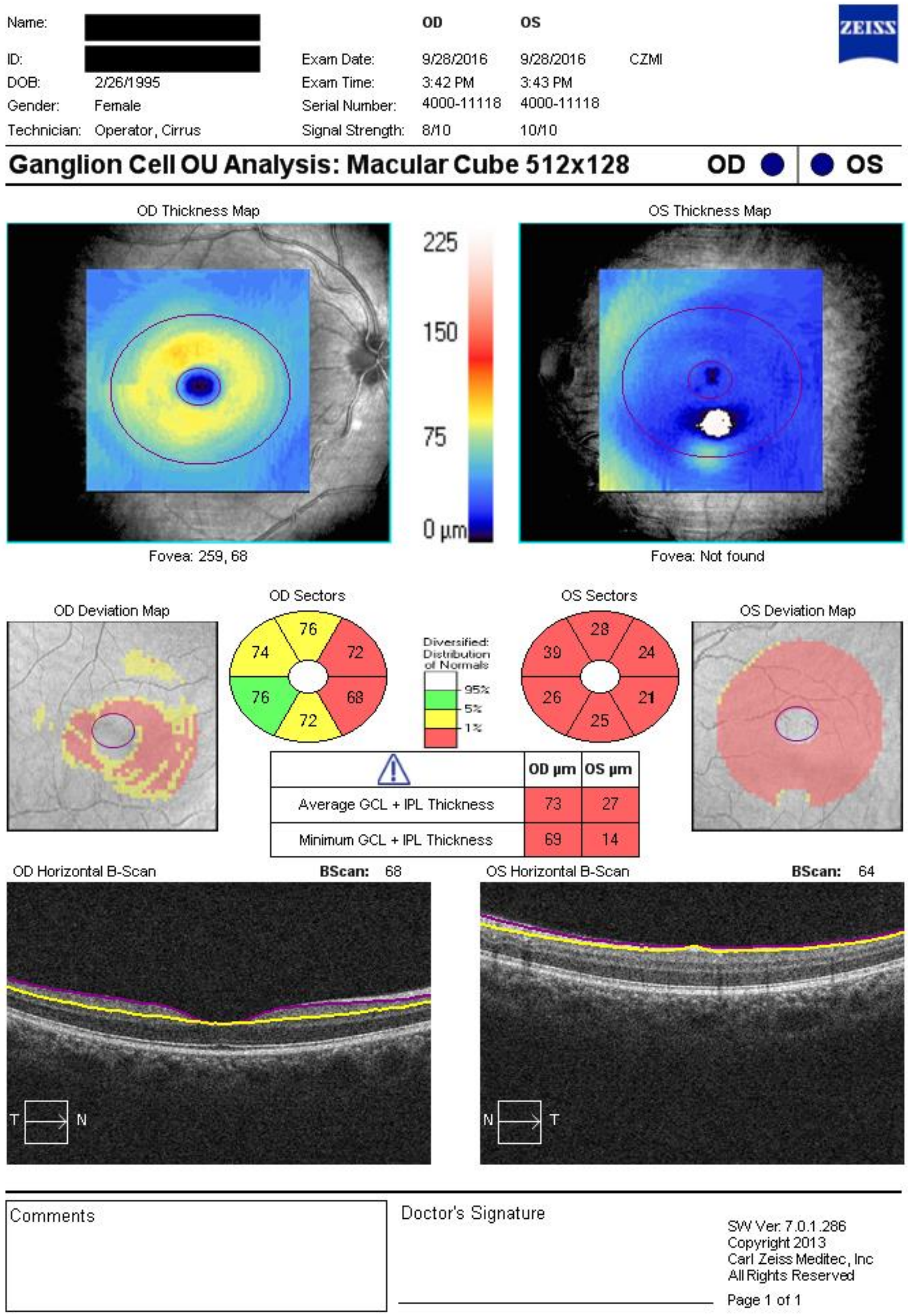
Comments
white arrow shows area suspicious of disc edema.

