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Optical coherence tomography: A role in monitoring multiple sclerosis

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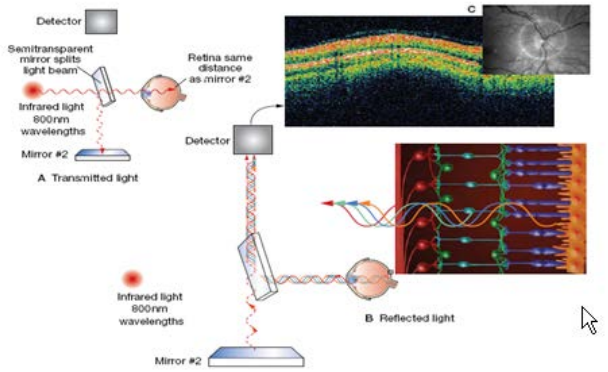
London , 17.10.2013

Optical coherence tomography

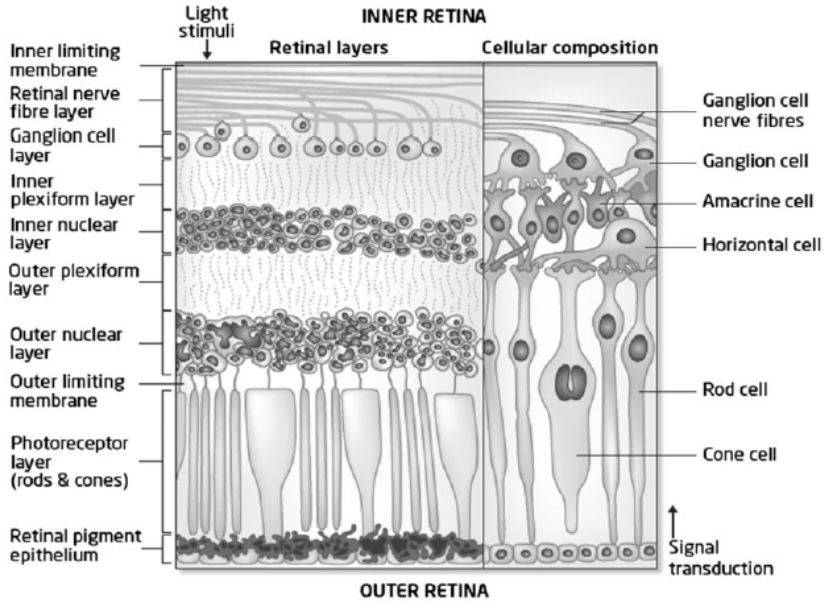
- Quick, non-invasive, quantitative, reproducible, cheap technology
- High resolution images
- Correlation with clinical parameters
- Sensible to longitudinal changes
- Creates precise image of retinal structures
- Enables the quantification of axonal and neuronal layers of the retina



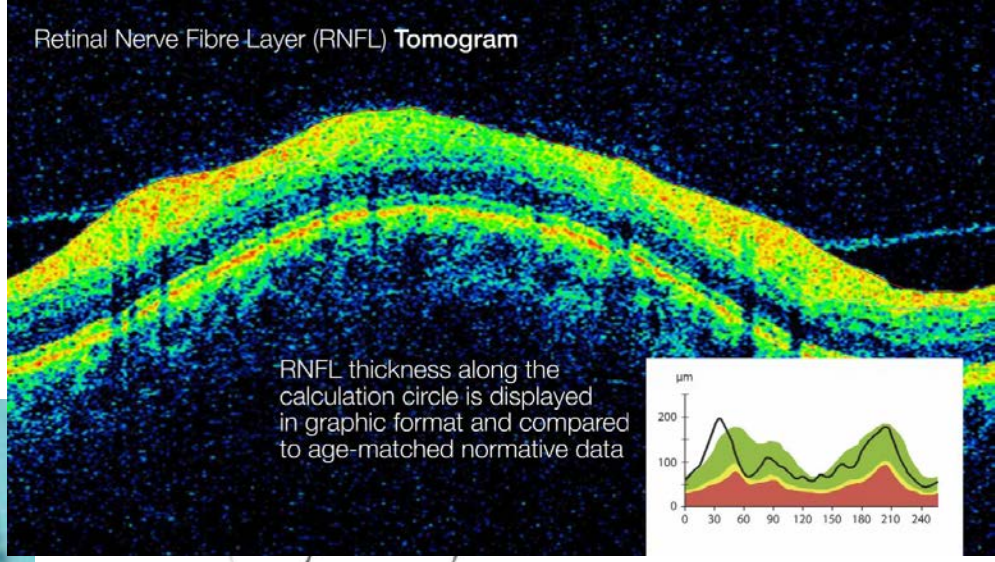
The OCT is useful to quantify the thickness of retinal nerve fiber layer (RNFL) and the macula.

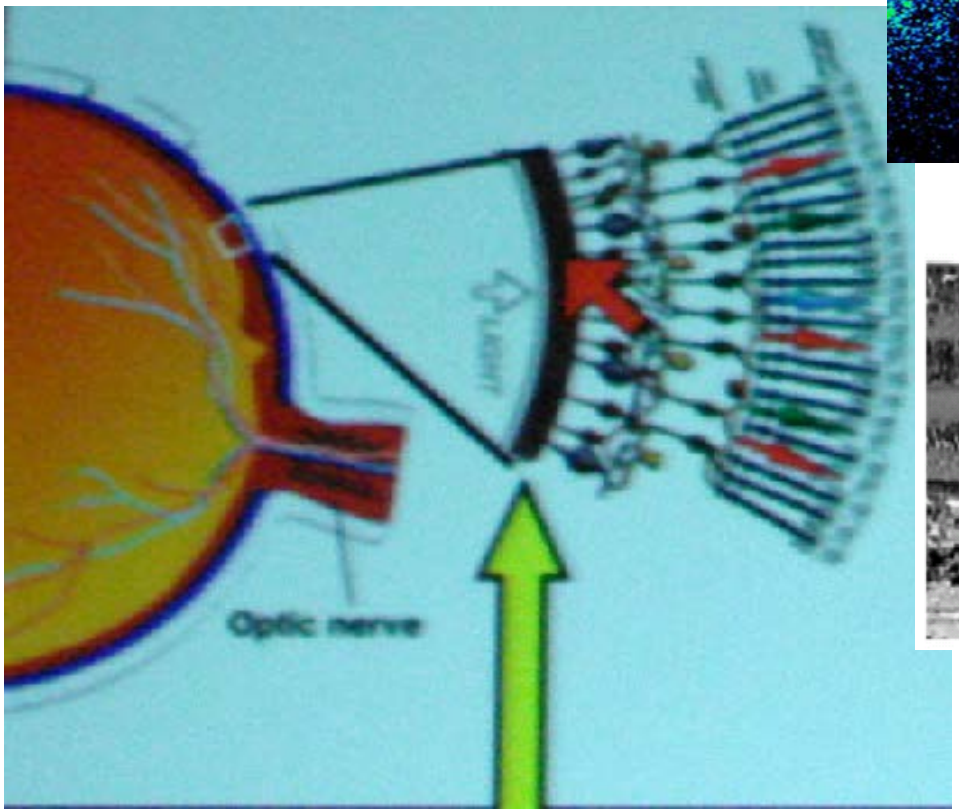
The spectral-domain OCT (fourth generation) is capable of visualizing and quantifying specific layers of the retina with impressive precision.

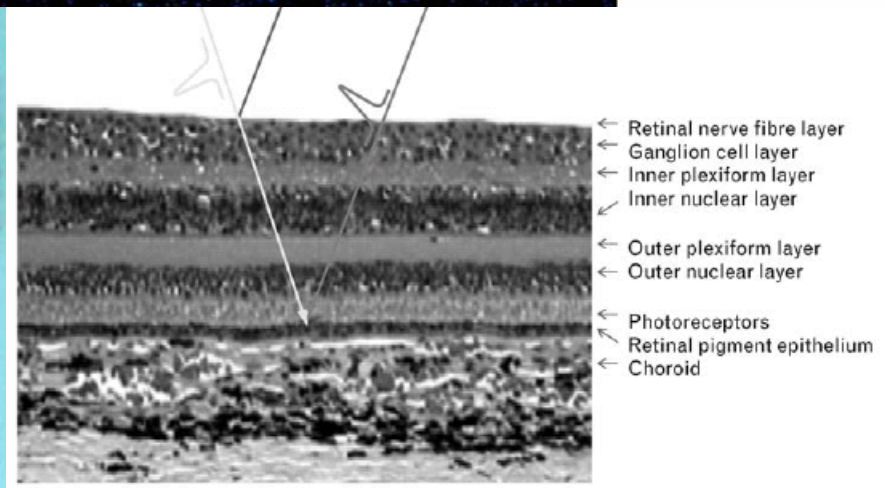
The use of OCT to quantify axonal loss is a promising tool to evaluate the disease progression in MS.



Visual pathway



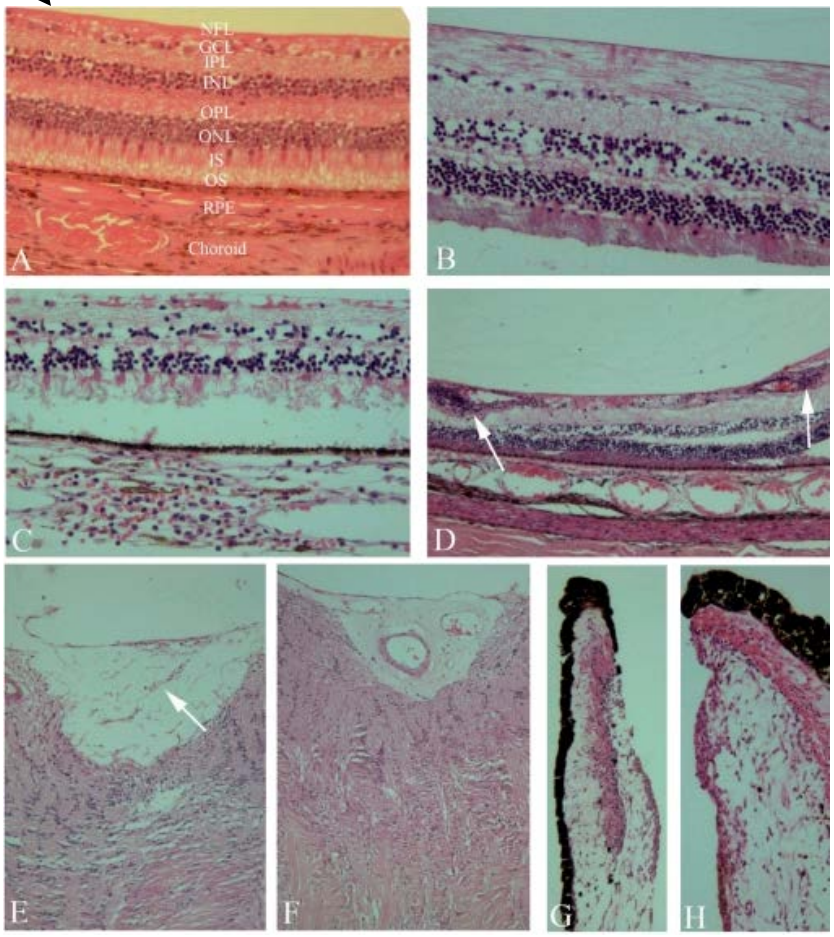




Retinal Nerve Fiber Layer (RNFL)

