Acute Optic Neuropathy & Residual Chiasmopathy due to Ethambutol therapy for Pulmonary Mycobacterium Avium Complex Infection.

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Abstract:
A case of Ethambutol toxicity in a 65 year old male resulting in an acute optic neuropathy & chronic chiasmopathy. We utilized regular follow-up, OCT and Humphrey's visual field for diagnosis and management.

Case History
-Patient demographics
In August 2005 a 61 year old white male presented to our eye clinic per request from his infectious disease specialist. The doctor requested a baseline eye exam prior to starting the patient on Ethambutol. The patient's medical history at that time was significant for Tobacco Use Disorder, COPD, Hyperlipidemia & Pulmonary Mycobacterium Avium Complex Infection. His medications were consistent with his medical conditions and included; Albuterol, Formoterol Fumarate, Flunisolide, Ciprofloxacin, Clarithromycin, Rifampin and Ethambutol.

-Exam Findings
Our patient's baseline exam in **Aug. 2005** showed normal refractive error & ocular health. Following his baseline exam the patient returned to our clinic **March 8th 2006** complaining of decreased vision at distance and near. Our exam showed a Snellen visual acuity (VA) correctable to 20/20 OD & OS. Confrontation visual fields (CVF) were Full to Fingercounting OD & OS. His pupils were equal, round & reactive to light without an afferent papillary defect (PERRL – APD). The Amsler grid was normal without metamorphopsia or scotoma. Ishihara color was full. The anterior segment was unremarkable & the posterior segment showed cup to disc ratios of .35/.35 OD and .4/.4 OS with scattered macular drusen OU. Our assessment was Ethambutol without ocular manifestations. We educated him to return immediately if he experienced sudden blurred vision or loss of color vision.

On **April 12th 2006** our patient presented complaining of vision fluctuation, dim vision, difficulty seeing traffic signals & colored shadows around words. He had discontinued Ethambutol due to visual symptoms. His visual acuity was 20/20 OD and slightly reduced OS measuring 20/25- not improving with pinhole. Pupils remained PERRL – APD. His Amsler Grid showed areas of dimness OD & OS. Color vision with Ishihara plates remained normal. The anterior segment was unremarkable & the posterior segment was unchanged. Due to visual symptoms a Sita Fast 24-2 Humphreys Visual Field (HVF) was preformed. It showed a superior temporal quadrantopsia with an enlarged blind spot OD (MD -5.45, PSD 3.89, GHT ONL) and a corresponding superior temporal quadrantopsia with a few superior nasal defects OS. (MD -5.36, PSD 3.10, GHT ONL). (See appendix B) Fundus photos were taken on this date. Upon review mild temporal pallor OD is noted. (See appendix A) Our assessment was Ethambutol use with questionable ocular manifestations. The case was discussed w/ the infectious disease doctor who advised the patient to discontinue Ethambutol. We educated the patient and requested a repeat visual field in one month.

The patient returned **May, 12th 2006** for a repeat 24-2 HVF. He had remained off Ethambutol since the last exam. The HVF continued to show a superior temporal quadrantopsia which was slightly improved OD (MD -4.22, PSD 4.43, GHT ONL) and a superior temporal quadrantopsia with a few inferior defects, also improved OS. (MD -4.37, PSD 3.68, GHT ONL). (See appendix B)This test was reliable and did not correlate with the clinical appearance of the optic nerve head.

The patient returned for regular follow-up **September 12th 2006**. He felt his vision had returned to normal and he had been off Ethambutol therapy for 6 months. His VA was 20/20- OD & OS. His pupils were PERRL-APD. Areas of Dimness OD & OS persisted on the Amsler grid. The anterior segment was unremarkable & the posterior segment was unchanged. Intraocular pressure using Goldmann applanation was 11 mmHg OD & 13 mmHg OS. The 24-2 HVF showed a few superior defects OD, which continued to improve (MD -3.02, PSD 4.48, GHT ONL) and a few superior & inferior defects OS, also improved. (MD -3.92, PSD 3.64, GHT ONL). (See appendix B) Our assessment was Ethambutol use w/ improved visual symptoms & visual field. We planned a 6 month follow-up with visual field.

On **March 28th 2007** the patient returned as scheduled for follow-up. His VA was 20/20+ OD and 20/20 OS. Pupils were PERRL-APD. The Amsler Grid was negative OD & OS. Anterior segment remained unremarkable. Changes in the optic nerve appearance were noted, with a cup to disc OD of .45v/.4 with color vs contour difference and mild inferior temporal rim thinning. The cup to disc OS was measured slightly larger at.45/.45. The IOP was 11 mmHg OU. The 24-2 HVF showed mild superior temporal defects, improved OD. (MD -2.63, PSD 1.99, GHT Borderline) & mild superior defects, improved OS. (MD -3.86, PSD 2.31, GHT Borderline). (See appendix B) A Fast RNFL OCT scan was preformed showing inferior & temporal thinning OD with an average thickness of 74.81 microns & mild temporal thinning OS with an average thickness 86.36 microns. (See appendix C) Our Assessment was History of ocular complications from Ethambutol which continues to improve and normal tension glaucoma (NTG) suspect based on optic nerve appearance. Six month follow-up was again recommended.

The next follow-up was **Oct. 31st 2007**. The patient reported normal vision. The VA was 20/20 OD and 20/20- OS. Pupils were PERRL-APD. Amsler grid was negative OD & OS. Anterior & Posterior segments were unchanged. IOP was 8 mm Hg OD & 9 mm Hg OS. Systemic Beta-blocker???) Repeat fundus photos showed temporal pallor OU with OD more affected than OS. (See appendix A) A fast RNFL OCT showed inferior temporal thinning OD with average thickness of 72.03 and inferior temporal thinning OS with an average thickness of 73.28. It was worsened in both eyes but the left eye showed a significant increase in thinning. (See appendix C) The 24-2 HVF was clean OD (MD +0.95, GHT WNL) & essentially clean OS. (MD -2.39, GHT WNL). (See appendix B) Our assessment was Ethambutol vs. NTG and 6 month follow-up was recommended.

