OCT and MS
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Disclosures

• None
OCT and MS Objectives

• Understand the technique of ocular coherence tomography (OCT)
• Understand the applications of OCT to multiple sclerosis
• Understand anticipated advances in OCT
Optical Coherence Tomography OCT

• Interferometric imaging technique

• Origins in the field of optical coherence-domain reflectometry developed to localize reflections from faults in fiber optic networks

• Maps depth-wise reflections of near-infrared light

• Forms cross sectional images of morphological features

• Micrometer scale
Characteristics of OCT
Physical properties

• Optical analog of ultrasonography

• Generates cross-sectional images by measuring back-reflected echoes of light
  – As the speed of light is too fast to be measured by direct detection

• Current technology has 8-10 μm resolution
• Newer technology has 4-6 μm resolution
**OCT Instrumentation**

**Time Domain**

- Michelson-type interferometer
  - Low-coherence-length, superluminescent diode light source
- Two arms—Time Domain OCT
  - One directs light onto the sample and collects backscattered signal
  - A second reference arm with a reflecting mirror, mechanically scanned to vary time delay and measure interference
- Interference occurs only when the distance traveled by the light in the sample and reference arms match to within the coherence length
- Data set
  - 2- or 3-dimentional array, representing the optical backscattering in a cross section or volume of the tissue
  - Displayed as
    - 2 dimensions
    - Volumetric gray-scale
    - False-color image
OCT
Ophthalmology

• High-resolution imagery of subsurface retinal features

• Retinal nerve fiber layer (RNFL) differentiated from other structures
  – RNFL horizontal orientation correlates with high reflectivity
  – Nuclei and other structures correlate with low reflectivity
• Evaluates the integrity of
  – RNFL—average, quadrant, clock face sector
  – Macula—volume

• RNFL thinning and macular volume reductions correspond with declines in visual function as measured by
  – Visual acuity (low contrast)
  – Visual field analysis
OCT Images of the Internal Retinal Structures Technology

Frohman EM et al. (2008) Optical coherence tomography: a window into the mechanisms of multiple sclerosis
*Nat Clin Pract Neurol* 10.1038/ncpneuro0950
Figure 1. OCT report from a patient with MS. Zeiss Stratus OCT3™ with software 4.0 (Carl Zeiss Meditec, Inc) Time Domain

OCT
Fourier (Spectral) Domain

• Detects light echoes by measuring the interference spectrum from an interferometer with a stationary reference arm

• Spectrometer and high-speed line-scan camera record the interference spectrum

• Fourier transformed to obtain the magnitude and echo time delay of the light (the axial scan)

• Detects all light echoes simultaneously
  – Increase in sensitivity
  – High speed imagery
  – Enables retinal imaging with advanced camera technology

• Commercial instruments
  – Axial image resolution 4-6 µm
  – Imaging speeds 25,000 axial scans/sec—50 fold faster than time domain OCT
MS and the Afferent Visual Pathway

- MS frequently targets the anterior visual pathway

- 30-77% of MS patients have optic neuritis (ON) during the course of the disease

- Post-mortem studies show nearly all MS patients have characteristic changes in the optic nerve and retina
OCT
Optic Neuritis and MS

• Parisi, 1999—earliest application of OCT in MS
  – 14 MS, recovered from ON
  – RNFL thickness reduced (p<0.01)
    • 46% in affected eyes compared to controls
    • 28% in affected eyes compared to fellow eye
    • 26% in ‘unaffected’ fellow eyes compared to controls

• Trip, 2005
  – 11 MS pts, 14 CIS pts; all with single clinical ON episode
  – Corroborated Parisi’s previous findings
  – Macular volume reduced (p<0.001)
    • 11% in eyes of pts with hx of ON compared to controls
    • 9% in affected eyes vs fellow eyes
  – RNFL and macular findings correlated with PVEP
    • Amplitude (more so)—axonal function
    • Latency(less so)—myelin integrity
OCT Optic Neuritis and MS

• Costello, 2006
  – MS patients 3-6 months post ON
  – RNFL loss of 10-40 μm

• MS, ON RNFL loss across studies
  – Range 5-40 μm
  – Average 10-20 μm
  – RNFL loss of about 75 μm reduces the chances of visual recovery

• RNFL—norms
  – 110-120 μm by age 15 years
  – 0.017% RNFL loss per year, 10-20 μm over 60 years
OCT and MS
Visual Disability

• Visual acuity
  – Snellen—RNFL loss correlation in most, but not all studies
  – ETDRS (logarithmic scale)—RNFL loss more consistent
  – Low-contrast letter acuity—RNFL correlation

• Visual field, automated perimetry—mixed results
  – Costello, 2006—75 μm RNFL loss, poor prognosis for visual field by Humphrey analyzer
  – Other studies did not confirm a linear relationship
  – OCT may detect RNFL loss below level of sensitivity of automated perimetry
OCT and MS
RNFL over Time