Doctor's Signature

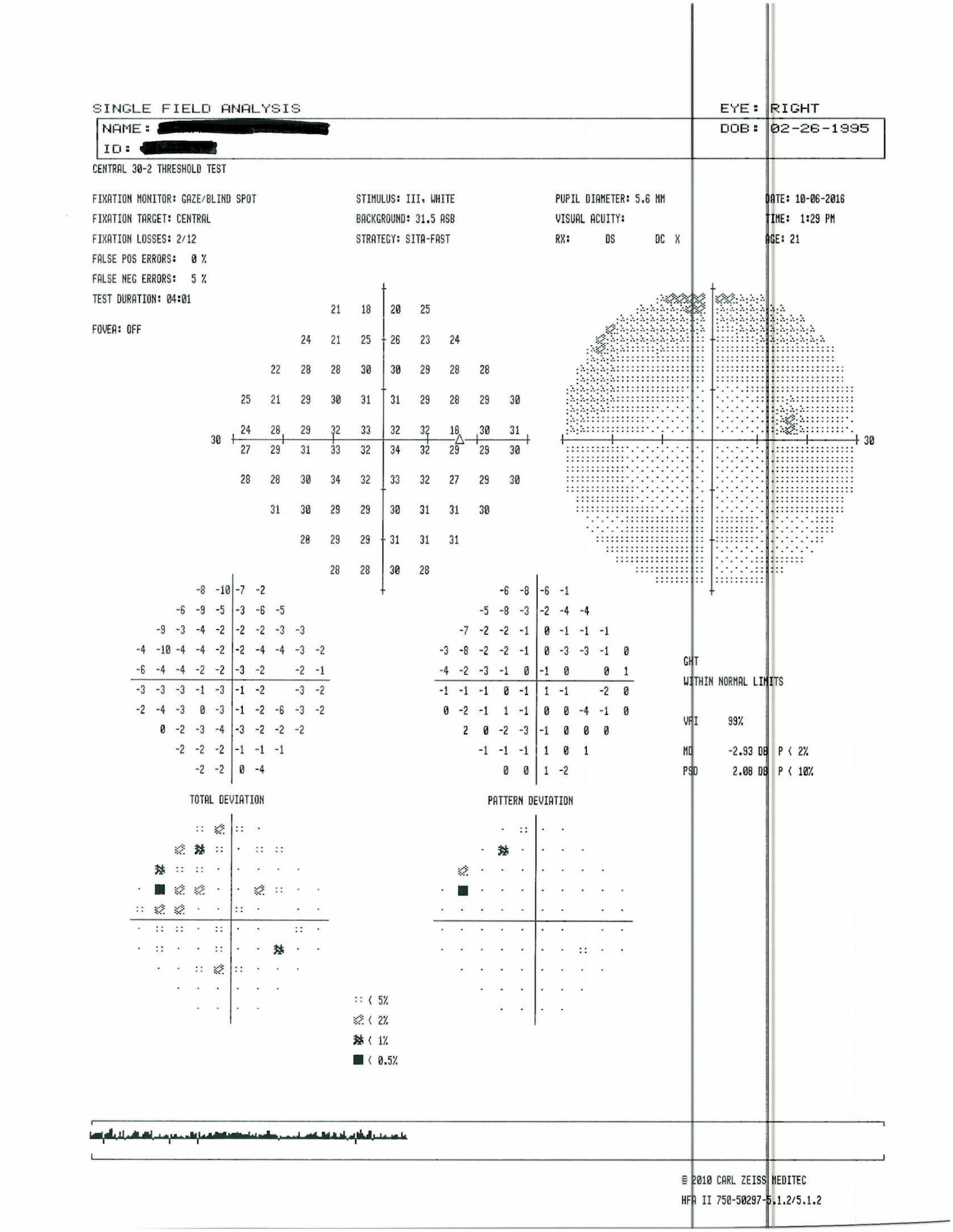
SW Ver: 7.0.1.286

Page 1 of 1

Appendix G


Name: [redacted]
ID: [redacted]
DOB: 2/26/1995
Gender: Female
Technician: Operator, Cirrus
OD OS
Exam Date: 9/28/2016 9/28/2016 CZMI
Exam Time: 3:42 PM 3:43 PM
Serial Number: 4000-11118 4000-11118
Signal Strength: 8/10 10/10
ZEISS
Ganglion Cell OU Analysis: Macular Cube 512x128
OD OS
OD Thickness Map
OS Thickness Map
225
150
75
0 µm
Fovea: 259, 68
Fovea: Not found
OD Deviation Map
OD Sectors
76 72 68 72 76 74
Diversified: Distribution of Normals
95%
5%
1%
OS Sectors
28 24 21 25 26 39
OS Deviation Map
OD µm OS µm
Average GCL + IPL Thickness 73 27
Minimum GCL + IPL Thickness 69 14
OD Horizontal B-Scan
BScan: 68
OS Horizontal B-Scan
BScan: 64
T N
N T
Comments
Doctor's Signature
SW Ver: 7.0.1.286
Copyright 2013
Carl Zeiss Meditec, Inc
All Rights Reserved
Page 1 of 1

Appendix H



SINGLE FIELD ANALYSIS | EYE: RIGHT

NAME: [redacted] | DOB: 02-26-1995

ID: [redacted]

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 2/12
FALSE POS ERRORS: 0 %
FALSE NEG ERRORS: 5 %
TEST DURATION: 04:01

FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 5.6 MM
VISUAL ACUITY:
RX: DS DC X

DATE: 10-06-2016
TIME: 1:29 PM
AGE: 21

```
            21 18 | 20 25
         24 21 25 | 26 23 24
      22 28 28 30 | 30 29 28 28
   25 21 29 30 31 | 31 29 28 29 30
   24 28 29 32 33 | 32 32 18 30 31
30 ---------------+--------------- 30
   27 29 31 33 32 | 34 32 29 29 30
   28 28 30 34 32 | 33 32 27 29 30
      31 30 29 29 | 30 31 31 30
         28 29 29 | 31 31 31
            28 28 | 30 28
```

```
          -8 -10 | -7 -2
       -6 -9  -5 | -3 -6 -5
    -9 -3 -4  -2 | -2 -2 -3 -3
-4 -10 -4 -4  -2 | -2 -4 -4 -3 -2
-6  -4 -4 -2  -2 | -3 -2    -2 -1
-----------------+----------------
-3  -3 -3 -1  -3 | -1 -2    -3 -2
-2  -4 -3  0  -3 | -1 -2 -6 -3 -2
     0 -2 -3  -4 | -3 -2 -2 -2
       -2 -2  -2 | -1 -1 -1
          -2  -2 |  0 -4
```

TOTAL DEVIATION

```
         -6 -8 | -6 -1
      -5 -8 -3 | -2 -4 -4
   -7 -2 -2 -1 |  0 -1 -1 -1
-3 -8 -2 -2 -1 |  0 -3 -3 -1  0
-4 -2 -3 -1  0 | -1  0     0  1
---------------+----------------
-1 -1 -1  0 -1 |  1 -1    -2  0
 0 -2 -1  1 -1 |  0  0 -4 -1  0
    2  0 -2 -3 | -1  0  0  0
      -1 -1 -1 |  1  0  1
          0  0 |  1 -2
```

PATTERN DEVIATION

GHT
WITHIN NORMAL LIMITS

VFI 99%

MD -2.93 DB P < 2%
PSD 2.08 DB P < 10%

:: < 5%
< 2%
< 1%
< 0.5%

HFA II 750-50297-5.1.2/5.1.2

Appendix I

SINGLE FIELD ANALYSIS

EYE: LEFT

NAME: [redacted]

DOB: 02-26-1995

ID: [redacted]

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 3/12 XX
FALSE POS ERRORS: 0 %
FALSE NEG ERRORS: 8 %
TEST DURATION: 04:03

