Glaucoma: a disease of the macula?

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Disclosure Statement:

Honoraria:  Alcon
          Allergan
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The traditional paradigm

Glaucoma is an optic neuropathy that causes mid-peripheral visual field loss, sparing the central field until end stage disease.

Conventional diagnostic testing included clinical assessment of the optic nerve and RNFL, and 24- or 30-2 visual field analysis.
An evolving paradigm

The evolution of optical coherence tomography enabled more objective analysis of the ONH and RNFL
A (not so) new paradigm

Since the late 1960s it has been recognized that glaucoma can cause initial VF defects that threaten fixation\(^1\)

However, macular involvement received little attention because conventional analyses were poorly suited to detect it.

Now, OCT assessment of macular retinal ganglion cell thickness has rekindled interest in glaucomatous damage of the macula.

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Despite representing only 2% of the total retinal surface, the macula contains over 30% of the RGCs in the human retina, and is mapped to an area occupying 60% of the visual cortex\textsuperscript{1-3}.

Why is macular involvement important?

Visual field loss within 10° of fixation:
- is part of the definition of advanced (severe) glaucoma\textsuperscript{1}
- has a significant impact on activities of daily living\textsuperscript{2}
- necessitates aggressive intervention to minimize progression

Glucomatous damage of the macula is common in early disease, but can easily go undetected by current (conventional) analyses\textsuperscript{3}

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Macular damage is common

‘More than 50% of the eyes with ... mild to moderate glaucomatous field loss showed defective locations in the ... superior paracentral region within an eccentricity of 3°.’

1

‘Macular damage, as seen on 10-2 VFs, appears to occur almost as frequently as peripheral defects in patients with ... early glaucoma.’

2

‘Given the prevalence of early macular damage, patients should not be screened with only the 24-2 VF.’

3

Macular damage is overlooked

A 24-2 grid has 54 points (only 4 in the central 8°) separated by 6°
A 10-2 grid has 68 points (all in the central 10°) separated by 2°

A paracentral scotoma can ‘fall between the cracks’ of the 24-21,2

In this histological section, a **photoreceptor** 0.52mm from the fovea is separated from its **ganglion cell body** by nearly 0.6mm due to the length of the intermediate Henle fiber (**red arrowheads**) and RGC dendrite (**green arrowheads**)\(^1\)

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The central 10° is poorly sampled by the 24-2 grid, particularly after RGC displacement at the fovea is accounted for (on right)\(^1\)

Note the **inferior RGC loss** that would be missed by the 24-2 grid

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RGC displacement and a 2° grid

The 10-2 grid is better, but still samples the area immediately adjacent to fixation relatively poorly after RGC displacement is accounted for (on right)¹

24-2 versus 10-2 defects

A single abnormal paracentral point on 24-2 analysis may prove to be a characteristic superior arcuate scotoma on 10-2\(^1\)

24-2 versus 10-2 defects

A paracentral scotoma can ‘fall between the cracks’ of the 24-2\textsuperscript{1}
• 23% of eyes with a ‘normal’ 24-2 showed an abnormal 10-2

Nearly 62% of eyes with early glaucoma classified as \textbf{normal on 24-2} testing showed \textbf{abnormalities on 10-2} testing\textsuperscript{1}.

‘... a large proportion of eyes within the glaucoma continuum have abnormal 10-2 visual field results despite normal 24-2 results …’

‘... \textit{many patients … called suspects or preperimetric … may in fact have established glaucomatous functional damage …}’

On the other hand, 85% of eyes with early glaucoma classified as \textbf{normal on 10-2} testing showed \textbf{abnormalities on 24-2} testing.

Therefore, it’s not a question of 24-2 or 10-2 … it’s \textbf{24-2 and 10-2}.