On **June 16th 2008** the patient returned for follow-up. Subjective vision was normal. The VA was 20/20- OD and 20/25- OS. CVF where Full to Fingercounting, pupils were PERRL-APD and Amsler Grid was negative OD & OS. The anterior and posterior segments were unremarkable. IOP was 10 mmHg OD and 9 mmHg OS. The fast RNFL OCT was stable OU showing borderline inferior temporal thinning OD with average thickness of 73.07 microns and borderline inferior temporal thinning OS with average thickness of 75.40 microns. (See appendix C). Our assessment was Ethambutol vs. NTG and 6 month follow-up was again recommended.

The patient returned to clinic **Dec. 8th 2008** for a regular exam. The VA was 20/20 OD & OS, Amsler grid was negative OD & OS and pupils were PERRL-APD. Anterior and posterior segments were unchanged. The IOP was 9 mmHg OD and 8 mmHg OS. The 24-2 HVF showed a few, shallow random defects OD (MD -1.05, PSD 1.92, GHT WNL) and a slightly enlarged blind spot OS (MD -1.34, PSD 2.41, GHT WNL). (See appendix B) Our assessment was Ethambutol vs. NTG and 6 month follow-up was recommended.

At the patients next six month follow-up on **June 12th 2009** the exam findings remained stable. His VA was 20/20- OD & OS, CVF were Full to finger counting, pupils were PERRL-APD and Amsler grid was negative. The anterior and posterior segments were unchanged. The IOP was 8 mmHg OD and 9 mmHg OS. The Fast RNFL OCT was stable showing thinning temporally and borderline inferior thinning OD with average thickness of 71.06 and thinning temporally OS with average thickness of 77.66. (See appendix C) Our assessment was Ethambutol vs. NTG and 6 month follow-up was recommended.

The patient's most recent exam was on **Jan. 27th 2010**. His VA was 20/25 PH20/20 OD and 20/20- OS, pupils were PERRL-APD, Amsler grid was negative OD & OS. The anterior and posterior segments were unchanged. IOP was 8 mmHg OD and 7 mmHg OS. The 24-2 HVF was worsened and resembled baseline. The right eye showed a superior temporal quadrantopsia (MD -3.66, PSD 5.41, GHT ONL) and the left eye also demonstrated a superior temporal quadrantopsia (MD -2.77, PSD 4.23, GHT ONL). (See appendix B) Our assessment was Ethambutol vs. NTG vs. Chiasm Lesion. We educated the patient and scheduled a neuro-ophthalmology consult and MRI.

-Radiology studies – MRI Brain

Impressions:
1. No acute intracranial process
2. Bilateral focal areas of T2 hyperintensity involving the deep periventricular white matter, centrum semi-oval, para-atrial & subcortical white matter, nonspecific, suggest nonspecific demyelinating process such as chronic microvascular dz but also MS, vasculitis or inflammatory process. Some of the lesions in the peri-atrial region may be affecting the optic tracts.

Differential diagnosis

-Pituitary Macroadenoma

The first differential to rule out in our patient was a pituitary macroadenoma due to a recurrence of a bitemporal, superior quadrantopsia. Pituitary adenomas are the most common intracranial tumor with neuro-ophthalmological findings. Adenomas have a tendency to involve the anterior chiasm first causing a superior temporal quadrantopsia. These visual field defects are progressive, as the tumor continues to grow the inferior temporal quadrants become involved. This diagnosis is typically confirmed with an MRI. If confirmed, an endocrinological evaluation is indicated because these tumors commonly secrete hormones such as; prolactin, FSH, TSH and growth hormones at high levels.[3] This diagnosis was ruled out in our patient due to a normal MRI and a non-progressive field defect.

-Normal Tension Glaucoma

Normal Tension Glaucoma is another differential. It is a variant of primary open angle glaucoma. The mechanism is unknown but is believed to be vascular in nature. It is diagnosed when the IOP is below 21mmHg in the presence of an open anterior chamber angle, an optic nerve with glaucomatous damage and a correlating visual field defect. Patients affected are typically older than those with POAG. Females are affected at a 2:1 ratio compared to males. The IOP is typically in the low teens, if pressure is asymmetric the damage is also asymmetric with more damage occurring in the eye with the higher IOP. Optic nerve findings specific to NTG are splinter hemorrhages and optic disc notching. Threshold visual fields commonly demonstrate defects that are deeper, steeper and localized closer to fixation. NTG is commonly asymmetric. A patient with unilateral field loss has a 40% chance of developing damage in the other eye within 5 years. The prognosis in NTG is variable. Without treatment 40% of patients will not progress. With treatment that lowers IOP by 30%, 80% of patients will not progress. [3] This diagnosis can not be completely ruled out in our patient, however the exam findings seem to correlate more closely with Ethambutol toxicity.

Discussion

-Mechanism of Action

The mechanism of action by which Ethambutol causes cellular toxicity resulting in an optic neuropathy/chiasmopathy remains unclear. The mechanism results from mitochondrial insufficiency in the nerve head fibers leading to impairment of axonal transport. The most cohesive theory is discussed below. The mitochondria are responsible for energy production through the process of oxidative phosphorylation. This pathway creates a proton gradient allowing electron transfer to oxygen and the production of ATP. Cytochrome C oxidase is a key enzyme in electron transport and requires copper as a cofactor. The metabolite of Ethambutol is a strong chelator of copper. This decreases available copper and energy production. The amount of ATP produced is then insufficient for axonal transport and the compensatory mechanisms produce free radicals. Free radicals are the most damaging to neurons with long, thin, unmylinated axons like those found in the papillomacular bundle. [1,2,4]

-Causative/Associated Factors

Ethambutol optic neuropathy is dose dependant. Higher doses result in a higher incidence of optic neuropathy. Commonly accepted incidence statistics are 50% of patients taking 60-100 mg/kg/day will be affected, 5-6% taking 25 mg/kg/day and only 1% taking 15 mg/kg/day. The normal dose for Ethambutol is 15 mg/kg/day, however if the patient has been treated previously for a mycobacterial

infection they are started on 25 mg/kg/day for 60 days and then lowered to the normal dose. 60-100 mg/kg/day is not indicated in the treatment of mycobacterium infections. [2]

It has been shown that additional disease states increase the incidence of optic neuropathy. Renal disease is the biggest factor for complications. 70% of each dose of Ethambutol is excreted by the kidneys. In patients with renal disease the dose and systemic concentration of Ethambutol must be monitored closely.[2]

