Challenging the Glaucoma Archetype 1

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NewsFlash!!!

• 528 IU/DAY D3 ASSOCIATED WITH 7-8% DECREASE IN DEATH RATE
• Therefore

DO NOT RECOMMEND VIT D3 SUPPLEMENT AS YOU WANT YOUR GLAUCOMA PATIENT TO DIE BEFORE THEY GO BLIND

Definition of Glaucoma

GLAUCOMA IS OCULAR DEMENTIA, INFLAMMATION, AND ISCHEMIA LEADING TO GANGLION CELL DEATH WITH SUBSEQUENT RNFL DEATH AND COINCIDENT FUNCTIONAL LOSS, EVEN COMPROMISE TO THE CORTEX
Several studies have identified similarities in the pathogenic processes underlying AD and glaucoma with a higher incidence of glaucoma in AD. The relationship may be associated with cerebrospinal fluid pressure anomalies.


The Proposed Genesis of RGC/AXONAL Destruction in Glaucoma

IOP BLOCKS AXOPLASMIC FLOW @ LAMINA CRIBROSA
INTERFERENCE OF DELIVERY OF NEUROTROPHIC GROWTH FACTORS FROM THE LGN TO THE RGCS
DEATH OF RGCS AND SPREAD TO OTHER RGCS
MICROGLIA ASTROCYTES INFLAMMATION
ISCHEMIA & MICROcirculation CHANGEs COMPROMISE EXCESSIVE GLUTAMATE

RGCS DIE BEFORE RNFL
MAYBE THE BEST WAY TO TREAT GLAUCOMA IS 15 MINUTES PER DAY IN A HOT TUB.

WHY IN HEAVEN’S NAME WOULD I EVER SAY THAT?

LARRY IS DEFINITELY GETTING SENILE!!!!

JAMES WHITE COMES IN TO SEE YOU AND HE IS 53 YEARS OLD. HE CAN’T SEE GOOD NO MORE UP CLOSE AND HE JUST MISSED A 72 POINT BUCK AT 20 FEET CAUSE “I DIDN’T SEE HIM A COMIN.” IT IS HIS FIRST EYE EXAMINATION AND HE IS CORRECTABLE TO 20/25 WITH THE TUMBLING E. HIS IOP IS 18 AND HE HAS CUP EROSION AND SOME VF DEFECTS. THE OCT IS COMPROMISED. HE AIN’T BEEN TO SEE NO DOCTOR EVER.

TELL ME WHAT YOU ARE THINKIN REGARDING WHETHER OR NOT HE IS GOING TO PROGRESS WITH OR WITHOUT TREATMENT.

Check for Diabetes?
Check for Hypothyroidism?
Do Diurnal IOP Variations?
Do Postural IOP Variations?
Screen VF or Digitized Imaging?
Do Routine Anti-cardiolipin Antibodies?
Do Routine MRIs?
Check for Raynaud’s?

I ASK YOU, HOW DO YOU ARRIVE AT THE SUSPICION OF GLAUCOMA?
HEMI-STRUCTURE

DISEASE IS OFTEN MANIFESTED AS INTER-EYE AND INTRA-EYE STRUCTURAL ASYMMETRY

INTRA USUALLY REFERS TO ASYMMETRY OF THE SUPERIOR DISC AND THE INFERIOR DISC AND INTER REFERS TO BETWEEN THE EYES

Example of a Congenital Optic Pit in the Right Eye and the Left Eye With a Difference in Disc Sizes. There is Inter- and Intra-Disc Structure Variation.

Example of An Acquired Variation-Glaucomatous Optic Neuropathy in the Left Eye More Advanced than the Right Eye. Note The Inferior Notch OS. There is Inter- and Intra-Disc Structure Variation.

HEMI-FUNCTION

DISEASE IS OFTEN MANIFESTED AS INTER-EYE AND INTRA-EYE FUNCTIONAL ASYMMETRY

INTRA USUALLY REFERS TO ASYMMETRY OF THE SUPERIOR VISUAL FIELD AND THE INFERIOR VISUAL FIELD

The Ganglion Cell Complex in Diagnosis and Management

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ISCHEMIA & MICROCIRCULATION CHANGES

IMMUNE CELL EXCESSIVE GLUTamate

MICROGLIA ASTROCYTES INFLAMMATION

RGCS DIE BEFORE RNFL
The ganglion cell complex (ILM – IPL)

Inner retinal layers provide complete Ganglion cell assessment:
- Nerve fiber layer (g-cell axons)
- Ganglion cell layer (g-cell body)
- Inner plexiform layer (g-cell dendrites)
Patient Data

- 54 yo wf
- Routine Eye Evaluation
- Knows doctors were concerned about her eyes years ago and had ordered CT and MRI all of which were "normal"
- Best Corrected VA OD 20/20 OS 20/20
- CCT 533, 537 IOP 17
- Well defined inferior VF defects

Fundus Shots

Optic Nerve and RNFL

Ganglion Cell Complex
What does she have and what do you do?
Is it congenital or acquired?
Is there any relationship to glaucoma?
Does the RNFL match the GCC?