Structure/function correlation

Glaucomatous VF loss results from damage to the RGC axons at the level of the lamina cribrosa of the ONH

The characteristic shape and location of these nerve fiber bundle defects is determined by the anatomy of the RNFL\textsuperscript{1,2}

Superimposing the 24-2 grid on photographs of well-defined RNFL defects allowed VF locations to be mapped to regions of the ONH, correlating functional loss with structural change. 

Structure/function correlation
Macular vulnerability zone

Most axons from the inferior-temporal macula project to the **macular vulnerability zone**, while those from the superior macula project to the less vulnerable temporal quadrant\(^1,2\)

Inferior macular damage

RGC damage in the inferior macula can be extreme and central, leading to superior VF loss that is deep and threatens fixation\(^1\).

RNFL analysis (as an NSTIN curve, putting the macula centrally) shows extreme local thinning at the border of the temporal and inferior quadrants: the macular vulnerability zone.

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Seeing macular involvement: 
**TSNIT** versus **NSTIN**
Superior macular damage

In contrast, RGC damage in the superior macula tends to be more subtle, leading to shallower inferior VF loss further from fixation\(^1\).

As such, RNFL analysis can appear nearly normal, showing a relatively shallow depression at the border of the temporal and superior quadrants … … but look at the obvious macular RGC asymmetry.

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Diffuse macular damage

Macular damage can also be diffuse, with **relatively widespread loss of macular RGC and RNFL** and shallow VF depression\(^1\)

**Be vigilant:** diffuse macular damage is easily overlooked

Even with diffuse damage, the inferior macula is more involved: note the **deeper superior VF defect** and more extreme RNFL thinning in the inferior **macular vulnerability zone**

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Patterns of macular damage

Damage to axons in the **macular vulnerability zone** results in a superior arcuate defect that threaten fixation\(^1\)

Examples of early, moderate, and advanced defects on 10-2 AVF

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The MVZ explains patterns of macular damage

The region within the red borders of the 10-2 grid corresponds to the macular vulnerability zone, while the region within the blue oval corresponds to the section of the inferior macula projecting to the less vulnerable temporal quadrant.

Paracentral arcuate scotomas deepen 3 to 5° above fixation, then spread laterally **sparing the area just temporal to fixation**\(^1\)

Only two 24-2 points sample the area representing the inferior macular vulnerability zone\(^2\)

As a result, over 70% of eyes with paracentral scotomas progressing on 10-2 were missed by 24-2 (see above)\(^3\)

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RNFL scans underestimate macular damage

Focusing only on summary (global) measures of RNFL thickness or temporal quadrant thickness often misses macular damage\(^1\)

<table>
<thead>
<tr>
<th>Scrutinizing clock hour 7 of the RNFL thickness profile improves detection by capturing most of the MVZ, but still misses nearly 40% of subtle macular damage clearly seen with macular RGC and 10-2 analyses(^2)</th>
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‘… in addition to the disc cube scan, macula scans should be incorporated into clinical protocols for detecting glaucomatous damage …’

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Evaluating macular OCT

The macula shows less anatomic variability than the ONH/RNFL
• particularly valuable in the presence of an anomalous ONH and/or high myopia
  1,2
• less helpful in the presence of concurrent macular disease

An on-axis macular scan is also easier for patient and technician

Evaluate minimum and inferior-temporal GCIPL thickness

Be suspicious of:
• asymmetry between eyes
• asymmetry above and below the horizontal raphe

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Cirrus Ganglion Cell Analysis showing inferior GCIPL thinning in the left eye (temporal>nasal): asymmetry across the horizontal raphe causing a superior paracentral scotoma near fixation¹

Structure/function: RNFL/24-2
Structure/function: GCIPL/10-2
Objective imaging caveats

**Objective imaging complements but does not replace systematic clinical assessment and sound clinical judgment**

**Macular analysis complements but does not replace RNFL analysis**

‘... a thorough clinical examination combined with a healthy dose of common sense is superior to imaging technology ...’

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Paracentral OAG?