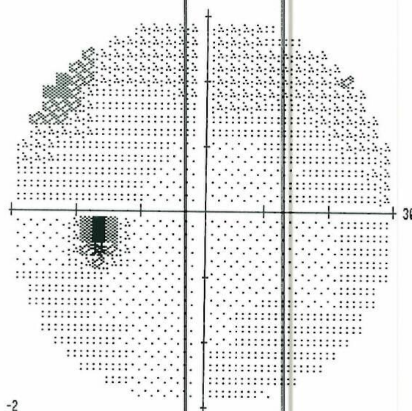
FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 4.2 MM
VISUAL ACUITY:
RX: DS DC X

DATE: 10-06-2016
TIME: 1:34 PM
AGE: 21

				21	23	25	26			
			24	24	22	24	24	23		
		17	28	29	27	24	26	25	22	
	24	26	27	28	31	31	30	29	25	24
	28	28	26	30	33	33	32	29	28	25
30	31	31	<0	33	34	34	33	31	30	26
	30	30	30	33	31	31	34	31	30	28
		28	31	32	32	31	28	30	30	
			28	31	32	30	29	29		
				32	31	30	31			



			-6	-4	-3	-3			
		-5	-5	-8	-6	-6	-7		
	-14	-3	-3	-5	-8	-6	-6	-9	
-8	-6	-5	-4	-2	-3	-4	-4	-7	-6
-3	-4		-4	-2	-2	-2	-4	-4	-5
0	-1		-1	-1	-1	-1	-3	-2	-4
-1	-2	-3	-1	-3	-3	0	-2	-2	-2
	-4	-1	-1	-1	-2	-4	-2	-1	
		-4	0	0	-1	-2	-2		
			0	1	0	2			

TOTAL DEVIATION

			-5	-3	-1	-2			
		-4	-4	-7	-5	-5	-6		
	-13	-2	-1	-4	-7	-5	-5	-8	
-7	-5	-4	-3	-1	-1	-3	-3	-5	-4
-2	-3		-3	0	0	-1	-3	-3	-3
1	0		0	0	0	0	-2	-1	-2
0	0	-2	0	-2	-2	1	-1	-1	-1
	-3	0	0	0	-1	-3	-1	0	
		-3	1	1	0	-1	0		
			1	2	1	3			

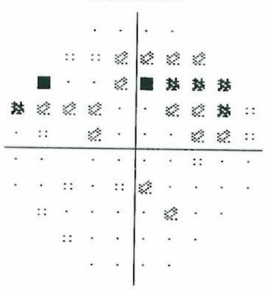
PATTERN DEVIATION

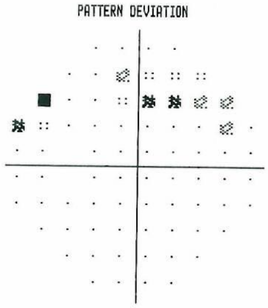
*** LOW TEST RELIABILITY ***

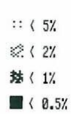
GHT
OUTSIDE NORMAL LIMITS

VFI 98%

MD -3.03 DB P < 2%
PSD 2.57 DB P < 5%







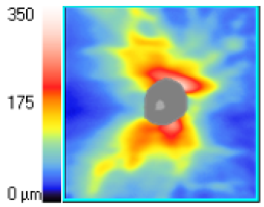
HFA II 750-50297-5.1.2/5.1.2

Appendix J

Name:	[redacted]		OD	OS	
ID:	[redacted]	Exam Date:	10/6/2016	10/6/2016	CZMI
DOB:	2/26/1995	Exam Time:	3:01 PM	3:02 PM	
Gender:	Female	Serial Number:	4000-11118	4000-11118	
Technician:	Operator, Cirrus	Signal Strength:	9/10	9/10	

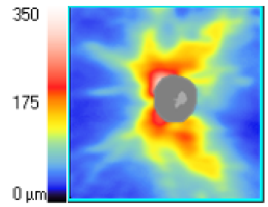
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD ● ● OS

RNFL Thickness Map

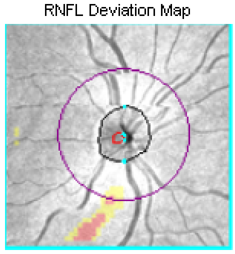


⚠	OD	OS
Average RNFL Thickness	99 µm	96 µm
RNFL Symmetry	74%	
Rim Area	1.50 mm²	1.49 mm²
Disc Area	1.58 mm²	1.62 mm²
Average C/D Ratio	0.22	0.29
Vertical C/D Ratio	0.23	0.27
Cup Volume	0.016 mm³	0.014 mm³