-Common Clinical Features

Ethambutol optic neuropathy is typically bilateral & asymmetric. The toxicity is specific for small caliber papillomacular bundle axons causing an optic neuropathy with antrograde progression to involve the chiasm leading to a chiasmopathy. Optic Atrophy develops months after fibers are lost and is visible as temporal nerve head pallor due to papillomacular bundle involvement. When the chiasm becomes involved it most commonly affects the anterior chiasm first. The inferior nasal fibers cross in the anterior chiasm causing a superior temporal quadrantopsia. The onset of the optic neuropathy was previously thought to be 2-5 months after initiation of treatment. However, new analysis of cases shows presentation at an average of 235 days or about 8 months. The prognosis for these patients is hard to determine because some make a complete recovery while others suffer severe, permanent vision loss. [2,4,5,6]

Treatment, management

-Treatment

If a patient presents with symptoms or clinical signs consistent with Optic Neuropathy the most common treatment is to discontinue Ethambutol. Some clinicians use high dose vitamins for neuroprotection and systemic prednisone. With corticosteroid use the vision may recover more rapidly but the final level of improvement/impairment is the same. [5]

-Symptoms and Signs

Symptoms of optic neuropathy include but are not limited to; blurred vision, changes in color vision, and loss of central vision. Signs of an optic neuropathy include; decease in VA, acquired R/G or B/Y color changes, central scotoma, bitemporal visual field defect, temporal pallor with nerve fiber layer thinning, decreased contrast sensitivity, an abnormal visually evoked potential (VEP) and a normal MRI. Many patients on Ethambutol develop subclinical optic neuropathy which can be detected using contrast sensitivity and VEP. [2,4,5,6]

-Follow-up and Exam Components

Prior to initiating Ethambutol therapy a complete baseline exam is indicated. Following the exam, the patient should be educated on the symptoms of optic neuropathy and be given a take home Amsler grid to monitor for central scotoma. During treatment the literature recommends exams every 1-3 months and immediately at onset of symptoms. At every exam certain components are indicated. The clinician should measure visual acuity with pinhole. Check Amsler grid, color vision and contrast sensitivity monocularly. The pupils should be evaluated for an afferent papillary defect. A dilated fundus exam should be performed with special attention to the appearance of the optic nerve. Special testing should include regular Humphreys Visual Fields, Fast RNFL OCTs and a VEP if possible. [2,4,5,6]

Clinical Pearls

1. Even with regular exams, permanent & severe vision loss can occur.
2. When the chiasm is involved the visual field defect may not correspond to the optic nerve appearance.
3. Toxicity has an affinity for Papillo-macular Bundle & Anterior Chiasm.
4. Onset occurs around 8 months of treatment.
5. Symptoms may precede clinical signs.
6. Extra caution indicated in patients with renal disease.

Bibliography

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2. Fraunfelder, Frederick, Alfredo Sadun, and Terry Wood. "Update on ethambutol optic neuropathy." *Expert Opinion* 5.5 (2006): 615-618. Print.

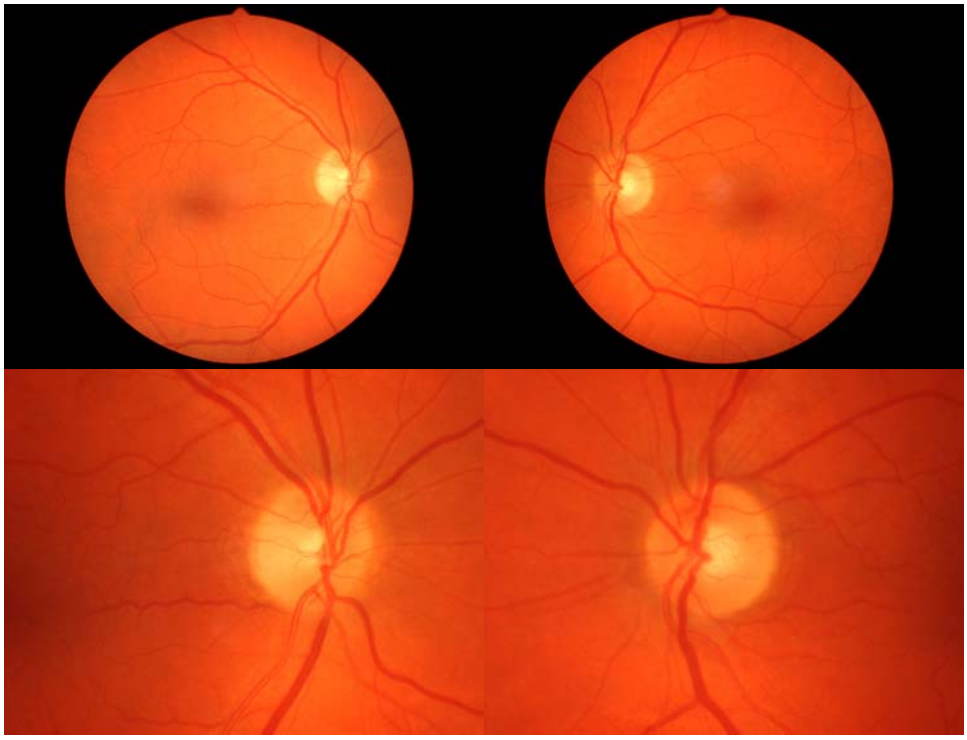
3. Kanski, Jack J. *Clinical Ophthalmology: a Systematic Approach*. Edinburgh: Butterworth-Heinemann/Elsevier, 2007. Print.

4. Melamud, Alex, Gregory Kosmorsky, and Michael Lee. "Ocular Ethambutol Toxicity." *Mayo Clin Proc* 78 (2003): 1409-1411. Print.