Topless Disc Syndrome or Superior Optic Nerve Hypoplasia

Patient Data
- 35 Year Old White Female
- 14 Year History of Diabetes With Hemoglobin A1C of 6.4
- Best VA of 20/20 O.U.
- Normal IOP not Being Treated for Glaucoma

CASE

Living by Grace
Grace is doing for another being kindnesses he doesn’t deserve, hasn’t earned, could not ask for and can’t repay.

McIlroy
O.D. AND O.S. NOTE LOSS OF RNFL REFLEX SUPERIOR

O.D. Inferior Arcuate Loss  
O.S. Inferior Arcuate Loss

Superior 
RNFL and GCC loss OU

The Cup
The Rim

Abnormal RNFL Parameters O.U.
Abnormal GCC Parameters O.U.
Abnormal RNFL TSNIT graph O.U.
Conclusions

- In this case we have
  - RNFL OU does correlate very well with VF as does superior GCC
  - This case has severe loss of structure and function secondary to developmental issues

Patient Data

- 25 year old Pakistani female
- C/O blurred vision that seems to be getting worse
- “Should I continue in College or am I going blind?” Dad doesn’t see too well and was told he has macular degeneration.
- BCVA O.U. 20/30 with O.D. -4.75-1.25 X 155 and O.S. -3.50-2.25 X 005
- IOP 20 mm Hg O.U.
- 20/20 vision in the past, confirmed by call to previous doctor
STRUCTURAL LOSS?

SUGGESTION OF TEMPORAL OPTIC ATROPHY

FUNCTIONAL COMPROMISE

POSSIBLE VISUAL FIELD DEFECT

STRUCTURAL LOSS VERIFIED

AVERAGE ANALYSIS

STRUCTURAL LOSS FURTHER CORROBORATED

TABLE OUTPUT
What does she have and what do you do?

*Is it congenital or acquired?*

Does she need neuroimaging?

Does the RNFL match the macular thickness?

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**Patient Data**

**Her DAD**

- 66 year old Pakistani male Cardiovascular surgeon still in practice
- BCVA O.D. 20/70 O.S. 20/200
- IOP 15 mm Hg O.U.
- Cataracts removed with BCVA post surgery at 20/70 O.U.
- Hypertension and thyroid issues
- Was told in past ARMD

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**Functional Loss**

Possible Early VF Defects

**Structural Loss**

Temporal Optic Atrophy
Autosomal Hereditary Dominant Optic Atrophy

Vision loss typically begins as the affected individual reaches school age. The onset and progression are insidious – most patients are unable to identify a precise age of onset. As many as 50% of patients with Dominant Optic Atrophy experience a progressive loss of vision with advancing age. Dyschromatopsia (color blindness) is frequently present but its manifestations are variable. Initially, Dominant Optic Atrophy was thought to be most closely associated with blue color vision deficits (Kline 1979), but more recent studies have demonstrated that mixed color deficits are most common (81%) (Votruba 1998).

Optic disc pallor is one of the defining characteristics of Dominant Optic Atrophy. About half of the affected individuals have disc pallor that is limited to the temporal side of the disk while the remaining patients have diffuse disc pallor. The degree of pallor tends to correlate with the severity of vision loss. In a recent series of patients with proven OPA1 mutations (see below), 69% had peripapillary atrophy, 31% had a temporal grey crescent, and 48% had a cup to disc ratio of <0.5 (Votruba 2003). The most common visual field defects are central or centrocecal scotomas, although altitudinal defects also have been described in patients with documented OPA1 mutations (Brown 1997). Histopathologic studies have shown loss of retinal ganglion cells, especially in the papillomacular bundle, and diffuse atrophic changes of the optic nerve (Johnston 1979).

Case CA 1

61 YO Glaucoma
THE TEMPLATE
Lower Limit of Normal on RNFL 5%-

AVERAGE 87.88

OD: 95.90
57.70
105.40

OS: 95.90
56.45
105.40

Hemi Structure RNFL Average of the 3 Studies

Overall Average RNFL 82.17

94.66
100.09

SSI
THE TEMPLATE

Ganglion Cell Complex (GCC) Lower Limit of Normal (bottom 5% cut-off)

