Optical coherence tomography: A role in monitoring multiple sclerosis

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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)
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)

Green. Et al, Brain 2010
Prospects for OCT in MS

– biomarker of disease prognosis
– monitoring disease course
– Defining response to therapy
OCT can measure (colour code):

- Acute phase: papilledema = 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

Pathological OCT
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)

OCT IN OPTIC NEURITIS
AXONAL LOSS IN MS EVEN WITHOUT ACUTE ON

**Tabla 3** Pacientes con atrofia de la capa de fibras nerviosas

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ojo afecto</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sin atrofia</td>
<td>8 (42,1%)</td>
<td>3 (25%)</td>
<td>12 (66,7%)</td>
<td>23 (46,9%)</td>
</tr>
<tr>
<td>Con atrofia</td>
<td>11 (57,9%)</td>
<td>9 (75%)</td>
<td>6 (33,3%)</td>
<td>26 (53,1%)</td>
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<tr>
<td><strong>Ojo contralateral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sin atrofia</td>
<td>17 (100%)</td>
<td>6 (54,5%)</td>
<td>10 (58,8%)</td>
<td>33 (73,3%)</td>
</tr>
<tr>
<td>Con atrofia</td>
<td>0</td>
<td>5 (45,5%)</td>
<td>7 (41,2%)</td>
<td>12 (26,7%)</td>
</tr>
</tbody>
</table>

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

Mean RNFL thickness in PPMS and SPMS by quadrant

Henderson et al., Brain 2008
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.

<table>
<thead>
<tr>
<th></th>
<th>DIS MRI criteria</th>
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<tr>
<td></td>
<td>None</td>
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<td>None</td>
<td>≥1</td>
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<tr>
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<td>4</td>
<td>4</td>
<td>8</td>
<td></td>
<td></td>
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<td>16</td>
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<tr>
<td>Total</td>
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<td>13</td>
<td>17</td>
<td>7</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative criteria</td>
<td>Quadrants &lt;5%</td>
<td></td>
<td>Quadrants &lt;1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(OCB+ at least two lesions in MRI)</td>
<td>None</td>
<td>≥1</td>
<td>None</td>
<td>≥1</td>
<td></td>
<td></td>
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<tr>
<td>Fulfilled</td>
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<td>6</td>
<td>6</td>
<td>3</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Not fulfilled</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>12</td>
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<td></td>
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<tr>
<td>Total</td>
<td>8</td>
<td>13</td>
<td>14</td>
<td>7</td>
<td>21</td>
<td></td>
<td></td>
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</tbody>
</table>

DIS: dissemination in space; OCB: oligoclonal bands.
doc: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.

<table>
<thead>
<tr>
<th></th>
<th>¼ Barkhof MIR criteria</th>
<th>MIR and OCB criteria</th>
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<tr>
<td></td>
<td>&lt;5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>75</td>
<td>50%</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>56.25%</td>
<td>81.25%</td>
</tr>
</tbody>
</table>

doc: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
RNFL thickness is linked to progression in MS

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
RNFL thickness is linked to progression in MS

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 Graves¹ and Ari J. Green¹,³

A
Baseline

B
5 months later

Expanded Disability Score Scale (EDSS)

P = 0.0002

No oedema
n = 603

Microcystic Macular Oedema
n = 15

<table>
<thead>
<tr>
<th></th>
<th>Eyes without macular oedema (n = 606)</th>
<th>Eyes with microcystic macular oedema (n = 20)⁴</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior symptomatic optic neuritis in that eye, n (%)</td>
<td>161 (27)</td>
<td>10 (50)</td>
<td>0.02⁵</td>
</tr>
<tr>
<td>Total RNFL thickness (µm), mean (SD)</td>
<td>87 (15)</td>
<td>66.7 (15.4)</td>
<td>&lt;0.001⁶</td>
</tr>
<tr>
<td>Macular volume (mm³), mean (SD)</td>
<td>3.01 (0.22)</td>
<td>2.9 (0.15)</td>
<td>0.12⁷</td>
</tr>
<tr>
<td>Foveal thickness (µm), mean (SD)</td>
<td>271.2 (21.9)</td>
<td>276.4 (28.8)</td>
<td>0.50⁸</td>
</tr>
<tr>
<td>Visual acuity (logMAR), median (IQR)</td>
<td>−0.1 (−0.1 to 0)</td>
<td>0.17 (0 to 0.4)</td>
<td>0.001⁹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.03⁹</td>
</tr>
</tbody>
</table>
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, BA¹, Esther R. Bisker, MD¹, David J. Sackel, BS¹, David A. Long Jr., BS¹, Kristin M. Galetta, MS¹, John N. Ratchford, MD⁵, Deacon J. Lile, BA¹, Sheena K. Farrell, BS⁵, Michael J. Loguidice, BA¹, Gina Remington, BSN, RN⁶, Amy Conger, COA⁶, Teresa C. Frohman, BS⁶, Dina A. Jacobs, MD¹, Clyde E. Markowitz, MD¹, Gary R. Cutter, PhD⁷, Gui-Shuang Ying, PhD³,⁴, Yang Dai, PhD³,⁴, Maureen G. Maguire, PhD⁷,⁸, Steven L. Galetta, MD¹,³, Elliot M. Frohman, MD, PhD⁶, Peter A. Calabresi, MD⁵, and Laura J. Balcer, MD, MSCE¹,²,³