An OAG subtype that attacks central vision characterized by:
- lower untreated IOP (although not only NTG)\(^1\)
- prelaminar NFL defects within the cup noted on OCT\(^2\)
- frequent disc hemorrhages
- systemic hypotension
- Raynaud’s phenomenon; migraine; sleep apnea (?)
- genetic predisposition to impaired nitric oxide regulation\(^3,4\)

Patients with paracentral OAG require aggressive IOP reduction

Patient OD

History
• 68 y/o Caucasian woman
• general health: good (ACEI for hypertension)
• family history: diabetes
• ophthalmic history: unremarkable
• low ATR astigmatism with good BCVA (6/6)
• normal binocularity, pupil reactions, and confrontation VFs
• normal anterior segment structures

November 2009
• IOPs 17/19
• CCTs 524/528
Patient OD

December 2009  untreated IOPs: 15/19
Patient OD

June 2011  untreated IOPs: 18/21
Patient OD

December 2009  IOP: 19  April 2013  IOP: 22
Patient OD

April 2013

untreated IOPs: 20/22
Patient OD

April 2013  IOP: 22  October 2013  IOP: 24
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<th>March 2014</th>
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<td>Patient OD</td>
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[Image of an eye with a red arrow pointing to a specific area.]

[Image of an eye test chart.]
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<tr>
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<th>IOP: 20</th>
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<tr>
<td>Feb. 2017</td>
<td>IOP: 20</td>
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Patient OD

24-2 GPA (2009 to 2017): event-based progression near fixation
Patient OD

Patient OD

Swept-source OCT (SS-OCT) and image integration will allow simultaneous imaging/analysis of RNFL and macular RGC\(^1\)

Single-page (Hood) report from a single wide-field Topcon SS-OCT scan

Zeiss Panomap integration of individually acquired RNFL and GCIPL scans (for patient OD)

Swept-source OCT (SS-OCT) and image integration will allow simultaneous imaging or analysis of RNFL and macular RGC\(^1\)

Single-page (Hood) report from a single wide-field Topcon SS-OCT scan

Zeiss Forum combined report showing structure/function correlation (for patient OD)

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The future of AVF

Adding strategic points to the 24-2 AVF grid (perhaps from the 10-2 grid; mirroring RNFL distribution; weighting central points) may assist in diagnosing and monitoring macular damage

Modifying the conventional 24-2 grid with a subset of 10-2 points (examples above) ...

... or using the Octopus G-pattern (to right) can improve detection of macular damage

But what should we do now?

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<th>Macular and RNFL analyses are complementary, and GCIPL thinning can precede RNFL loss\textsuperscript{1,2}</th>
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<td>Obtain and critically analyze both RNFL and macular scans</td>
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Current OCT segmentation algorithms aren’t foolproof:
- carefully inspect each scan to ensure its accuracy\textsuperscript{3,4} |
- ensure quality: strong signal, no movement/blink artifacts\textsuperscript{5} |
- recognize the limitations of reference databases\textsuperscript{6} |

Never rely solely on summary parameters: **qualitatively assess** and **look for focal change** in both RNFL and macular scans\textsuperscript{7}

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But what should we do now?

24- and 10-2 VF analyses are also complementary

‘Macular damage, as seen on 10-2 VFs, appears to occur almost as frequently as peripheral defects in patients with ... early glaucoma.’

Don’t default to 24-2 analyses in isolation:
obtain 10-2 baseline early and retest intermittently

Particularly with:
- loss of inferior GCIPL
- central abnormality in the 24-2 grid
- symptoms not commensurate with 24-2 status
- glaucomatous optic neuropathy at lower IOP
- disc hemorrhages
- systemic hypotension/migraine/Raynauds/OSA

Are there any questions about my presentation?

Yes.

Did you brush your teeth too aggressively and accidentally stab yourself in the brain?

Can you be more specific?

Frontal lobes?
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