EVIDENCES OF LOSS OF RNFL

Healthy volunteers



Green. Et al, Brain 2010

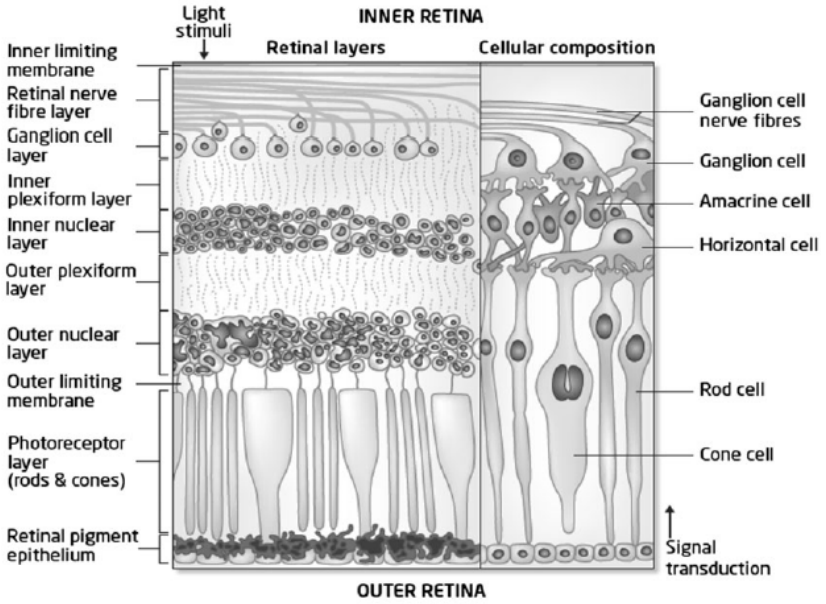
The loss of RNFL is confirmed in different studies:

- In vivo (Saidha et al, Brain 2011; Syc et al., Brain 2011)

- in animals(Levkovitch et al. 2001)

- electrophysiological (Davison et al., 1982; Kaufman et al. 1985)

- Postmortem (Green, 2010; Kerrison et al., 1994)



Prospects for OCT in MS

– biomarker of disease prognosis

– monitoring disease course

– Defining response to therapy

OCT can measure (colour code) :

- Acute phase:

papiledema = RNFL

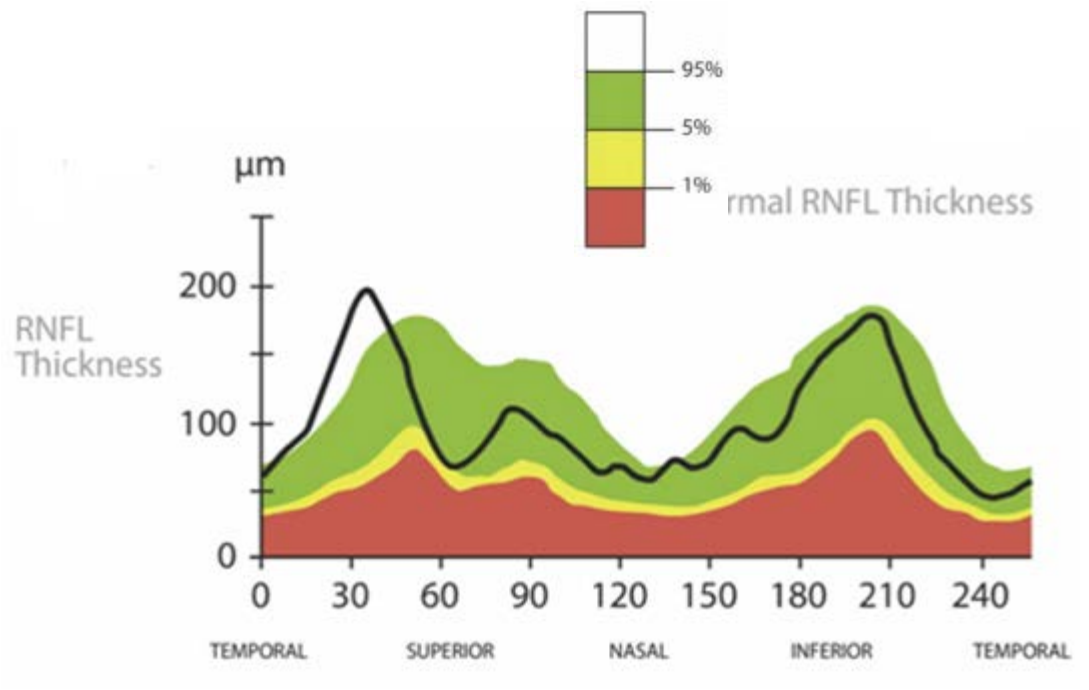
- Chronic phase: RNFL

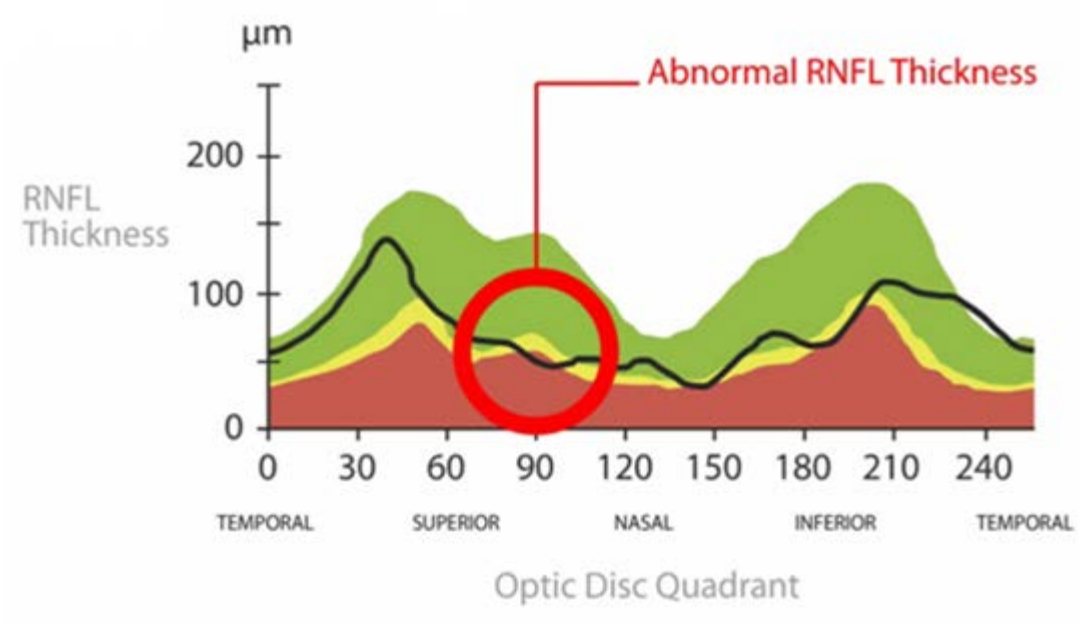
There is a predominance temporal quadrant .

The thickness of RNFL by month 3 (stable> 6 mo.)

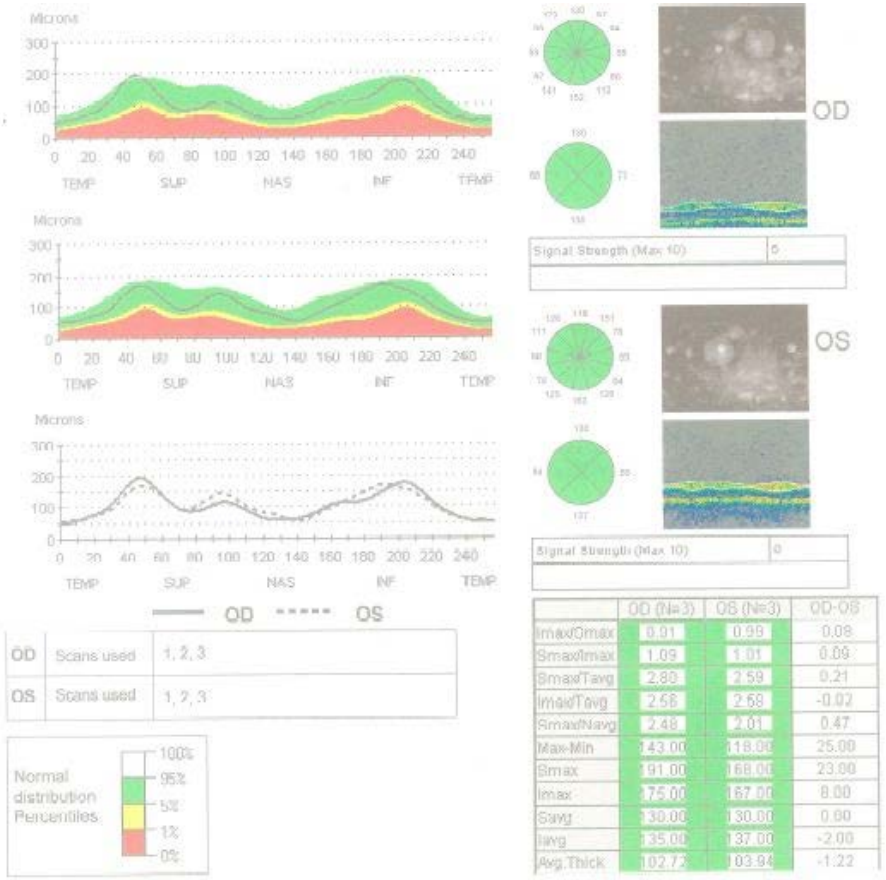
• RNFL thickness by mo. 6

predicts disability (<75 µm)