A

Follow-up interval, all MS eyes

n=201
n=242, p=0.06
n=109, p<0.001 *

n=41, p<0.001 *

B

Follow-up interval, MS non-ON eyes

n=127
n=155, p=0.11
n=75, p<0.001 *

n=24, p=0.001 *

C

Follow-up interval, MS ON eyes

n=72
n=34, p=0.24
n=85, p=0.19

n=17, p=0.003 *
The OSCAR-IB Consensus Criteria for Retinal OCT Quality Assessment

Prejaas Tewarie¹, Lisanne Balk¹, Fiona Costello², Ari Green³, Roland Martin⁴*, Sven Schippling⁴*, Axel Petzold⁵*

1 MS Centre Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands, 2 University of Calgary, Departments of Clinical Neurosciences and Surgery, Calgary, Alberta, Canada, 3 Multiple Sclerosis Center, Department of Neurology, University of California San Francisco, San Francisco, California, United States of America, 4 Institute for Neuroimmunology and Clinical Multiple Sclerosis Research (Inims), University Medical Center Hamburg Eppendorf, Hamburg, Germany, 5 UCL Institute of Neurology, London, United Kingdom

Optical coherence tomography as a potential readout in clinical trials

Benjamin M. Greenberg and Elliot Frohman
Current trials using OCT

- MSC
- Fingolimod (safety)
- Ocrelizumab RRMS
- Anti-Lingo (AON)
- NT-KO-003
- AON (fingolimod)
Clinical trial monitoring with MS

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

Kurt-Wolfram Sühs MD1,2, Katharina Hein MD3, Muriel B. Sattler MD3, Anke Görlitz4, Christoph Ciupka MD5, Kerstin Scholz MD6, Barbara Käsmann-Kellner MD7, Panagiotis Papanagiotou MD8, Nina Schäffler MD9, Cordula Restemeyer MD9, Diana Bittersohl MD10, Andrea Hassenstein MD10, Berthold Seitz MD7, Wolfgang Reith MD9, Klaus Fassbender MD1, Reinhard Hilgers PhD11, Chris Heesen MD9, Mathias Bähr MD3, R Diem MD1,12.

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

Suhs et al., Ann neurol 2012
Retinal Nerve Fibre Layer Thinning in Patients with Clinically Isolated Optic Neuritis and Early Treatment with Interferon-Beta

Kurt-Wolfram Sühs¹,², Katharina Hein³, Jens R. Pehlke¹,⁴, Barbara Käsmann-Kellner⁵, Ricarda Diem¹,⁶*

¹Department of Neurology, Saarland University, Homburg, Germany, ²Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany, ³Department of Neurology, Georg-August University, Göttingen, Germany, ⁴Department of Addiction Disorders, LWL Clinic Münster, Münster, Germany, ⁵Department of Ophthalmology, Saarland University, Homburg, Germany, ⁶Department of Neuro-oncology, University Clinic Heidelberg, Heidelberg, Germany

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 therapy (DMT). The parameter of interest was change in RNFL thickness assessed at baseline and at weeks 4, 8, and 16. Change in 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 eye; p = 0.67, t-test, 95% confidence interval: −15.77 to 10.48). Parameters of visual function did not show a significant difference between the groups either.

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

![Graph showing RNFL thickness over weeks]
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

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?
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