RNFL Thickness Map

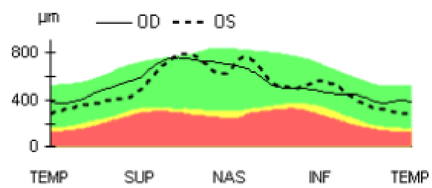


RNFL Deviation Map

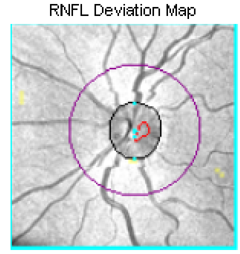


Disc Center(0.12,0.06)mm

Neuro-retinal Rim Thickness

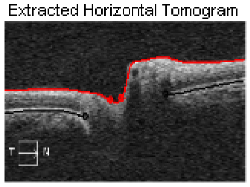


RNFL Deviation Map

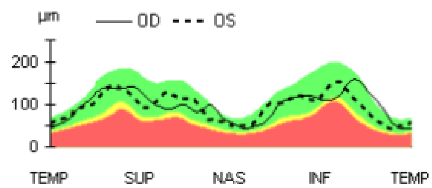


Disc Center(0.27,0.18)mm

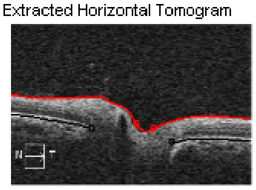
Extracted Horizontal Tomogram



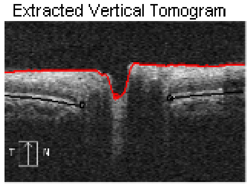
RNFL Thickness

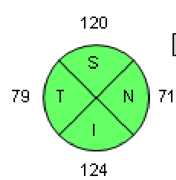


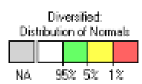
Extracted Horizontal Tomogram



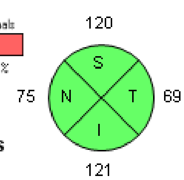
Extracted Vertical Tomogram



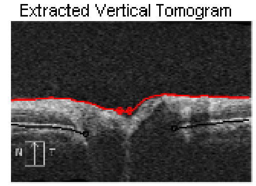




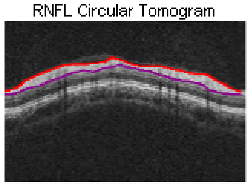
RNFL Quadrants

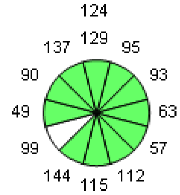


Extracted Vertical Tomogram

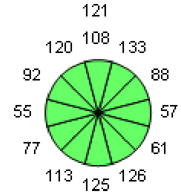


RNFL Circular Tomogram

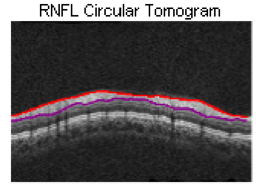




RNFL Clock Hours



RNFL Circular Tomogram



Comments

Doctor's Signature

SW Ver: 7.0.1.286

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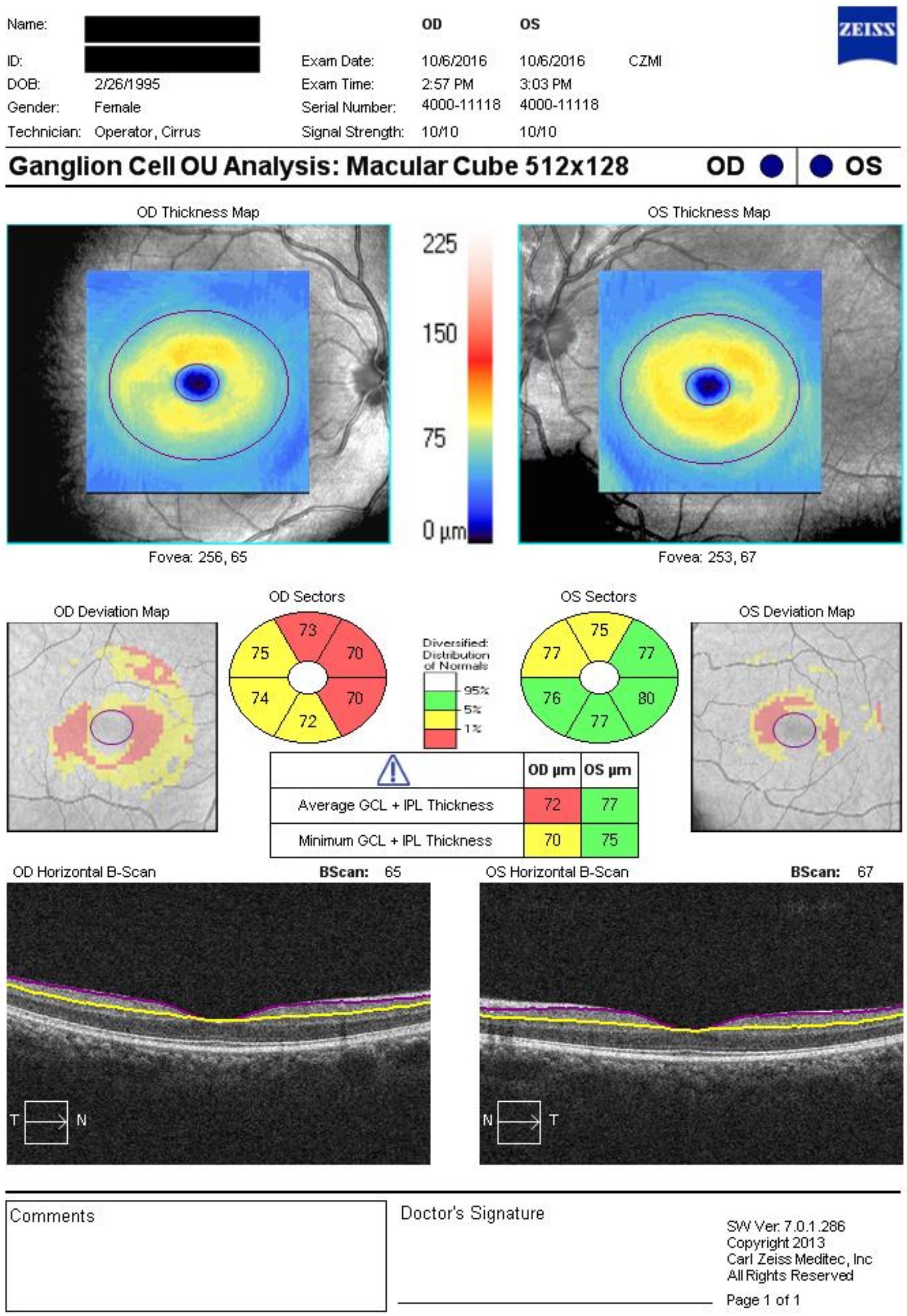
Appendix K



			OD	OS	
Name:	[redacted]				
ID:	[redacted]	Exam Date:	10/6/2016	10/6/2016	CZMI
DOB:	2/26/1995	Exam Time:	2:57 PM	3:03 PM	
Gender:	Female	Serial Number:	4000-11118	4000-11118	
Technician:	Operator, Cirrus	Signal Strength:	10/10	10/10	