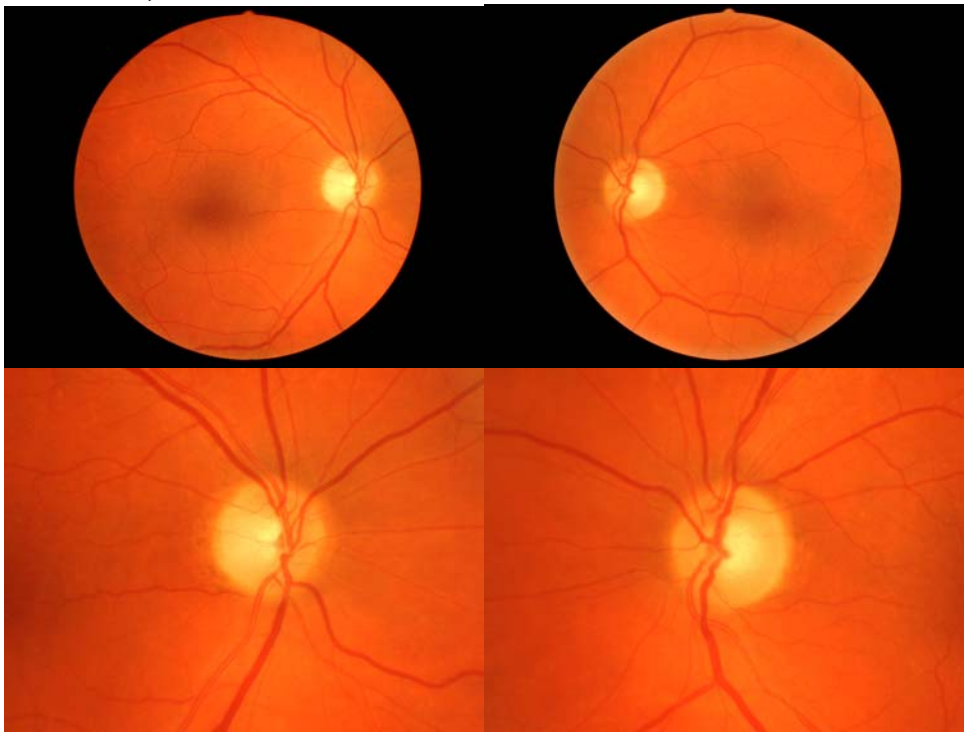
5. SB, Kokkada, Barthakur R, Natarajan M, Palaian S, Chhetri AK, and Mishra P. "Ocular side effects of antitubercular drugs-A focus on prevention, early detection and management." *Kathmandu University Medical Journal* 3.4 (2005): 438-441. Print.

6. Su-Ann, Lim. "Ethambutol-associated Optic Neuropathy." *Annals Academy of Medicine* 35.4 (2006): 274-278. Print.

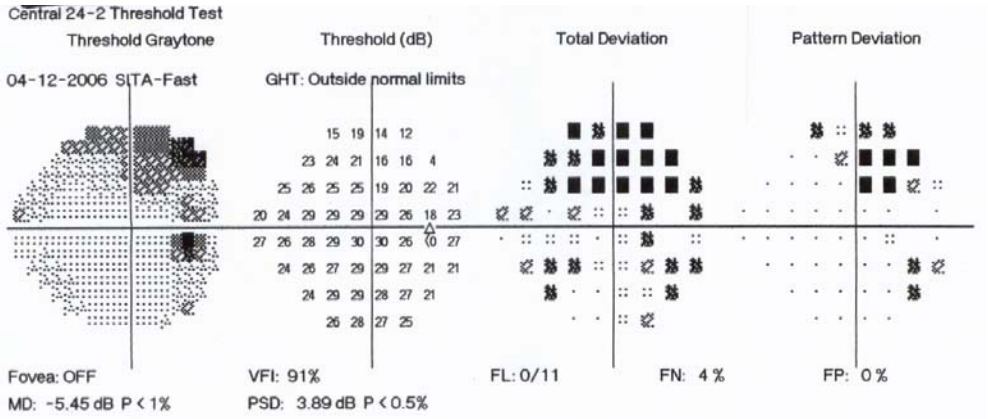
Imaging studies:
Appendix A-Fundus Photos
April 12th, 2006