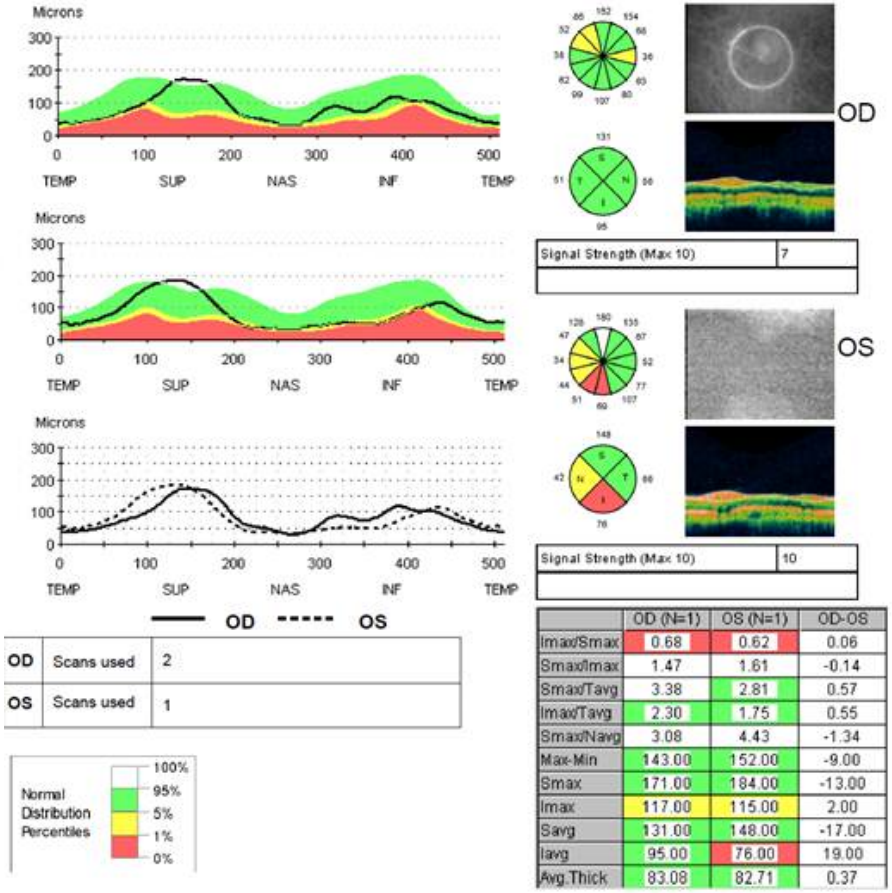




OCT normal



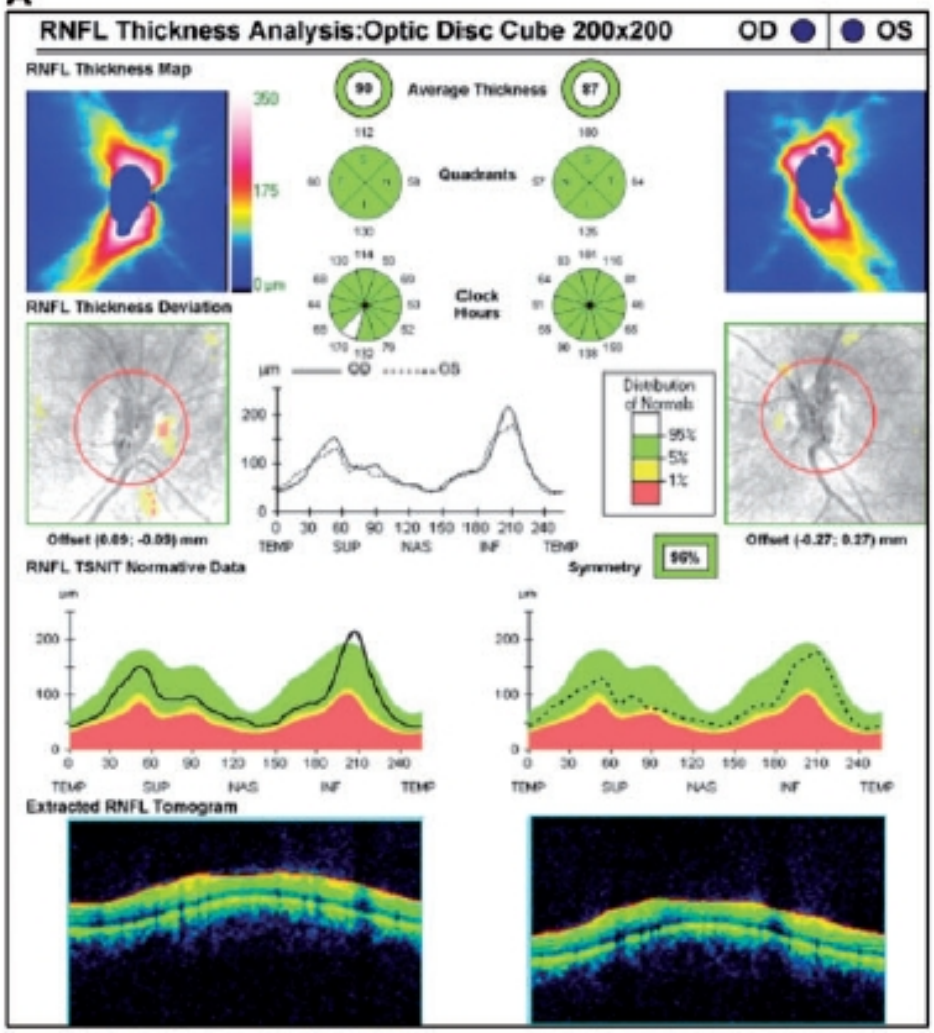
	OD (N=3)	OS (N=3)	OD-OS
Imax/Smax	0.91	0.99	0.08
Smax/Imax	1.09	1.01	0.09
Smax/Tavg	2.80	2.59	0.21
Imax/Tavg	2.56	2.58	-0.02
Smax/Navg	2.48	2.01	0.47
Max-Min	143.00	118.00	25.00
Smax	191.00	168.00	23.00
Imax	175.00	167.00	8.00
Savg	130.00	130.00	0.00
Iavg	135.00	137.00	-2.00
Avg.Thick	102.72	103.94	-1.22



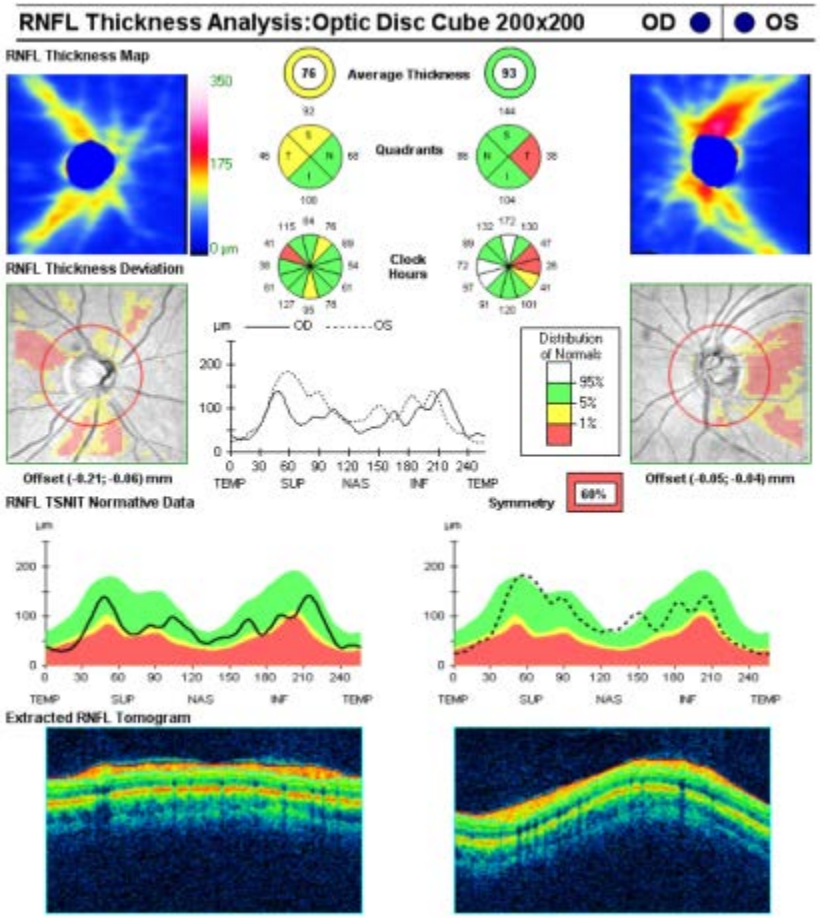
	OD (N=1)	OS (N=1)	OD-OS
Imax/Smax	0.68	0.62	0.06
Smax/Imax	1.47	1.61	-0.14
Smax/Tavg	3.38	2.81	0.57
Imax/Tavg	2.30	1.75	0.55
Smax/Navg	3.08	4.43	-1.34
Max-Min	143.00	152.00	-9.00
Smax	171.00	184.00	-13.00
Imax	117.00	115.00	2.00
Savg	131.00	148.00	-17.00
Iavg	95.00	76.00	19.00
Avg.Thick	83.08	82.71	0.37