Ganglion Cell OU Analysis: Macular Cube 512x128 **OD** **OS**

	OD µm	OS µm
Average GCL + IPL Thickness	72	77
Minimum GCL + IPL Thickness	70	75

Comments

Doctor's Signature

SW Ver: 7.0.1.286

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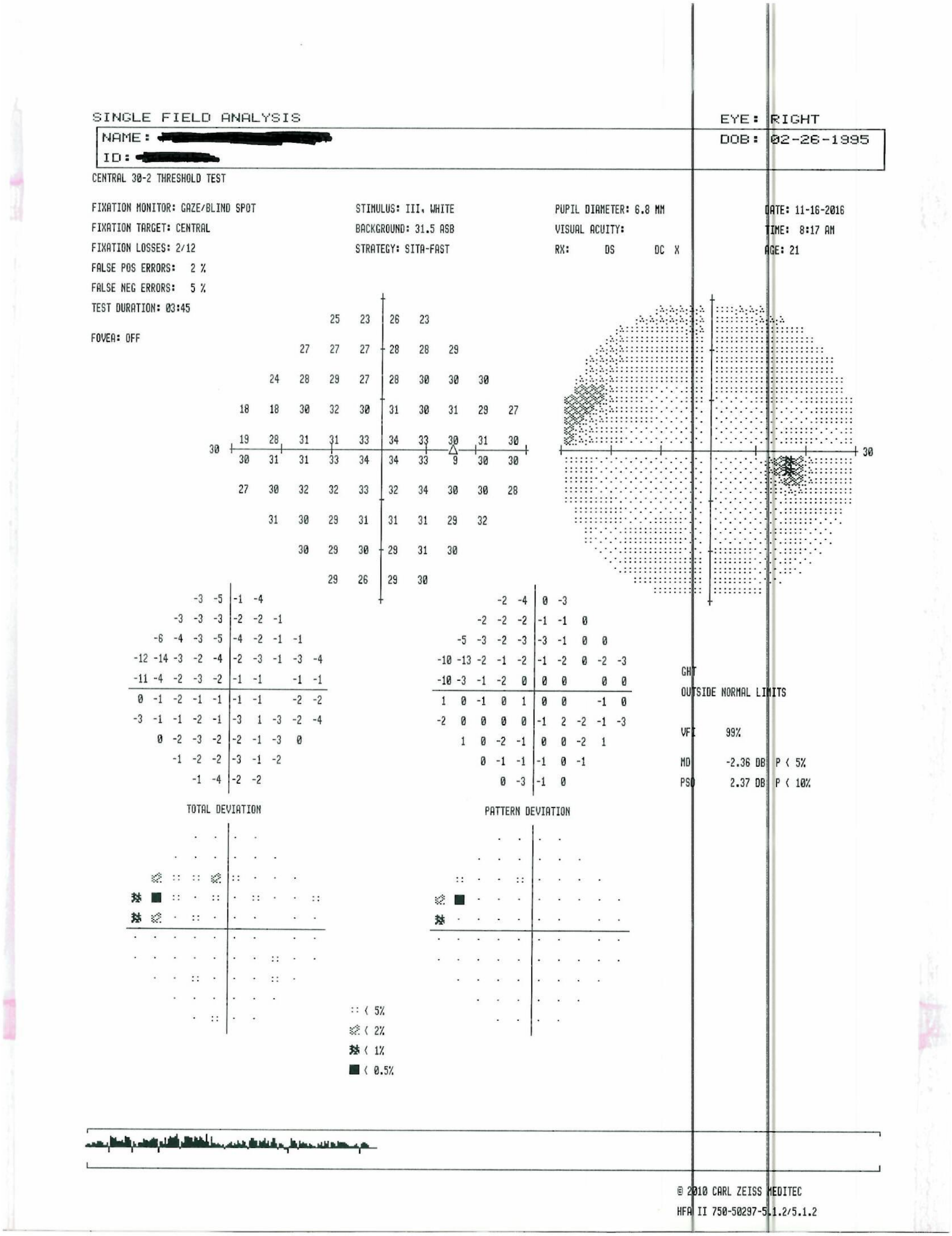
Appendix L


SINGLE FIELD ANALYSIS

EYE: RIGHT

NAME: [redacted]

ID: [redacted]

DOB: 02-26-1995

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 2/12
FALSE POS ERRORS: 2 %
FALSE NEG ERRORS: 5 %
TEST DURATION: 03:45

FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 6.8 MM
VISUAL ACUITY:
RX: DS DC X

DATE: 11-16-2016
TIME: 8:17 AM
AGE: 21

25 23 | 26 23
27 27 27 | 28 28 29
24 28 29 27 | 28 30 30 30
18 18 30 32 30 | 31 30 31 29 27
30 — 19 28 31 31 33 | 34 33 30 31 30 — 30
30 31 31 33 34 | 34 33 9 30 30
27 30 32 32 33 | 32 34 30 30 28
31 30 29 31 | 31 31 29 32
30 29 30 | 29 31 30
29 26 | 29 30

-3 -5 | -1 -4
-3 -3 -3 | -2 -2 -1
-6 -4 -3 -5 | -4 -2 -1 -1
-12 -14 -3 -2 -4 | -2 -3 -1 -3 -4
-11 -4 -2 -3 -2 | -1 -1 -1 -1
0 -1 -2 -1 -1 | -1 -1 -2 -2
-3 -1 -1 -2 -1 | -3 1 -3 -2 -4
0 -2 -3 -2 | -2 -1 -3 0
-1 -2 -2 | -3 -1 -2
-1 -4 | -2 -2

TOTAL DEVIATION

-2 -4 | 0 -3
-2 -2 -2 | -1 -1 0
-5 -3 -2 -3 | -3 -1 0 0
-10 -13 -2 -1 -2 | -1 -2 0 -2 -3
-10 -3 -1 -2 0 | 0 0 0 0
1 0 -1 0 1 | 0 0 -1 0
-2 0 0 0 0 | -1 2 -2 -1 -3
1 0 -2 -1 | 0 0 -2 1
0 -1 -1 | -1 0 -1
0 -3 | -1 0

PATTERN DEVIATION

GHT
OUTSIDE NORMAL LIMITS

VFI 99%

MD -2.36 DB P < 5%
PSD 2.37 DB P < 10%

:: < 5%
< 2%
< 1%
< 0.5%

HFA II 750-50297-5.1.2/5.1.2

Appendix M

SINGLE FIELD ANALYSIS

NAME: [redacted]

ID: [redacted]