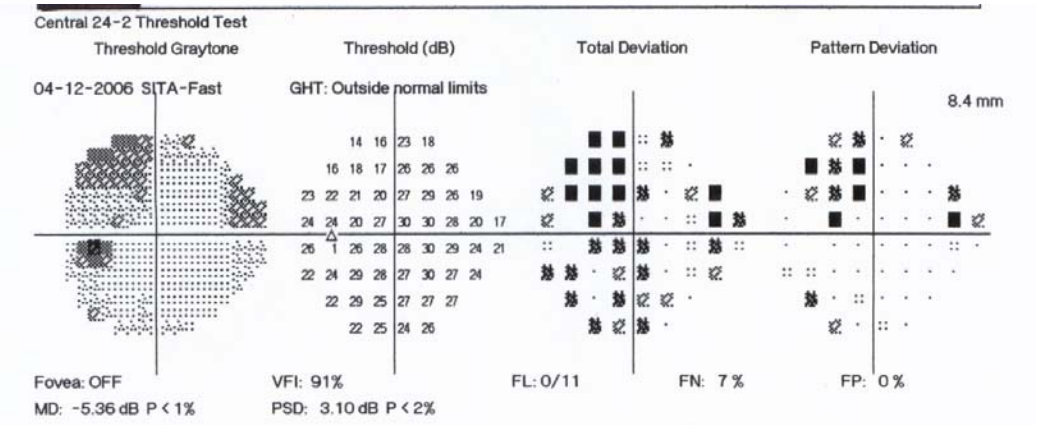


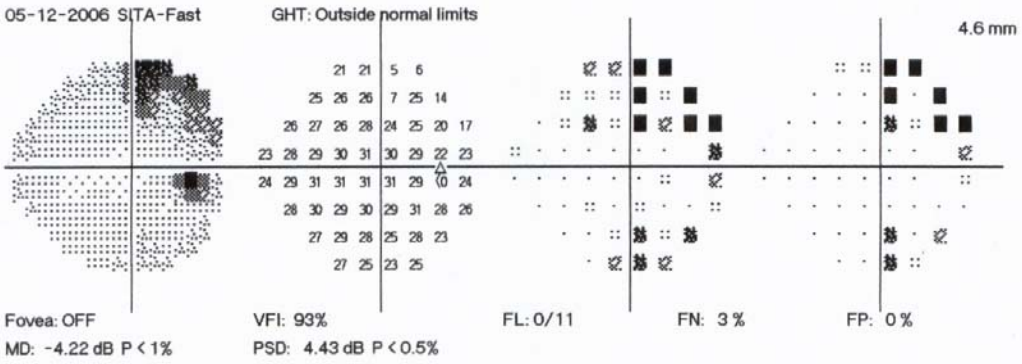
October 31st, 2007

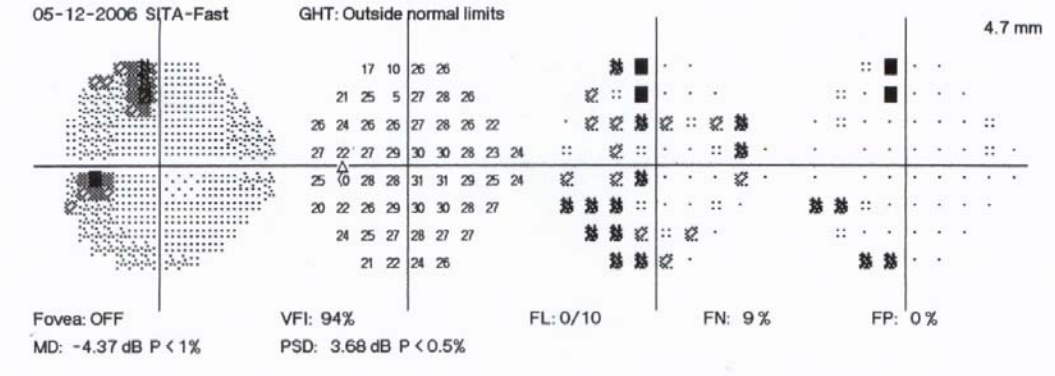


Appendix B-Serial 24-2 Humphrey's Visual Field


Central 24-2 Threshold Test
Threshold Graytone
Threshold (dB)
Total Deviation
Pattern Deviation
04-12-2006 SITA-Fast
GHT: Outside normal limits
Fovea: OFF
VFI: 91%
FL: 0/11
FN: 4 %
FP: 0 %
MD: -5.45 dB P < 1%
PSD: 3.89 dB P < 0.5%


Central 24-2 Threshold Test
Threshold Graytone
Threshold (dB)
Total Deviation
Pattern Deviation
04-12-2006 SITA-Fast
GHT: Outside normal limits
8.4 mm
Fovea: OFF
VFI: 91%
FL: 0/11
FN: 7 %
FP: 0 %
MD: -5.36 dB P < 1%
PSD: 3.10 dB P < 2%


05-12-2006 SITA-Fast
GHT: Outside normal limits
4.6 mm
Fovea: OFF
VFI: 93%
FL: 0/11
FN: 3 %
FP: 0 %
MD: -4.22 dB P < 1%
PSD: 4.43 dB P < 0.5%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GHT: Outside normal limits
4.7 mm
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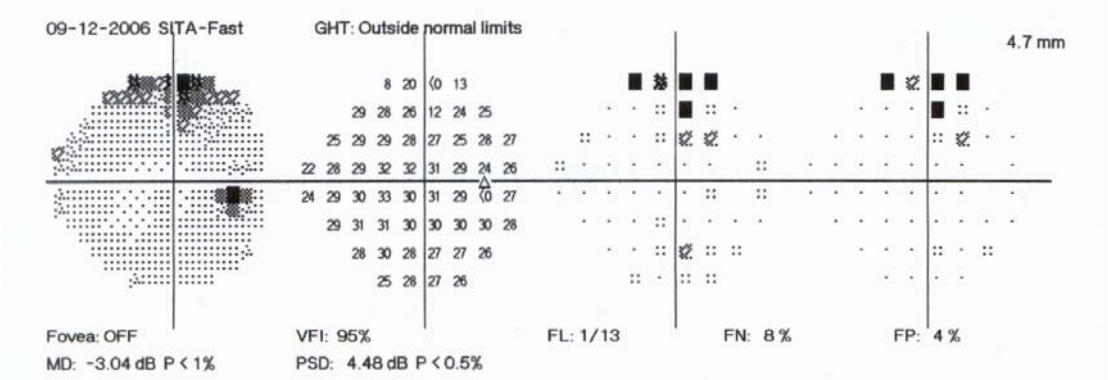
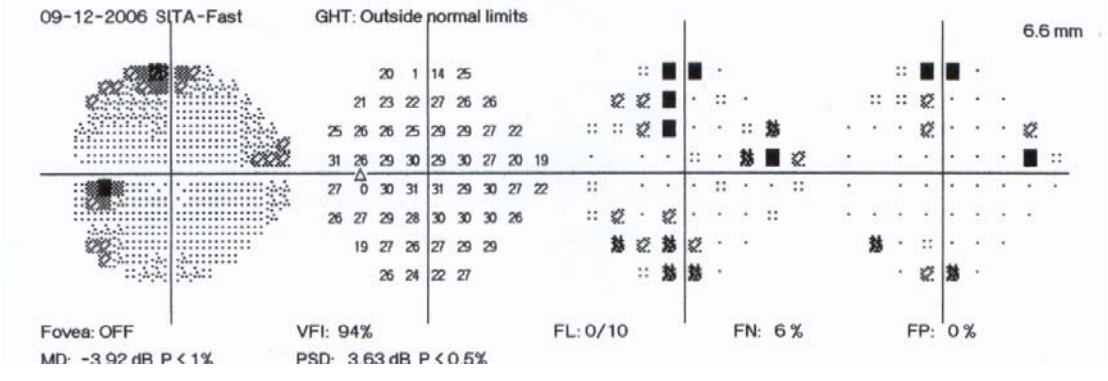
FN: 9 %
FP: 0 %
MD: -4.37 dB P < 1%
PSD: 3.68 dB P < 0.5%