Pathological OCT

A

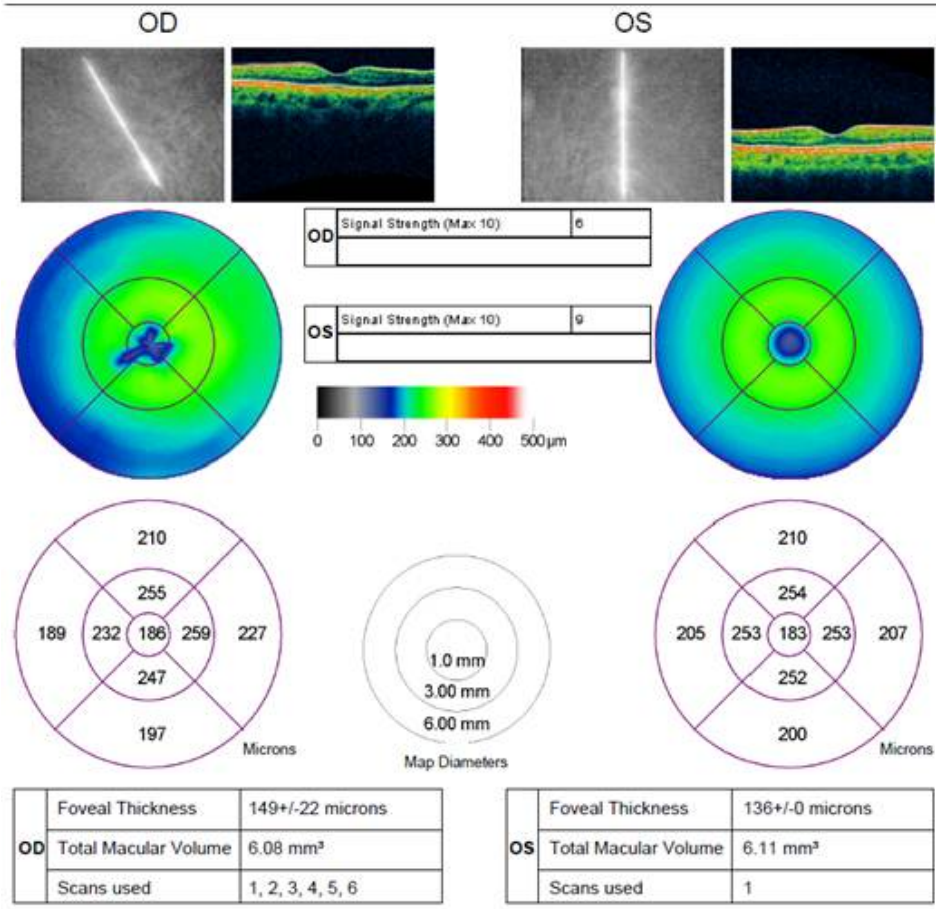


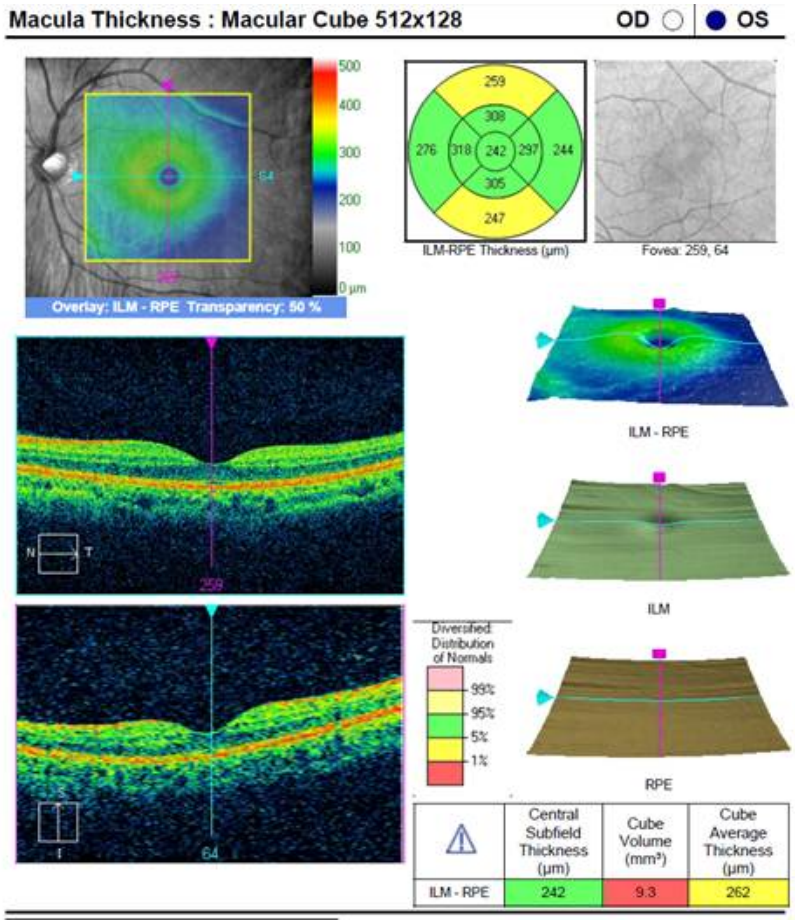
OCT normal



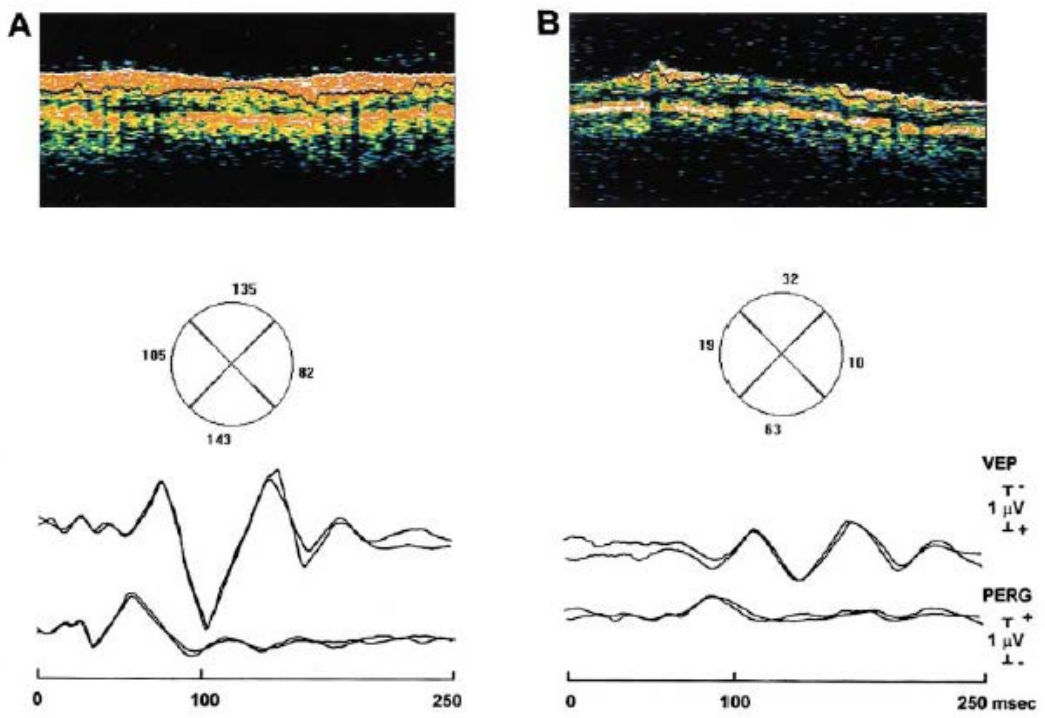
Pathological OCT

EXPLORATION OF MACULA





First OCT study in MS



Parisi, 1999

Significant reduction of RNFL thickness among the ON-eyes, MS- eyes and healthy controls. There is a correlation between PERG changes and NFL thickness in MS patients previously affected by optic neuritis, but there is no correlation between VEP changes and RNFL thickness

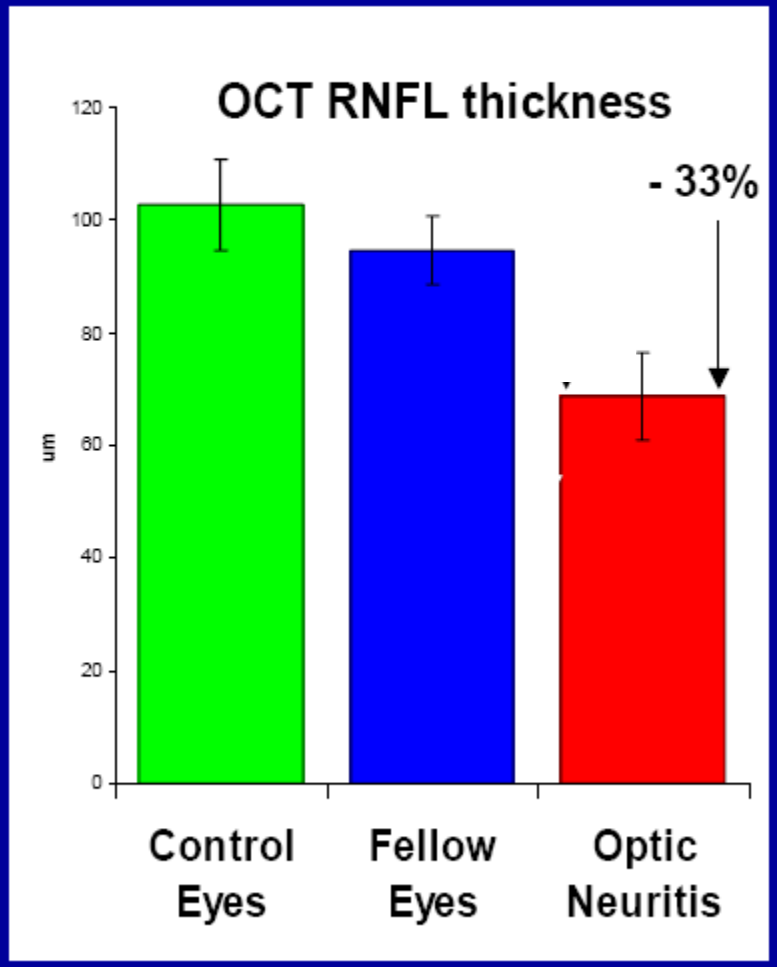
Meta-analysis (32 studies, Petzold et al., Lancet 2010)

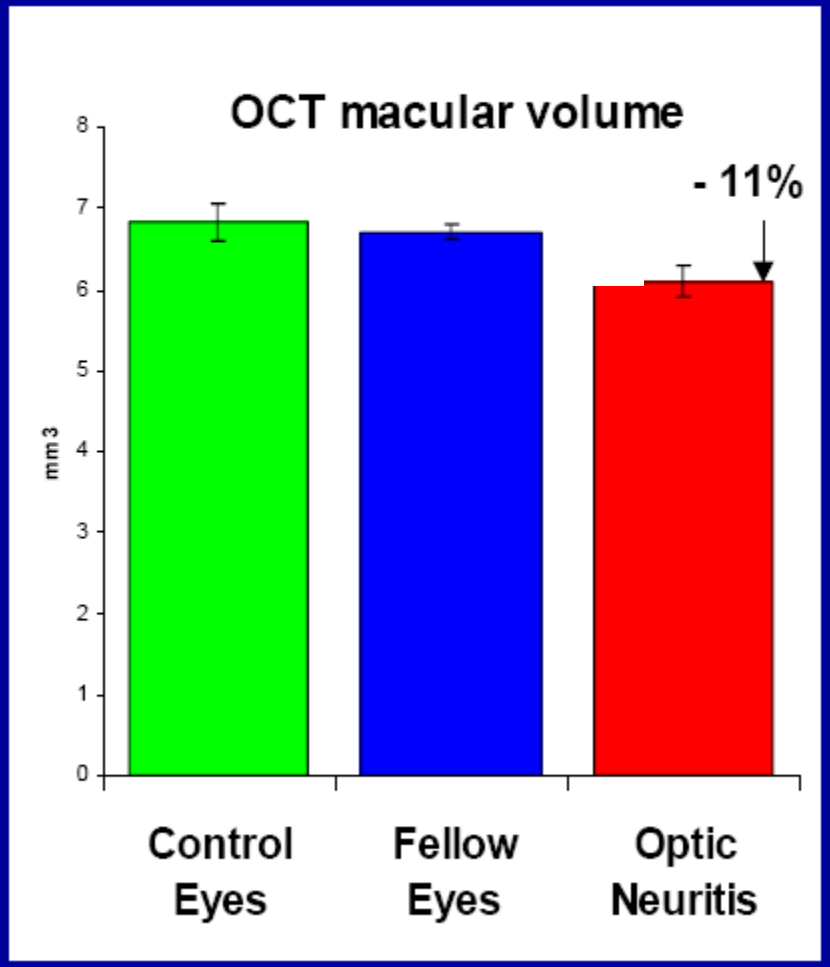
RNFL average in healthy controls 105 µm

MS-ON vs HS -20,38 µm

MS without ON vs HS -7,08 µm

25 patients > 1 year post optic neuritis with incomplete recovery vs 15 controls
~30% mean loss of RNFL, ~10% decrease in macular volume
(all differences compared to affected eyes: p < 0.001)