- Talman, 2010
  - MS patients without acute ON
    - 593 eyes, 299 patients
  - OCT RNFL measurements every 6 months, mean follow-up 18 months
  - RNFL thinning increased over time (p<0.001)
    - 2.9 $\mu$m average at 2-3 years
    - 6.1 $\mu$m average at 3-4.5 years
    - 2 $\mu$m average each year

- RNFL loss detectable by OCT at about 3 months after acute ON
  - RNFL thinning of 2 $\mu$m is below TD-OCT but theoretically within the resolution of SD/FD-OCT
  - Heidelberg Spectralis and Zeiss Cirrus HD-OCT (4-6 $\mu$m) require approximately 2 years FU in MS patients without ON
OCT and MS
Global Clinical Scores

• EDSS
  – Inverse relationship between RNFL thickness and EDSS found in about ½ studies reported
  – Strongest correlation found for MS patients without acute optic neuritis
  – The strong correlation of RNFL in ON may mask subtle changes caused by axonal damage or trans-synaptic axonal degeneration

• Multiple Sclerosis Severity Score
  – Naismith, 2009—no correlation found with RNFL
OCT and MS Neuroimaging

- Correlation between RNFL thickness and MRI measures of brain atrophy in several studies, e.g. brain parenchymal fraction
  - Gordon-Lipkin, 2007
  - Grazioli, 2008

- Consensus not yet reached on which atrophy measure is most relevant
OCT
MS, Gray Matter, and the Eye

• Green, 2010—Ocular pathology in MS
  – Postmortem 82 patients
  – Retinal atrophy with shrunken neurons
  – Retinal ganglion cell (RGC) dropout in 79% of eyes
  – Inner nuclear layer atrophy (amacrine and bipolar cells) in 40% of eyes
  – First report of inner nuclear layer cell loss in MS
OCT and MS

Macula

- OCT macular volume is reduced in MS patients compared to controls in most published studies.

- Macular volume correlated with RNFL loss in some studies.

- OCT macular studies provide a model for neuronal cell death—questions not resolved:
  - What mechanisms are involved in RGC apoptosis?
  - Could RGC apoptosis follow axonal pathology?
  - Could RGC apoptosis be primary neuronal injury independent of axonal injury?
OCT report for the macular region of the retina from the same patient with multiple sclerosis as is shown in Figure 1

OCT and MS
Future Developments

• Polarisation-sensitive OCT (PS-OCT)
  – Records polarisation of back-scattered light
  – RNFL birefringence may precede RNFL loss and potentially detect early axonal pathology

• Fluorescence labeling of annexin 5, a protein that binds to a key component initiating apoptosis
  – Allows real-time monitoring of RGC apoptosis
  – A potential surrogate for neuroprotection strategies
OCT and MS
Future Developments

• Retinal sector analysis
  – Certain sectors more vulnerable than others, eg maculopapillary bundle
  – Normal variation is significant

• RNFL thickness maps, combined with Polarization Sensitive-OCT

• Retinal layer segmentation by SD/FD-OCT
Figure 3 Fundus (left), nerve fiber layer maps (middle), and deviation maps (right; compared with normal individuals) derived from laser polarimetry (GDx) imaging of the same patient as is shown in Figure 1 and 2.

MS and OCT Summary

- Optical coherence tomography (OCT) is a noninvasive imaging technology that can measure changes in the structural architecture of the retina.

- As such OCT can measure axonal and neuronal loss in disorders of the anterior visual pathway, including multiple sclerosis.

- OCT metrics (RNFL thickness and macular volume) correlate with clinical measures of vision loss, and to a degree with brain imaging and other techniques.

- OCT may facilitate visualization of the disease process in MS and may be useful in monitoring the response to therapeutic agents.
OCT and MS
Supplemental Slides
The retina is devoid of myelin but contains ganglion cell neurons and their associated axons, and it thereby represents an ideal nervous tissue with which to model processes of axonal and neuronal degeneration in MS.