EYE: LEFT

DOB: 02-26-1995

CENTRAL 30-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 0/13
FALSE POS ERRORS: 3 %
FALSE NEG ERRORS: 1 %
TEST DURATION: 04:20

FOVEA: OFF

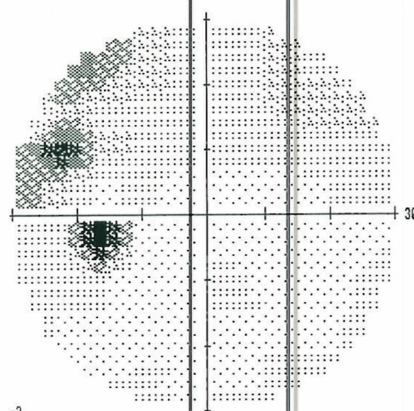
STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 6.1 MM
VISUAL ACUITY:
RX: DS DC X

DATE: 11-16-2016
TIME: 8:22 AM
AGE: 21

			21	26	26	25			
		17	24	26	26	25	26		
	23	27	27	27	28	26	23	24	
18	4	24	26	29	30	30	29	27	26
17	24	32	29	32	32	32	31	29	27
29	28	<0	31	34	31	33	33	32	31
28	30	30	33	33	29	33	31	31	28
	31	31	32	32	31	31	31	30	
		32	31	32	31	30	30		
			28	31	30	30			

30



			-7	-1	-2	-3			
		-13	-6	-3	-4	-5	-5		
	-8	-4	-4	-4	-4	-6	-8	-7	
-14	-28	-8	-7	-4	-4	-4	-4	-5	-4
-15	-8		-5	-3	-3	-2	-2	-3	-3
-2	-4		-3	-1	-4	-1	0	0	1
-4	-2	-3	-1	-1	-5	-1	-2	-1	-2
	-1	-1	-1	-1	-2	-2	-1	-1	
		0	0	0	-1	-1	-1		
			-3	0	0	0			

TOTAL DEVIATION

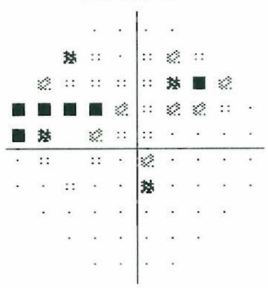
			-6	-1	-1	-3			
		-12	-5	-3	-4	-5	-4		
	-7	-3	-3	-4	-3	-5	-8	-6	
-13	-27	-7	-7	-4	-3	-3	-3	-4	-3
-14	-8		-5	-2	-2	-2	-1	-2	-2
-1	-3		-2	0	-3	0	0	0	1
-3	-1	-2	0	0	-5	0	-1	0	-1
	0	0	0	0	-1	-1	-1	0	
		0	0	1	0	0	0		
			-2	1	0	1			

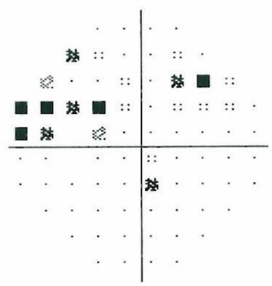
PATTERN DEVIATION

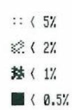
GHT
BORDERLINE

VFI 94%

MD -3.34 DB P < 1%
PSD 4.31 DB P < 0.5%







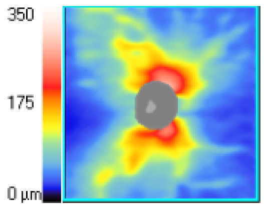
HFA II 750-50297-

Appendix N

Name:	[redacted]		OD	OS
ID:	[redacted]	Exam Date:	11/16/2016	11/16/2016 CZMI
DOB:	2/26/1995	Exam Time:	9:22 AM	9:24 AM
Gender:	Female	Serial Number:	4000-11118	4000-11118
Technician:	Operator, Cirrus	Signal Strength:	8/10	9/10

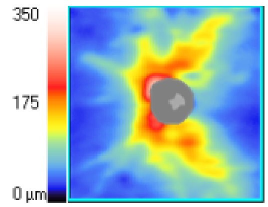
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD OS

RNFL Thickness Map

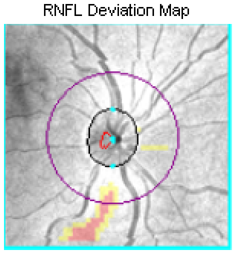


	OD	OS
Average RNFL Thickness	93 µm	97 µm
RNFL Symmetry	94%	
Rim Area	1.53 mm²	1.46 mm²
Disc Area	1.63 mm²	1.62 mm²
Average C/D Ratio	0.25	0.32
Vertical C/D Ratio	0.25	0.34
Cup Volume	0.021 mm³	0.018 mm³