Trip et al Ann Neurol 2005

OCT IN OPTIC NEURITIS

AXONAL LOSS IN MS EVEN WITHOUT ACUTE ON

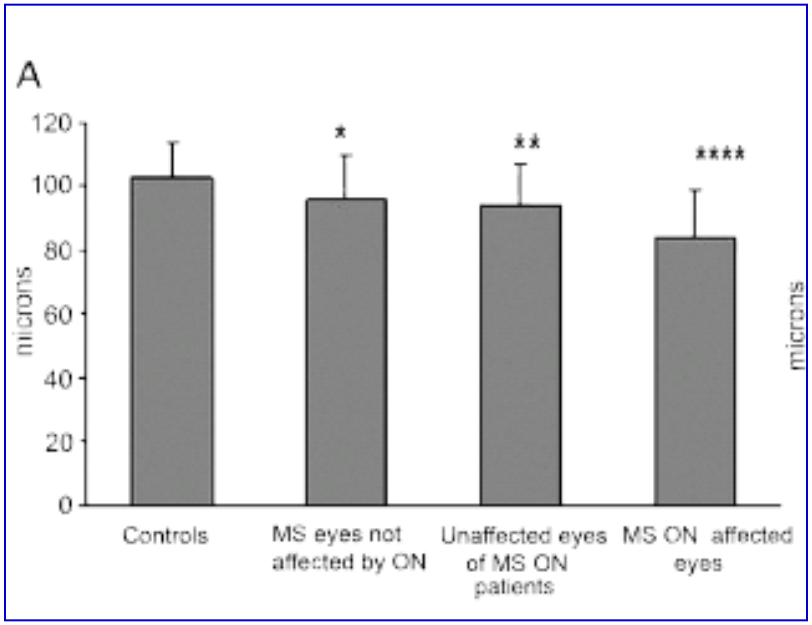
Tabla 3 Pacientes con atrofia de la capa de fibras nerviosas

	G1	G2	G3	Total
Ojo afecto (χ^2, p = 0,07)				
Sin atrofia	8 (42,1%)	3 (25%)	12 (66,7%)	23 (46,9%)
Con atrofia	11 (57,9%)	9 (75%)	6 (33,3%)	26 (53,1%)
Ojo contralateral (χ^2, p = 0,007)				
Sin atrofia	17 (100%)	6 (54,5%)	10 (58,8%)	33 (73,3%)
Con atrofia	0	5 (45,5%)	7 (41,2%)	12 (26,7%)

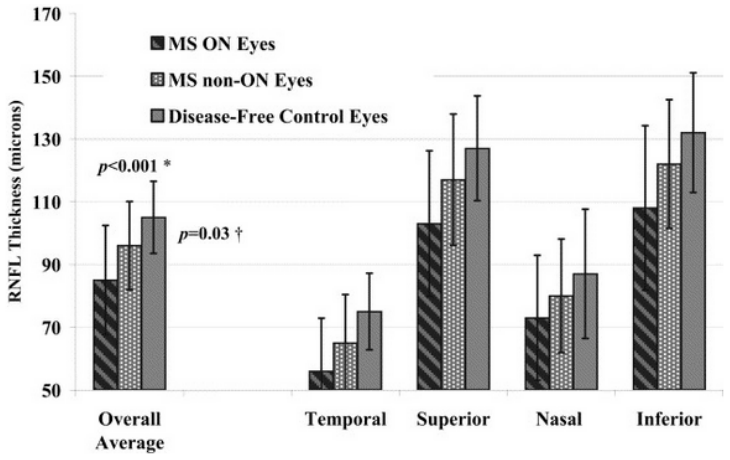
Se considera atrofia cuando el grosor medio está por debajo del percentil 5 en comparación con la base de datos normalizada.

G1: NO, G2: EM+NO , G3: EM

Oreja-Guevara C et. al, 2010

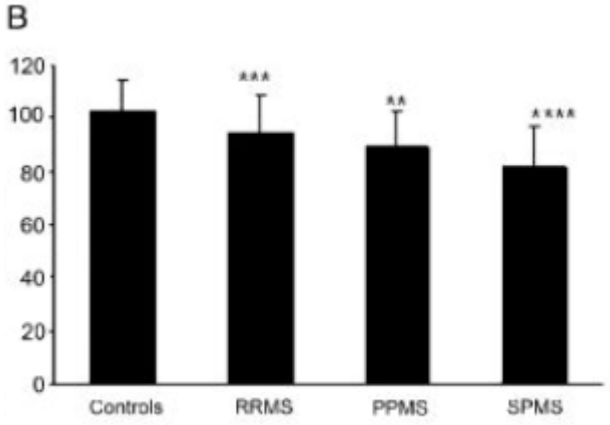


Pulicken, 2007

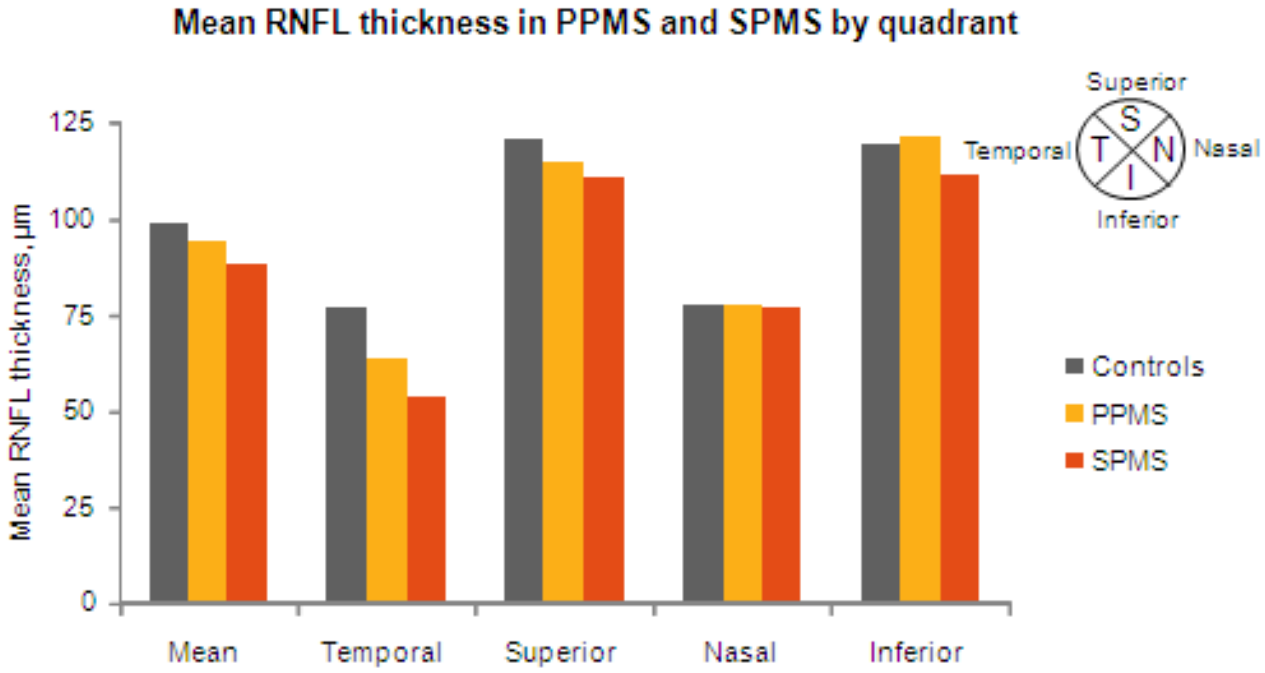


Fisher, 2007

AXONAL LOSS IN ALL SUBTYPES OF MS



Pulicken, 2007



Henderson et al., Brain 2008

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Clinically Isolated Syndromes Suggestive of Multiple Sclerosis: An Optical Coherence Tomography Study

Celia Oreja-Guevara[1]*, Susana Noval[2], Juan Alvarez-Linera[3], Laura Gabaldón[4], Beatriz Manzano[2], Beatriz Chamorro[1], Exuperio Diez-Tejedor[1]

Table 2. Crosstabulation between the two different criteria of spatial dissemination applied and OCT findings.

	Quadrants <5%		Quadrants <1%		
DIS MRI criteria	**None**	**≥1**	**None**	**≥1**	**Total**
Fulfilled	2	6	4	4	8
Not fulfilled	9	7	13	3	16
Total	11	13	17	7	24
Alternative criteria	**Quadrants <5%**		**Quadrants <1%**		
(OCB+ at least two lesions in MRI)	**None**	**≥1**	**None**	**≥1**	**Total**
Fulfilled	3	6	6	3	9
Not fulfilled	5	7	8	4	12
Total	8	13	14	7	21

DIS: dissemination in space; OCB: oligoclonal bands.
doi:10.1371/journal.pone.0033907.t002

Table 3. Sensibility and specificity for OCT findings according to MIR Barkhof criteria and MIR and OCB criteria for DIS.