09-12-2006 SITA-Fast
GHT: Outside normal limits
4.7 mm
Fovea: OFF
VFI: 95%
FL: 1/13
FN: 8 %
FP: 4 %
MD: -3.04 dB P < 1%
PSD: 4.48 dB P < 0.5%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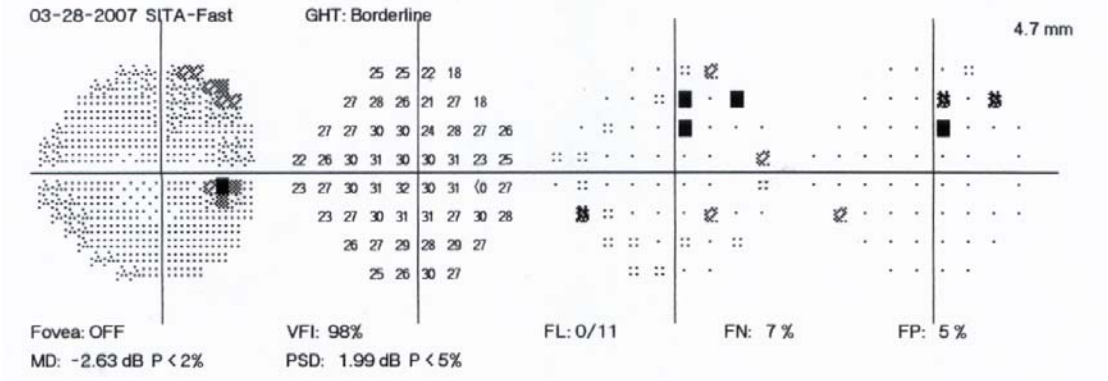
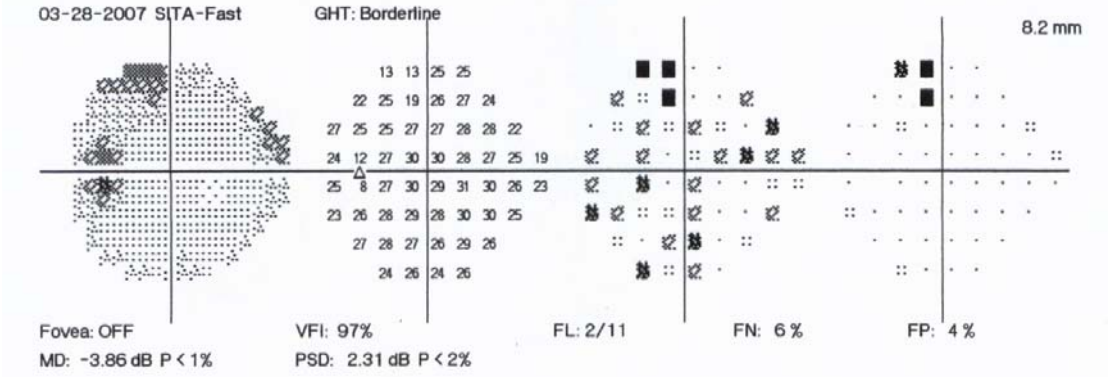
GHT: Outside normal limits
6.6 mm
Fovea: OFF
VFI: 94%
FL: 0/10
FN: 6 %
FP: 0 %


03-28-2007 SITA-Fast
GHT: Borderline
4.7 mm
Fovea: OFF
VFI: 98%
FL: 0/11
FN: 7 %
FP: 5 %
MD: -2.63 dB P < 2%
PSD: 1.99 dB P < 5%


03-28-2007 SITA-Fast
GHT: Borderline
8.2 mm
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VFI: 97%
FL: 2/11
FN: 6 %
FP: 4 %
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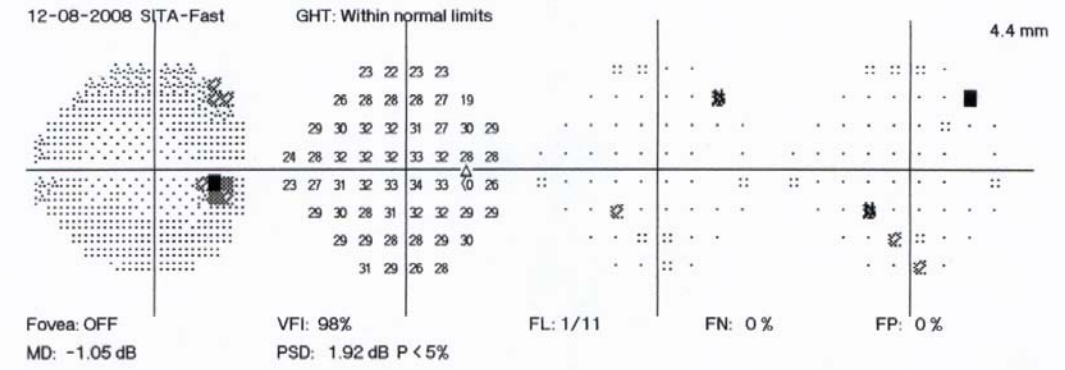
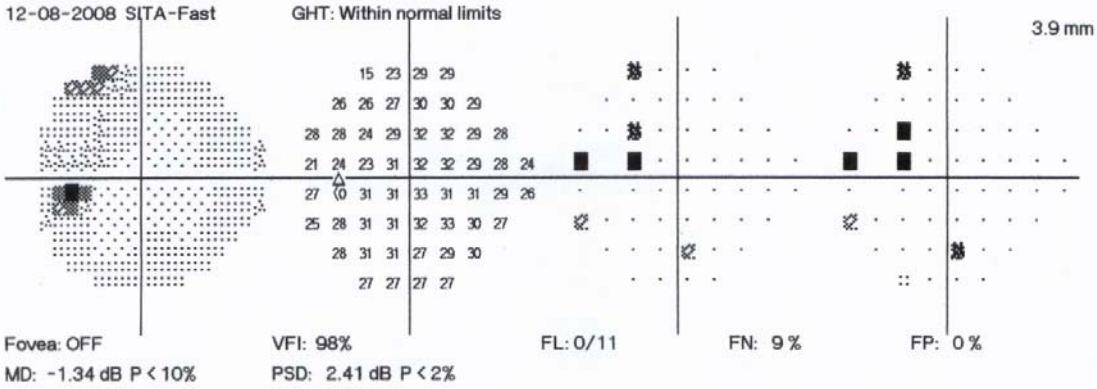
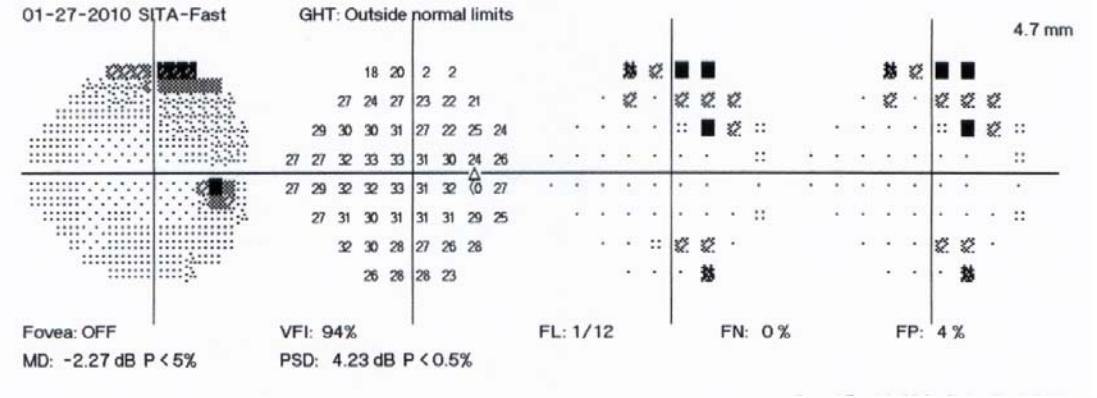
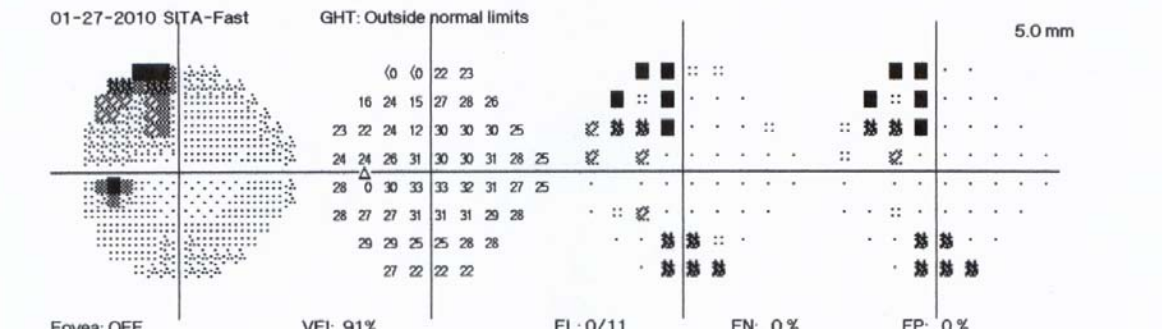
PSD: 2.31 dB P < 2%