More-advanced retinal imaging techniques are now available with the advantages of high definition, high speed, automatic optic disc centering, co-registration capability, and eye movement correction analysis, and they will ultimately bring us closer to more directly interrogating CNS tissues to understand the mechanisms of tissue damage and what can be done to prevent it.
• Imaging metrics (new technology)
• Full RNFL mapping
• Mapping of intraretinal layers in the macula
• Three-dimensional OCT of optic nerve head topography and internal structure
• Technology is new and metrics remain to be defined
• **Biomarker features and validation**
  • Correlates with high-contrast and low-contrast visual acuity
  • Pathological distribution predicts visual field changes
  • OCT metrics predict brain atrophy
  • Subtypes of multiple sclerosis predict severity of RNFL thinning
  • Measures of laser polarimetry with variable corneal compensation (GDx-VCC) corroborate OCT evidence of axonal degeneration
• **Application features**
  • Testing performance is quick and easy
  • Pupil dilation is typically not required
  • Low coefficient of variation for repeated measures
  • Low inter-individual and intra-individual variation
  • Low variability across different centers using the same device
  • Scan quality can be assured with disc centering and adequate signal strength
• Imaging metrics (current technology)
• Average retinal nerve fiber layer (RNFL) thickness
• Quadrant and clockface sector analyses
• Total macular volumes
• Quadrant assessment of parafoveal areas
• Inferior and superior quadrants of the RNFL are thickest (double hump waveform on temporal-superior-nasal-inferior-temporal [TSNIT] analyses)
IS/OS—junction between the inner and outer photoreceptor segments, Fig layer, ONL—outer nuclear layer, ELM—external limiting membrane, and RPE—retinal pigment epithelium. Images provided by Fujimoto and Drexler.

2 High-resolution OCT images showing normal retinal structures at 3-m axial resolution. Abbreviations: ILM—inner limiting membrane, NFL—nerve fiber layer, GCL—ganglion cell layer, IPL—inner plexiform layer, INL—inner nuclear layer, OPL—outer plexiform layer.
Figure 1 High-resolution images of the internal retinal structure taken with optical coherence tomography (OCT), demonstrating the processes involved in using this technology.
OCT
High-resolution Images of Internal Retinal Structure
High Resolution Spectral Domain Optical Coherence Tomography (SD-OCT) in Multiple Sclerosis: The First Follow Up Study over Two Years

- Abstract

  Background: “Non-invasive, faster and less expensive than MRI” and “the eye is a window to the brain” are recent slogans promoting optical coherence tomography (OCT) as a new surrogate marker in multiple sclerosis (MS). Indeed, OCT allows for the first time a non-invasive visualization of axons of the central nervous system (CNS). Reduction of retina nerve fibre layer (RNFL) thickness was suggested to correlate with disease activity and duration. However, several issues are unclear: Do a few million axons, which build up both optic nerves, really resemble billions of CNS neurons? Does global CNS damage really result in global RNFL reduction? And if so, does global RNFL reduction really exist in all MS patients, and follow a slowly but steadily ongoing pattern? How can these (hypothesized) subtle global RNFL changes be reliably measured and separated from the rather gross RNFL changes caused by optic neuritis? Before generally being accepted, this interpretation needs further critical and objective validation.

  Methodology: We prospectively studied 37 MS patients with relapsing remitting (n = 27) and secondary progressive (n = 10) course on two occasions with a median interval of 22.460.5 months [range 19–27]. We used the high resolution spectral domain (SD-)OCT with the Spectralis 3.5 mm circle scan protocol with locked reference images and eye tracking mode. Patients with an attack of optic neuritis within 12 months prior to the onset of the study were excluded.

  Principal Findings: Although the disease was highly active over the observation period in more than half of the included relapsing remitting MS patients (19 patients/32 relapses) and the initial RNFL pattern showed a broad range, from normal to markedly reduced thickness, no significant changes between baseline and follow-up examinations could be detected.

  Conclusions: These results show that caution is required when using OCT for monitoring disease activity and global axonal injury in MS.

**Figure 5** Fundus (left), nerve fiber layer maps (middle), and deviation maps (right; compared with normal individuals) derived from laser polarimetry (GDx) imaging of the same patient as is shown in **Figure 4**.
OCT report from a patient with MS
Zeiss Stratus OCT3™ with software 4.0 (Carl Zeiss Meditec, Inc)
Time Domain OCT
An optical coherence tomography (OCT) report for the macular region of the retina from the same patient with multiple sclerosis as is shown in Figure 2
Figure 6 High-definition, ultra-high-resolution optical coherence tomography (OCT) scans.
High-definition, ultra-high-resolution OCT scans

Box 2 Why model neurodegeneration in multiple sclerosis with optical coherence tomography (OCT) in optic neuritis?

- Optic neuritis is among the most common syndromes in multiple sclerosis
- Occult optic neuropathy occurs in most patients with multiple sclerosis
- Patients predictably seek medical attention early
- Visual, physiological, and structural measures can provide a signature for the syndrome
- Low-contrast letter acuity measures are valid patient performance outcomes that causally relate to structural changes in the retina
- The retinal nerve fiber layer (RNFL) has no myelin and can thereby be considered to be a highly enriched axonal tissue
- Changes in the RNFL and macula probably reflect mechanisms of inflammation, demyelination (retrobulbar), axonal degeneration, and neuronal degeneration
- The timing of the changes in RNFL that follow acute optic neuritis has been characterized
- The rapid changes in RNFL after acute optic neuritis make this syndrome ideal for testing neuroprotective strategies over a short time frame with precise and reproducible measures