	¾ Barkhof MIR criteria		MIR and OCB criteria	
	<5%	**<1%**	**<5%**	**<1%**
Sensitivity (%)	75	50%	66.67%	33.33%
Specificity (%)	56.25%	81.25%	58.33%	66.67%

doi:10.1371/journal.pone.0033907.t003

RNFL thickness is linked to disease activity in patients with Multiple Sclerosis

- Patients who experienced relapses had a significantly thinner average RNFL compared with those who remained relapse-free over a 2-year period
- Patients who had disease progression had a significantly thinner temporal RNFL compared with those who remained progression-free* over 2 years

	Relapse-free		Disability progression	
	Yes (42.8%)	No (57.2%)	No (69.0%)	Yes (31.0%)
Average RNFL				
Mean (SD) µm	87.5 (13.8)	**76.2 (14.1)****	83.5 (13.3)	76.6 (17.6)
Temporal RNFL				
Mean (SD) µm	59.0 (11.5)	54.3 (14.6)	61.0 (12.4)	**46.0 (9.1)****

**p<0.01

Toledo J *et al*. *Mult Scler* 2008

RNFL thickness is linked to progresion in MS

Table 6 Correlation between RNFL thickness and cognitive impairment

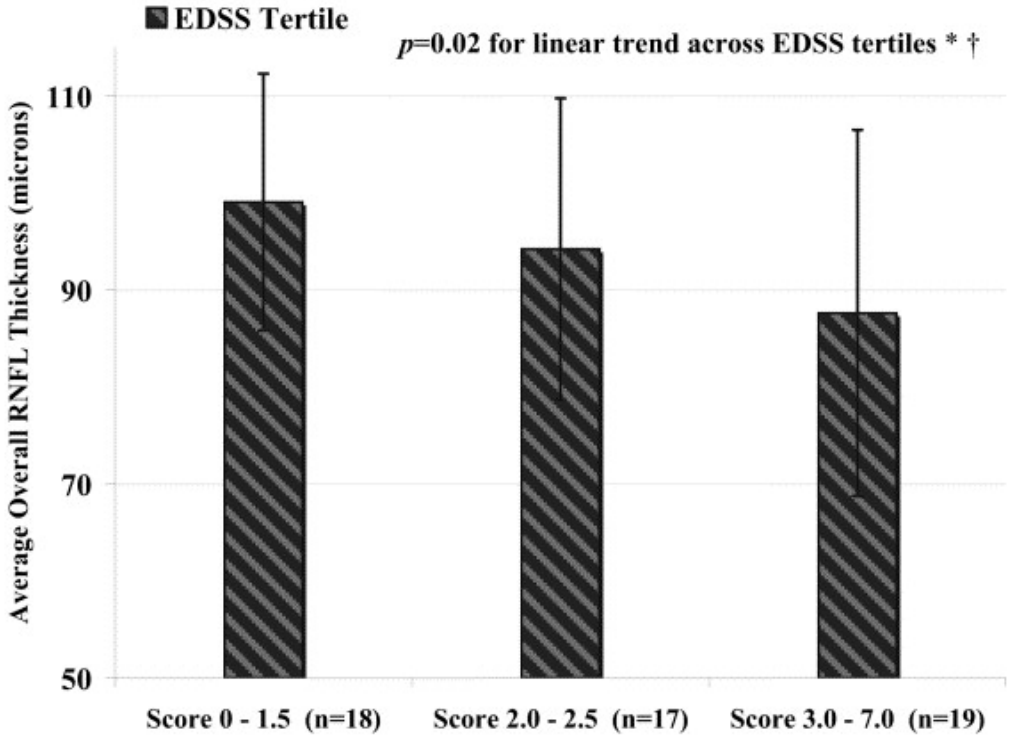
RNFL	Verbal memory			Visual memory		Executive and attention		Language fluency	
	SRT-S	SRT-R	SRT-D	SPART-S	SPART-D	SDMT	PASAT3	WLG-p	WLG-s
Average RNFL OCT	0.484*	0.247	0.220	0.428*	0.466*	0.463*	0.546**	0.195	0.214
Average RNFL HRT	0.032	0.226	0.001	0.009	0.056	0.174	0.139	−0.0323	0.045
Temporal RNFL OCT	0.441*	0.272	0.201	0.289	0.189	0.754***	0.268	0.176	0.141
Temporal superior RNFL HRT	0.113	0.205	0.061	0.174	0.157	0.175	0.250	−0.120	0.121

The degree of RNFL atrophy was correlated with cognitive disability,
mainly with the symbol digit modality test ($r = 0.754$, $P < 0.001$).
Moreover, temporal quadrant RNFL atrophy measured with OCT was associated
with physical disability.

Neurology, Toledo, 2008

	EDSS		MSFC	
	r	*P*	*r*	*P*
Average RNFL OCT	−0.399	0.010	0.227	0.158
Average RNFL HRT	−0.266	0.093	0.147	0.373
Temporal RNFL OCT	−0.587	0.00004	0.440	0.004
Temporal RNFL HRT	−0.370	0.017	0.048	0.771
Temporal superior RNFL HRT	−0.144	0.234	0.158	0.336
Temporal Inferior RNFL HRT	−0.235	0.139	0.265	0.103
Cup-disc area ratio HRT	0.241	0.129	−0.255	0.117
Rim-disc area ratio HRT	−0.020	0.900	−0.025	0.879
Global rim volume HRT	−0.399	0.010	0.227	0.158

RNFL thickness is linked to progresion in MS



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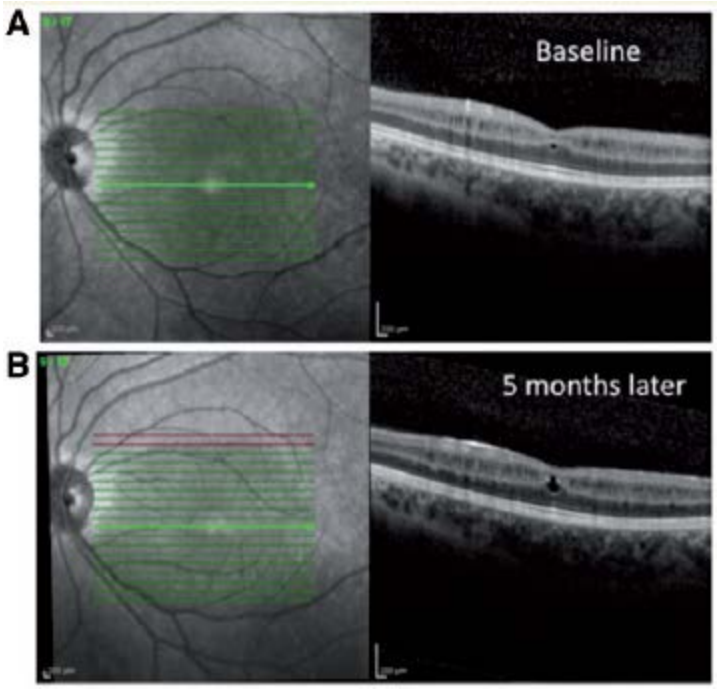
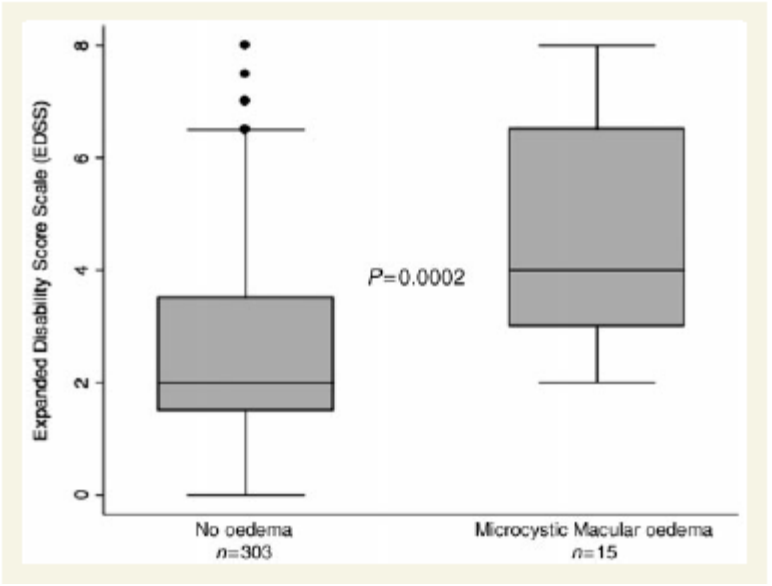
Fisher, 2007

Microcystic macular oedema in multiple sclerosis is associated with disease severity

Jeffrey M. Gelfand,[1] Rachel Nolan,[1] Daniel M. Schwartz,[2] Jennifer Graves[1] and Ari J. Green[1,3]





	Eyes without macular oedema ($n = 606$)	Eyes with microcystic macular oedema ($n = 20$)[a]	*P*-value
Prior symptomatic optic neuritis in that eye, *n* (%)	161 (27)	10 (50)	0.02[b]
Total RNFL thickness (μm), mean (SD)	87 (15)	66.7 (15.4)	<0.001[c]
Macular volume (mm^3), mean (SD)	3.01 (0.22)	2.9 (0.15)	0.12[c]
Foveal thickness (μm), mean (SD)	271.2 (21.9)	276.4 (28.8)	0.50[c]
Visual acuity (logMAR), median (IQR)	−0.1 (−0.1 to 0)	0.17 (0 to 0.4)	0.001[c] 0.03[d]

Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning

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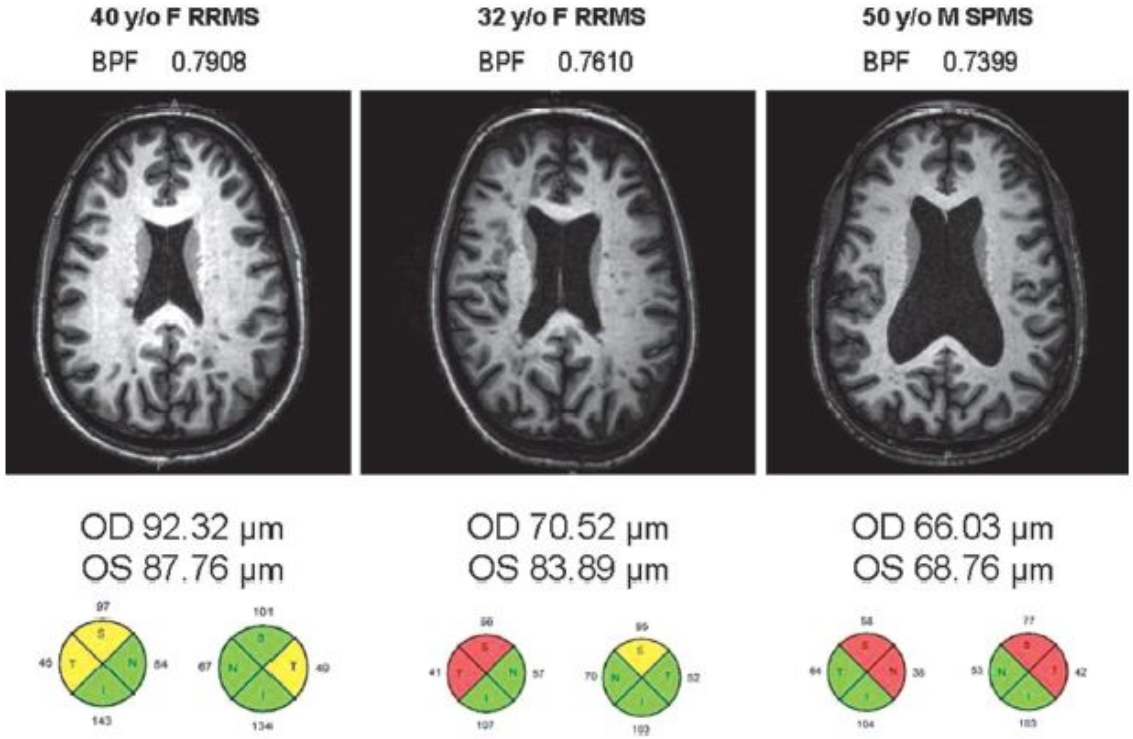
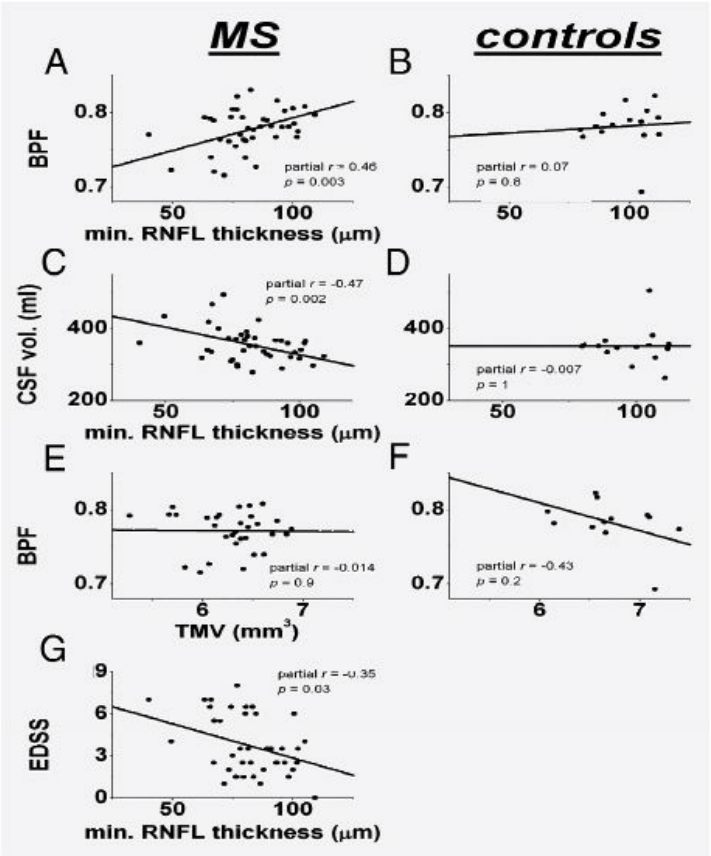
Elliot M. Frohman, MD, PhD
Peter A. Calabresi, MD