12-08-2008 S[TA-Fast
GHT: Within normal limits
4.4 mm
23 22 23 23
26 28 28 28 27 19
29 30 32 32 31 27 30 29
24 28 32 32 32 33 32 28 28
23 27 31 32 33 34 33 26
29 30 28 31 32 32 29 29
29 29 28 28 29 30
31 29 26 28
Fovea: OFF
MD: -1.05 dB
VFI: 98%
PSD: 1.92 dB P < 5%
FL: 1/11
FN: 0 %
FP: 0 %


12-08-2008 S[TA-Fast
GHT: Within normal limits
3.9 mm
15 23 29 29
26 26 27 30 30 29
28 28 24 29 32 32 29 28
21 24 23 31 32 32 29 28 24
27 31 31 33 31 31 29 26
25 28 31 31 32 33 30 27
28 31 31 27 29 30
27 27 27 27
Fovea: OFF
MD: -1.34 dB P < 10%
VFI: 98%
PSD: 2.41 dB P < 2%
FL: 0/11
FN: 9 %
FP: 0 %


01-27-2010 S[TA-Fast
GHT: Outside normal limits
4.7 mm
18 20 2 2
27 24 27 23 22 21
29 30 30 31 27 22 25 24
27 27 32 33 33 31 30 24 26
27 29 32 32 33 31 32 27
27 31 30 31 31 31 29 25
32 30 28 27 26 28
26 28 28 23
Fovea: OFF
MD: -2.27 dB P < 5%
VFI: 94%
PSD: 4.23 dB P < 0.5%
FL: 1/12
FN: 0 %
FP: 4 %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GHT: Outside normal limits
5.0 mm
22 23
16 24 15 27 28 26
23 22 24 12 30 30 30 25
24 24 26 31 30 30 31 28 25
28 0 30 33 33 32 31 27 25
28 27 27 31 31 31 29 28
29 29 25 25 28 28
27 22 22 22
Fovea: OFF
VFI: 91%
FL: 0/11
FN: 0 %
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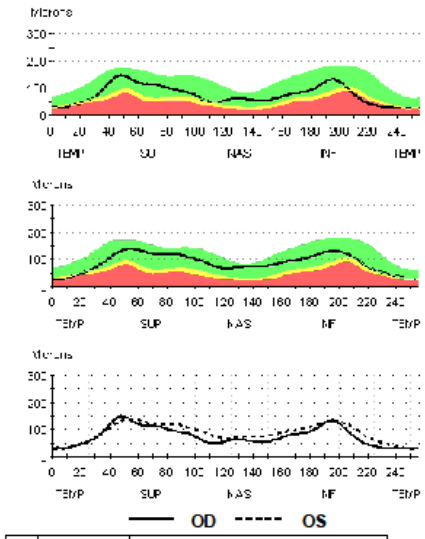
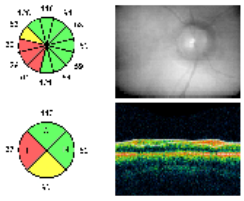
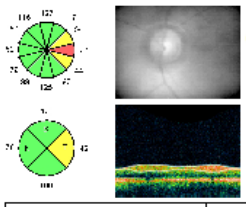
Appendix C-Fast RNFL OCT