RNFL Thickness Map

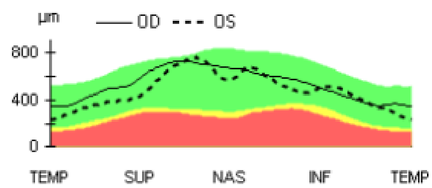


RNFL Deviation Map

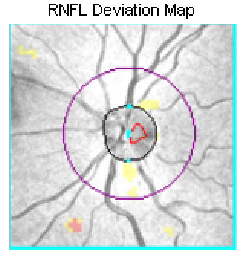


Disc Center(-0.15,-0.03)mm

Neuro-retinal Rim Thickness

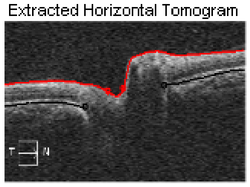


RNFL Deviation Map

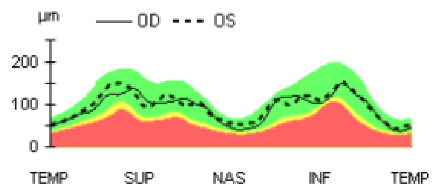


Disc Center(0.15,0.09)mm

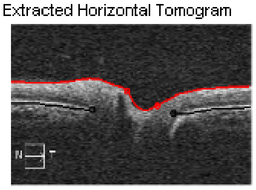
Extracted Horizontal Tomogram



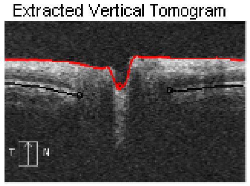
RNFL Thickness

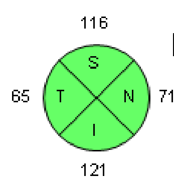


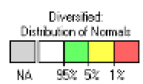
Extracted Horizontal Tomogram



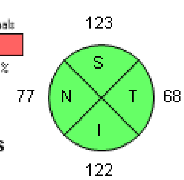
Extracted Vertical Tomogram



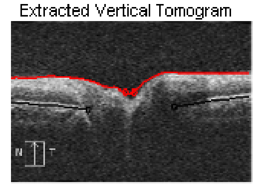




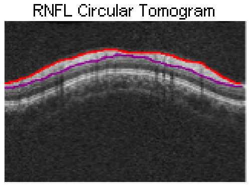
RNFL Quadrants

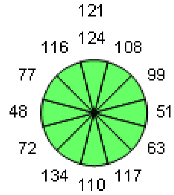


Extracted Vertical Tomogram

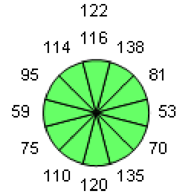


RNFL Circular Tomogram

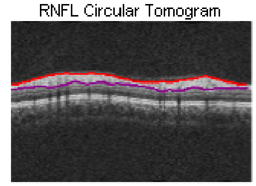




RNFL Clock Hours



RNFL Circular Tomogram



Comments

Doctor's Signature

SW Ver: 7.0.1.286

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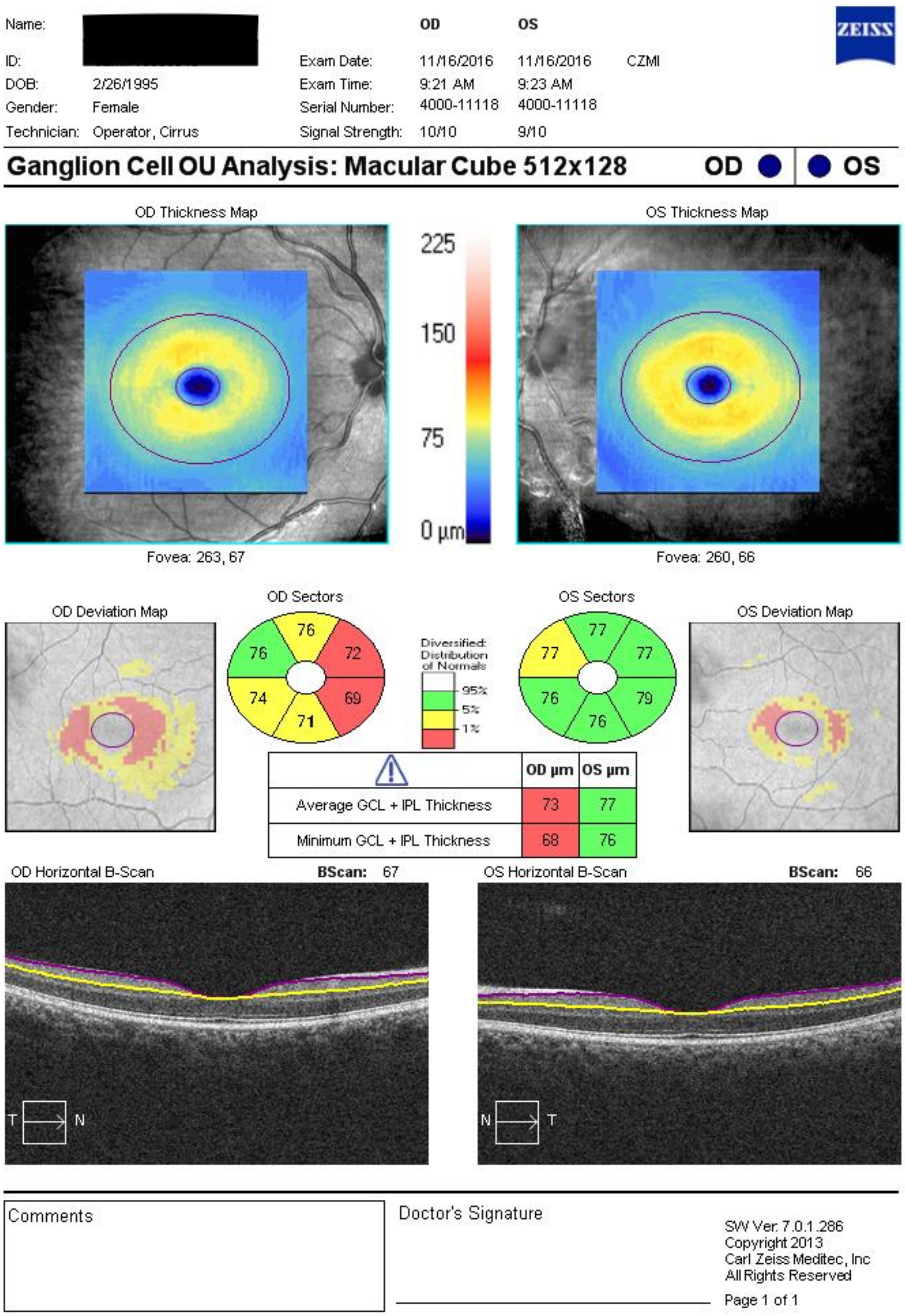
Appendix O



			OD	OS	
Name:	[redacted]				
ID:		Exam Date:	11/16/2016	11/16/2016	CZMI
DOB:	2/26/1995	Exam Time:	9:21 AM	9:23 AM	
Gender:	Female	Serial Number:	4000-11118	4000-11118	
Technician:	Operator, Cirrus	Signal Strength:	10/10	9/10	