	All MS/CIS vs HCs	RRMS vs HCs	SPMS vs HCs	PPMS vs HCs	CIS vs HCs
RNFL difference, μm (*p* value)	−7.26 (<0.001)	−7.50 (<0.001)	−9.05 (0.01)	−2.16 (0.58)	−2.31 (0.57)
GCIP difference, μm (*p* value)	−9.97 (<0.001)	−9.90 (<0.001)	−12.82 (<0.001)	−7.05 (0.006)	−6.93 (0.006)
Letter acuity difference, 100% contrast (*p* value)	−2.15 (0.12)	−1.77 (0.24)	−2.17 (0.25)	−4.10 (0.07)	−1.56 (0.42)
Letter acuity difference, 2.5% contrast (*p* value)	−5.32 (0.002)	−4.81 (0.007)	−2.31 (0.42)	−5.83 (0.08)	−9.92 (0.002)
Letter acuity difference, 1.25% contrast (*p* value)	−5.70 (<0.001)	−5.12 (0.004)	−4.76 (0.09)	−6.25 (0.04)	−5.48 (0.10)

Patients with more relapses, more new gd lesions and new T2 lesions had faster rates of annualized GCIP thinning. Macular GCIP thinning is more closely associated with radiologic and clinical measures of MS progression than is RNFL thinning.

Correlation between RNFL and brain atrophy





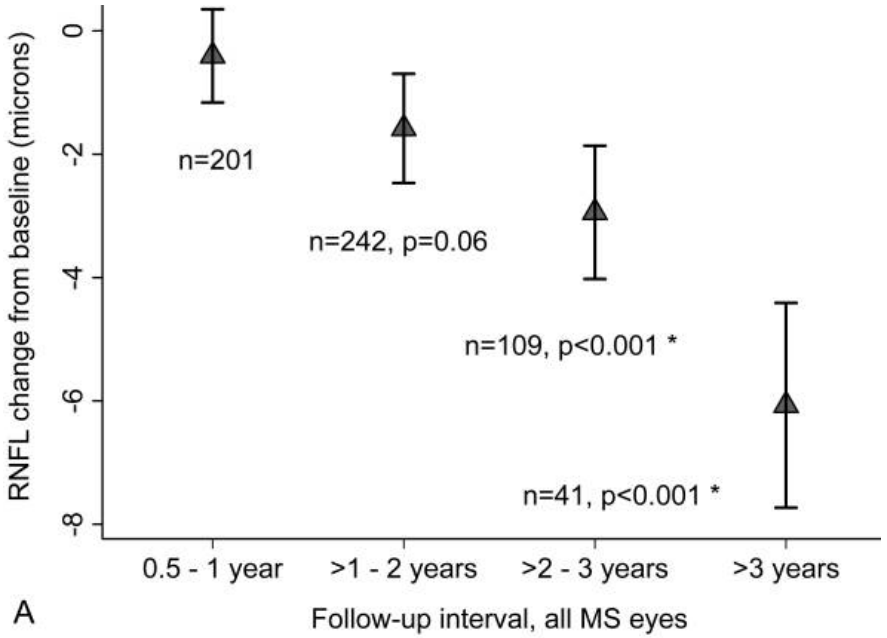
The thickness of RNFL is associated with the BPF (Gordon et al., 2007)

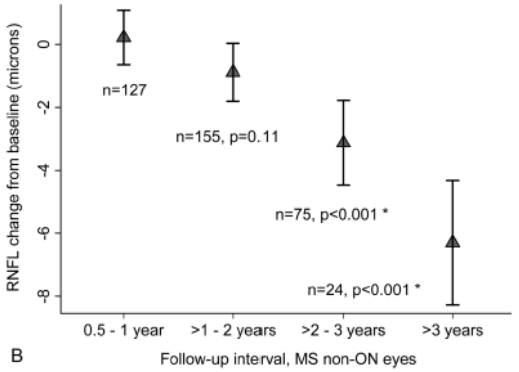
What happens to the RNFL over time in MS?

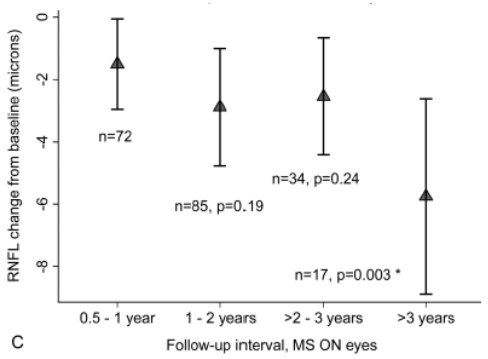
Longitudinal Study of Vision and Retinal Nerve Fiber Layer Thickness in MS

Lauren S. Talman, BA[1], Esther R. Bisker, MD[1], David J. Sackel, BS[1], David A. Long Jr., BS[1], Kristin M. Galetta, MS[1], John N. Ratchford, MD[5], Deacon J. Lile, BA[1], Sheena K. Farrell, BS[5], Michael J. Loguidice, BA[1], Gina Remington, BSN, RN[6], Amy Conger, COA[6], Teresa C. Frohman, BS[6], Dina A. Jacobs, MD[1], Clyde E. Markowitz, MD[1], Gary R. Cutter, PhD[7], Gui-Shuang Ying, PhD[3,4], Yang Dai, PhD[3,4], Maureen G. Maguire, PhD[3,4], Steven L. Galetta, MD[1,3], Elliot M. Frohman, MD, PhD[6], Peter A. Calabresi, MD[5], and Laura J. Balcer, MD, MSCE[1,2,3]

Ann Neurol. 2010 June ; 67(6): 749–760







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PLoS one

The OSCAR-IB Consensus Criteria for Retinal OCT Quality Assessment

Prejaas Tewarie[1], Lisanne Balk[1], Fiona Costello[2], Ari Green[3], Roland Martin[4¤], Sven Schippling[4¤], Axel Petzold[5]*

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Therapeutic Advances in Neurological Disorders *Review*

Optical coherence tomography as a potential readout in clinical trials

Benjamin M. Greenberg and Elliot Frohman

Ther Adv Neurol Disord

(2010) 3(3) 153–160

DOI: 10.1177/1756285610368890

Current trials using OCT

- MSC
- Fingolimod (safety)
- Ocrelizumab RRMS
- Anti-Lingo (AON)
- NT-KO-003
- AON (fingolimod)

Table 4 Sample size estimates for outcome measures (retinal nerve fibre layer thickness) at 12 months (panel a), 6 months (panel b) and 3 months (panel c) for a parallel-groups, placebo-controlled trial

Effect size	80% power			90% power		
	Method			Method		
	A	B	C	A	B	C
Panel a						
20	292	231	225	391	309	301
30	130	103	100	174	137	134
40	73	58	57	98	78	76
50	47	37	36	63	50	49
60	33	26	25	44	35	34
70	24	19	19	32	26	25
80	19	15	15	25	20	19
Panel b						
20	358	222	218	479	297	292
30	159	99	97	213	132	130
40	90	56	55	120	75	73
50	58	36	35	77	48	47
60	40	25	25	54	33	33
70	30	19	18	40	25	24
80	23	14	14	30	19	19
Panel c						
20	1024	608	596	1370	814	797
30	455	271	265	609	362	355
40	256	152	149	343	204	200
50	164	98	96	220	131	128
60	114	68	67	153	91	89
70	84	50	49	112	67	66
80	64	38	38	86	51	50

Clinical trial monitoring with MS

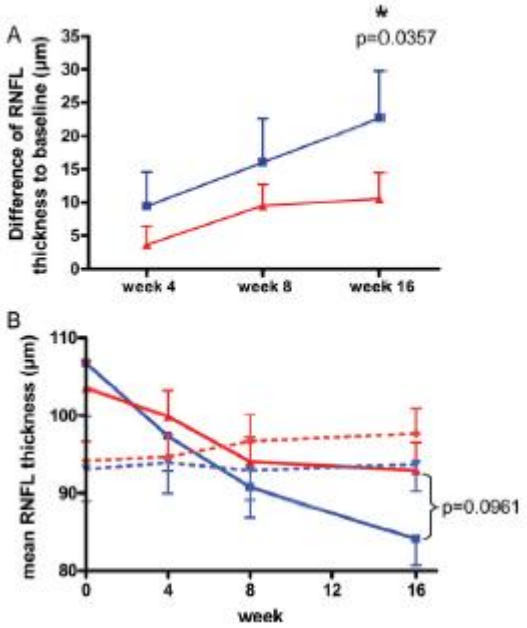
A randomized, double-blind, phase 2 study of erythropoietin in optic neuritis