March 28th 2007





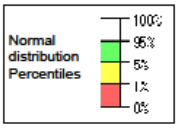
Signal Strength (max 10)	8



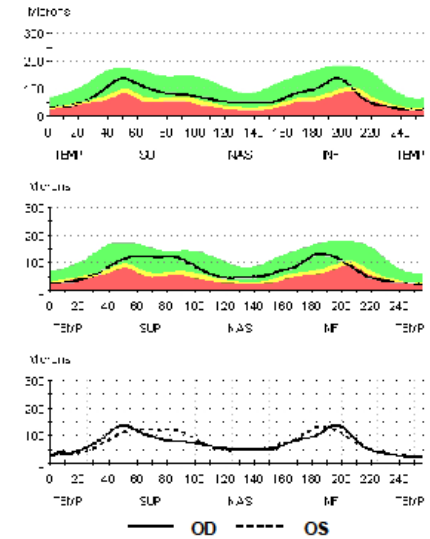
Signal Strength (Max 10)	7

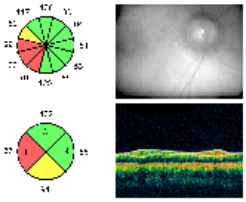
	OD (N=1)	OS (N=1)	OD-OS
Imax/Smax	0.90	0.95	-0.05
Imax/Imax	1.01	1.05	-0.05
Smax/Tavg	3.97	3.81	0.16
Imax/Tavg	3.56	3.14	0.42
Smax/Navg	2.50	1.72	0.79
MCX Vlf	120.00	113.00	7.00
Smax	148.00	137.00	11.00
Imax	132.00	130.00	2.00
Savg	113.00	120.00	-7.00
Iavg	92.00	106.00	-14.00
Avg.Thick	74.81	86.37	-11.56

OD	Scans used	1, 2, 3
OS	Scans used	1, 2, 3

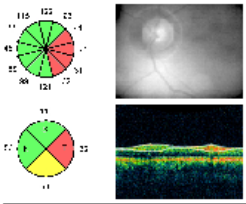


October 31st, 2007





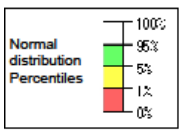
Signal Strength (max 10)	8



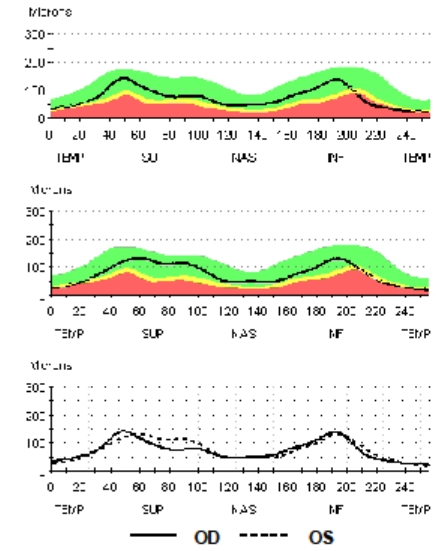
Signal Strength (Max 10)	6

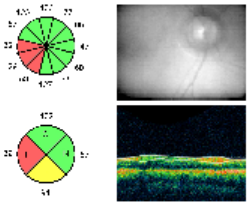
	OD (N=1)	OS (N=1)	OD-OS
Imax/Smax	1.01	1.07	-0.06
Imax/Imax	0.94	0.89	0.05
Smax/Tavg	3.64	3.78	-0.15
Imax/Tavg	3.60	4.03	-0.37
Smax/Navg	2.43	2.13	0.29
MCX Vlf	116.00	109.00	6.00
Smax	136.00	123.00	13.00
Imax	137.00	132.00	5.00
Savg	112.00	110.00	3.00
Iavg	94.00	84.00	9.00
Avg.Thick	72.03	73.28	-1.25

OD	Scans used	1, 2, 3
OS	Scans used	1, 2, 3

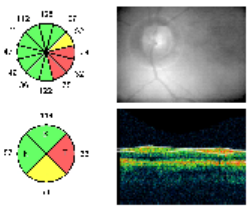


June 16th, 2008





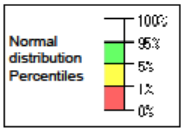
Signal Strength (Max: 10)	8



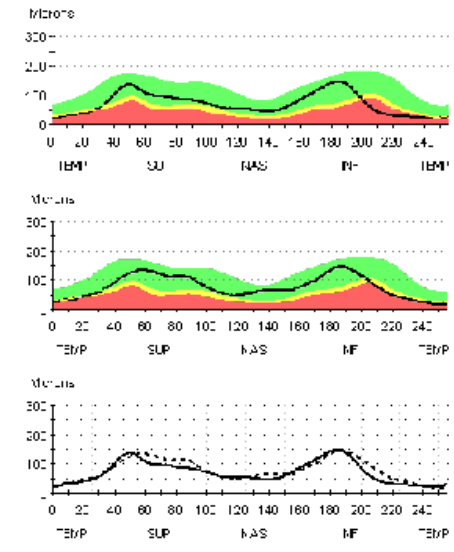
Signal Strength (Max: 10)	6

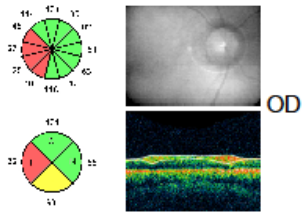
	OD (N=1)	OS (N=1)	OD-OS
Imax/Smax	0.97	0.93	0.03
Imax/Tmax	1.00	1.00	0.00
Smax/Tavg	3.62	3.65	-0.03
Imax/Tavg	3.62	3.58	0.04
Smax/Navg	2.47	2.31	0.17
MDX Min	118.00	113.00	5.00
Smax	142.00	137.00	5.00
Imax	138.00	128.00	10.00
Savg	122.00	114.00	8.00
Iavg	94.00	84.00	10.00
Avg.Thick	73.07	75.41	-2.34

OD	Scans used	1, 2, 3
OS	Scans used	1, 2, 3

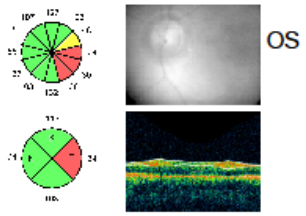


June 12th, 2009





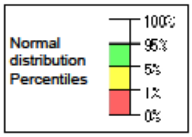
Signal Strength (Max: 10)	8



Signal Strength (Max: 10)	6

	OD (N=1)	OS (N=1)	OD-OS
Imax/Smax	1.07	1.08	-0.01
Imax/Tmax	90	119	-29
Smax/Tavg	4.24	3.94	0.30
Imax/Tavg	4.66	4.28	0.39
Smax/Navg	2.34	2.19	0.15
MDX Min	126.00	128.00	-2.00
Smax	137.00	134.00	3.00
Imax	146.00	146.00	0.00
Savg	121.00	113.00	8.00
Iavg	93.00	103.00	-10.00
Avg.Thick	71.06	77.66	-6.60

OD	Scans used	1, 2, 3
OS	Scans used	1, 2, 3



Appendix D: Fast RNFL Serial Analysis