Ganglion Cell OU Analysis: Macular Cube 512x128 OD ● ● OS

OD Thickness Map

225 150 75 0 µm

OS Thickness Map

Fovea: 263, 67

Fovea: 260, 66

OD Deviation Map

OD Sectors: 76, 72, 69, 71, 74, 76

Diversified: Distribution of Normals — 95%, 5%, 1%

OS Sectors: 77, 77, 79, 76, 76, 77

OS Deviation Map

⚠	OD µm	OS µm
Average GCL + IPL Thickness	73	77
Minimum GCL + IPL Thickness	68	76

OD Horizontal B-Scan **BScan:** 67

OS Horizontal B-Scan **BScan:** 66

T N

N T

Comments

Doctor's Signature

SW Ver: 7.0.1.286

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Appendix P

Bibliography

1. Liu, Grant T., Nicholas J. Volpe, and Steven L. Galetta. Neuro-ophthalmology: diagnosis and management. 2nd ed. Philadelphia: Saunders/Elsevier, 2010. 131-42. Print.
2. Zeid, Nuhad Abou, and M. Tariq Bhatti. "Acute Inflammatory Demyelinating Optic Neuritis." The Neurologist 14.4 (2008): 207-23. Web.
3. Pavan-Langston, Deborah. Manual of ocular diagnosis and therapy. 6th ed. Philadelphia, PA: Wolters Kluwer/Lippincott William & Wilkins, 2008. 380-1, 383-291. Print.
4. Onofrey, Bruce E., Leonid Skorin, Jr., and Nickey R. Holdeman. "19 Neuro-Ophthalmic Disease." Ocular therapeutics handbook. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011. 582-591. Print.
5. Keltner, John L. "Visual Field Profile of Optic Neuritis." Archives of Ophthalmology 128.3 (2010): 330. Web.
6. "The International Classification of Headache Disorders, 3rd edition (beta version)." Cephalalgia 33.9 (2013): 644-58. Web. 22 May 2017. <http://www.ihs-headache.org/binary_data/1437_ichd-iii-beta-cephalalgia-issue-9-2013.pdf>.
7. Cutrer, F. Michael, and Zahid H. Bajwa. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. Wolters Kluwer, n.d. Web. 20 May 2017.
8. Guyer, David R., Lawrence A. Yannuzzi, Stanley Chang, Jerry A. Shields, and W. Richard Green. Retina, Vitreous, Macula. Vol. 2. Philadelphia : Saunders: W. B. Saunders Company, 1999. 1243-45. Print.
9. Beck, Roy W. "Treatment of Acute Optic Neuritis." Archives of Ophthalmology 126.7 (2008): 994-95. Web.
10. Beck, Roy W., Patricia A. Cleary, Malcolm M. Anderson, Jr., John L. Keltner, William T. Shults, David I. Kaufman, and Edward G. Buckley. "A Randomized, Controlled Trial of Corticosteroids in the Treatment of Acute Optic Neuritis." The New England Journal of Medicine 326.9 (1992): 581-88. Web.
11. Fabian, Michelle T., Stephen C. Krieger, and Fred D. Lublin. "Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System." Bradley's Neurology in Clinical Practice. 7th ed. Philadelphia:Elsevier, 2016. 1159-1186.e4. Web.
12. Eckstein, Christopher, and M. Tariq Bhatti. "Currently approved and emerging oral therapies in multiple sclerosis: An update for the ophthalmologist." Survey of Ophthalmology 61.3 (2016): 318-32. Web.
13. Achiron, Anat, and Yoram Barak. "Multiple Sclerosis—From Probable to Definite Diagnosis." Archives of Neurology 57.7 (2000): 974-79. Web.
14. Polman, Chris H., Stephen C. Reingold, Brenda Banwell, Michel Clanet, Jeffrey A. Cohen, Massimo Filippi, Kazuo Fujihara, Eva Havrdova, Michael Hutchinson, Ludwig Kappos, Fred D. Lublin, Xavier Montalban, Paul Oconnor, Magnhild Sandberg-Wollheim, Alan J. Thompson, Emmanuelle Waubant, Brian Weinshenker, and Jerry S. Wolinsky. "Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria." Annals of Neurology 69.2 (2011): 292-302. Web.
15. Filippi, Massimo, Maria A. Rocca, Olga Ciccarelli, Nicola De Stefano, Nikos Evangelou, Ludwig Kappos, Alex Rovira, Jaume Sastre-Garriga, Mar Tintorè, Jette L. Frederiksen, Claudio Gasperini, Jacqueline Palace, Daniel S. Reich, Brenda Banwell, Xavier Montalban, and Frederik Barkhof. "MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines." The Lancet Neurology 15.3 (2016): 292-303. Web.

16. Beck, Roy W. "Brain Magnetic Resonance Imaging in Acute Optic Neuritis." Archives of Neurology 50.8 (1993): 841-46. Web.
17. Optic Neuritis Study Group. "Multiple Sclerosis Risk After Optic Neuritis: final follow-up from the Optic Nueritis Treatment Trial" Archives of Neurology65.6 (2008): 727-32. Web.
18. Kupersmith, Mark J., Therese Alban, Barbara Zeiffer, Daniel Lefton. "Contrast-enhanced MRI in acute optic neuritis: relationship to visual performance." Brain 125.4. (2002) 812-822. Web.
19. Andreadou, E., S. Chatzipanagiotou, V.c. Constantinides, A. Rombos, E. Stamboulis, and C. Nicolaou. "Prevalence of cerebrospinal fluid oligoclonal IgG bands in Greek patients with clinically isolated syndrome and multiple sclerosis." Clinical Neurology and Neurosurgery 115.10 (2013): 2094-098. Web.
20. Tremlett, Helen, Yinshan Zhao, Peter Rieckman, Michal Hutchinson. "New perspectives in the natural history of multiple sclerosis." Neurology. 74. (2010) 2004-2015. Web.
21. Plavina, Tatiana, M Subramanyam, G Bloomgren, S Richman, A Pace, S Lee, B Schlain, D Campagnolo, S. Belachew, B Ticho. "Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy." Annals of Neurology (2014). Web.
22. "Progressive Multifocal Leukoencephalopathy/JC Vireus Infection." National Institutes of Health. U.S. Department of Health and Human Services , 7 May 2013. Web. 01 June 2017. <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0>.