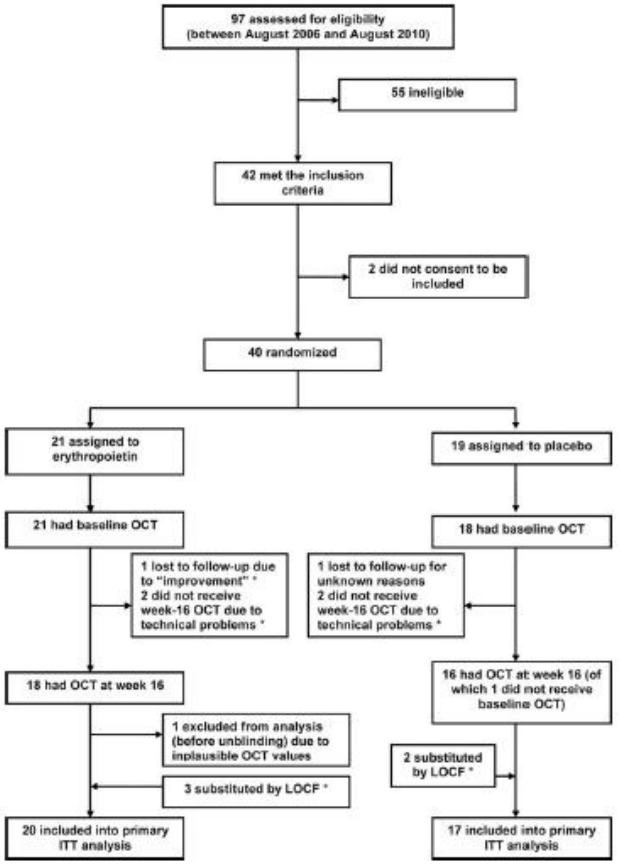
Kurt-Wolfram Sühs MD[1,2], Katharina Hein MD[3], Muriel B. Sättler MD[3], Anke Görlitz[4], Christoph Ciupka MD[5], Kerstin Scholz MD[6], Barbara Käsmann-Kellner MD[7], Panagiotis Papanagiotou MD[8], Nina Schäffler MD[9], Cordula Restemeyer MD[9], Diana Bittersohl MD[10], Andrea Hassenstein MD[10], Berthold Seitz MD[7], Wolfgang Reith MD[8], Klaus Fassbender MD[1], Reinhard Hilgers PhD[11], Chris Heesen MD[9], Mathias Bähr MD[3], Ri Diem MD[1,12,*]

Issue

Annals of Neurology

Volume 72, Issue 2, p
199–210, August 201





Decrease in retrobulbar diameter of the optic nerve was smaller in the erythropoietin group

Suhs et al., Ann neurol 2012

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PLOS ONE

Retinal Nerve Fibre Layer Thinning in Patients with Clinically Isolated Optic Neuritis and Early Treatment with Interferon-Beta

Kurt-Wolfram Sühs[1,2], Katharina Hein[3], Jens R. Pehlke[1,4], Barbara Käsmann-Kellner[5], Ricarda Diem[1,6]*

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Abstract

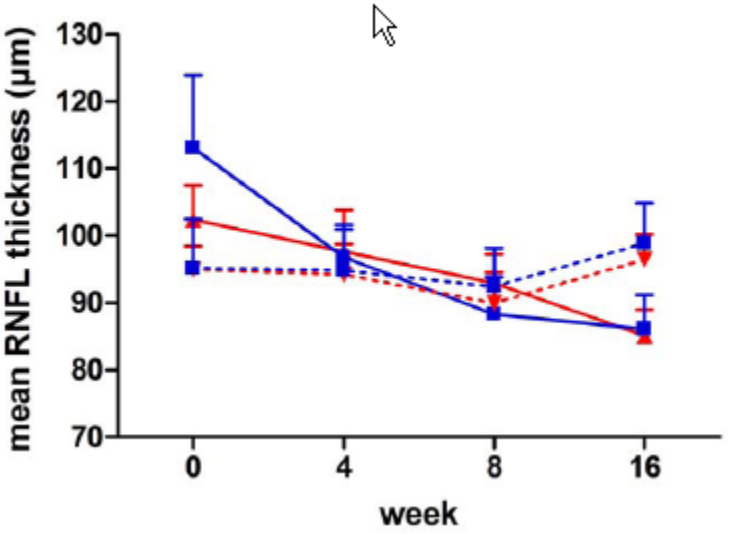
Background: Optic neuritis is associated with neurodegeneration leading to chronic impairment of visual functions.

Objective: This study investigated whether early treatment with interferon beta (IFN-β) slows retinal nerve fibre layer (RNFL) thinning in clinically isolated optic neuritis.

Methods: Twenty patients with optic neuritis and visual acuity decreased to ≤0.5 (decimal system) were included into this prospective, open-label, parallel group 4-month observation. After methylprednisolone pulse therapy, 10 IFN-β from week 2 onwards. This group was compared to 10 patients free of any disease modifying trea parameter of interest was change in RNFL thickness assessed at baseline and at weeks 4, 8, and 16. Chang visual field, and visual evoked potentials (VEPs) served as additional outcome parameters.

Results: RNFL thinning did not differ between the groups with a mean reduction of 9.80±2.80 µm in IFN-β (±SD) vs. 12.44±5.79 µm in patients who did not receive DMT (baseline non-affected eye minus affected p = 0.67, t-test, 95% confidence interval: −15.77 to 10.48). Parameters of visual function did not show between the groups either.

Conclusions: In isolated optic neuritis, early IFN-β treatment did not influence RNFL thinning nor had recovery of visual functions.



Effect of 4-aminopyridine on vision in multiple sclerosis patients with optic neuropathy

Neurology® 2013;80:1862-1866

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Amy Conger, COA
Darrel Conger, CRA
Gina Remington, RN
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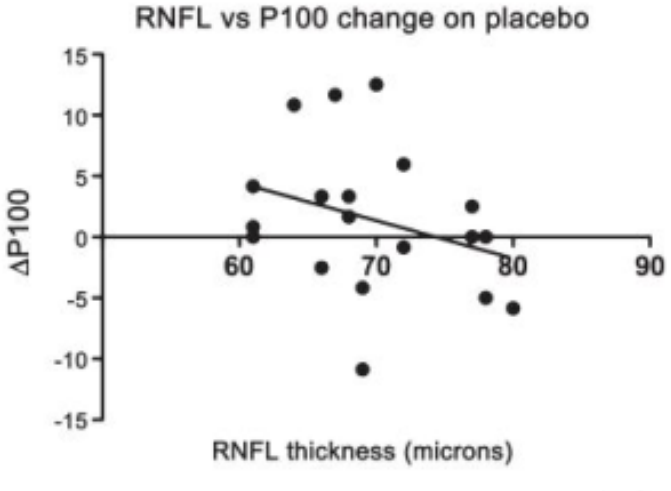
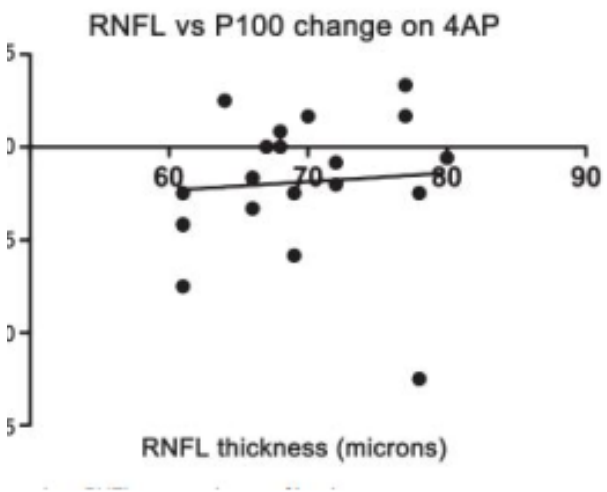
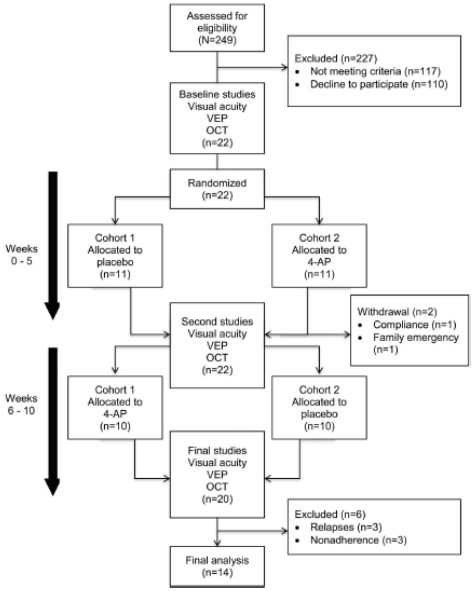






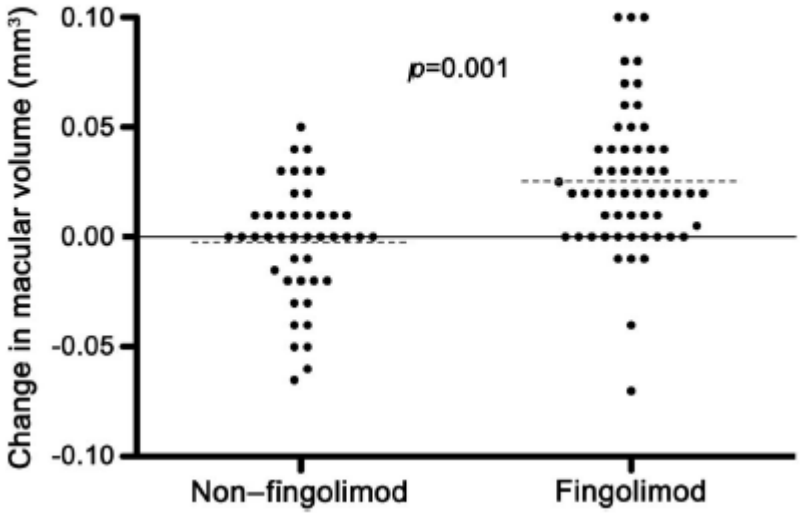
The eyes with an RNFL measure between 60 to 80 µm had the highest response rate.

Fingolimod treatment in multiple sclerosis leads to increased macular volume

Rachel Nolan, BA*
Jeffrey M. Gelfand, MD*
Ari J. Green, MD, MCR

Neurology,2013

Figure Fingolimod treatment in multiple sclerosis is associated with an increase in macular volume



Higher macular volume in patients with MS receiving fingolimod

Positive outcome or side effect?

Marc Dinkin, MD
Friedemann Paul, MD

Conclusions

- OCT is a promising imaging technique for monitoring axonal damage in MS.
- OCT can identify subtle changes in RNFL and macula over time.
- OCT measurements seem to correlate with clinical and MRI parameters.
- It is a candidate biomarker for becoming a surrogate end-point in clinical trials of MS.

THANK YOU