AVERAGE OF 82.04

76.69

77.25

Downward Trend

77
92
15

77
92
119
78
125
107
Case CA 5

72 YO Glaucoma
Downward Trend

SSI Variability
MYOPIA AND GLAUCOMA

Responses to Topical Corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>&lt;20 mm Hg</th>
<th>20-31 mm Hg</th>
<th>&gt; 31 mm Hg</th>
</tr>
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<tbody>
<tr>
<td>Volunteers</td>
<td>100</td>
<td>70%</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td>POAG</td>
<td>50</td>
<td>0%</td>
<td>8%</td>
<td>92%</td>
</tr>
<tr>
<td>POAG Offspring</td>
<td>100</td>
<td>10%</td>
<td>68%</td>
<td>22%</td>
</tr>
<tr>
<td>POAG Siblings</td>
<td>50</td>
<td>22%</td>
<td>52%</td>
<td>26%</td>
</tr>
<tr>
<td>&gt; -5 D</td>
<td>17</td>
<td>12%</td>
<td>59%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Prevalence of Glaucoma as Related to Axial Length

<table>
<thead>
<tr>
<th>Axial Length in mm</th>
<th>Total Subjects</th>
<th>Total Subjects with Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0 to 26.4 mm</td>
<td>192</td>
<td>3.125%</td>
</tr>
<tr>
<td>26.5 to 33.6 mm</td>
<td>196</td>
<td>11.224%</td>
</tr>
</tbody>
</table>
### Pigmentary Glaucoma and Refractive Error

<table>
<thead>
<tr>
<th>Refractive Error</th>
<th>% of Eyes with Pigmentary Glaucoma - 78.22 % Myopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>+3 D</td>
<td>0.49%</td>
</tr>
<tr>
<td>+.5 to +2 D</td>
<td>6.44%</td>
</tr>
<tr>
<td>-.25 to +.25 D</td>
<td>14.85%</td>
</tr>
<tr>
<td>-.50 to -2.00 D</td>
<td>31.19%</td>
</tr>
<tr>
<td>-2.25 to -4.00 D</td>
<td>23.27%</td>
</tr>
<tr>
<td>-4.25 to -6.75 D</td>
<td>19.80%</td>
</tr>
<tr>
<td>-7.00 to -9.00 D</td>
<td>1.98%</td>
</tr>
<tr>
<td>-10.00 to -13.50 D</td>
<td>1.98%</td>
</tr>
</tbody>
</table>

### POAG LTG and Refractive Error

<table>
<thead>
<tr>
<th></th>
<th>POAG</th>
<th>LTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>Mean Refract</td>
<td>0.0D</td>
<td>-5.1 D</td>
</tr>
<tr>
<td>Mean AL</td>
<td>22.9 mm</td>
<td>25.2 mm</td>
</tr>
<tr>
<td>Mean Max IOP</td>
<td>34.3 mm Hg</td>
<td>19.8 mm Hg</td>
</tr>
</tbody>
</table>

I Would Argue That Statistically Glaucoma Is a Greater Concern Than Retina in the Moderate to High Myopic Patient

Need IOP
Need RNFL
Need GCC
R/O Pigmentary Issues
Consider Axial Length

In longer eyes the sampling location of the RNFL layer is further away from the center of the ONH yielding artificially thinner measurements.


Signal strength and scan circle placement affects RNFL measurements.

Statistically significant differences in the structure of ONH and peripapillary retina in non glaucomatous high myopes compared to on glaucomatous emmetropes. OCT measurements of RNFL thicknesses different in non glaucomatous with tilted discs.


Case 4

58 yo
NOTE HEMI-STRUCTURE DIFFERENCES WITH O.D. NEGATIVE SUPERIOR THINNER AND O.S. POSITIVE INDICATING INFERIOR THINNER

THIS IS CONSISTENT WITH THE INTER-EYE RNFL DIFFERENCES WITH OS MORE ADVANCED THAN OD

Conclusions:
1. Dominant Inter-Eye Asymmetry on RNFL and GCC
2. Intra-Eye Asymmetry on Mild on RNFL and Moderated on GCC
3. OS Appears More Advanced by Inter Eye

Comparisons

<table>
<thead>
<tr>
<th></th>
<th>OD</th>
<th>OS</th>
<th>Inter Eye Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL S</td>
<td>102</td>
<td>74</td>
<td>28</td>
</tr>
<tr>
<td>RNFL I</td>
<td>104</td>
<td>69</td>
<td>35</td>
</tr>
<tr>
<td>Difference</td>
<td>2/0.98</td>
<td>5/1.07</td>
<td>3</td>
</tr>
<tr>
<td>GCC S</td>
<td>96</td>
<td>76</td>
<td>20</td>
</tr>
<tr>
<td>GCC I</td>
<td>108</td>
<td>67</td>
<td>41</td>
</tr>
<tr>
<td>Difference</td>
<td>-12</td>
<td>+9</td>
<td>21</td>
</tr>
</tbody>
</table>

Conclusion???
SYSTEMIC DISORDERS AND GLAUCOMA

There is a clear beneficial effect of the use of glaucoma medication on the likelihood of death. Patients taking topical PGAs, a-agonists and B-blockers for confirmed POAG associated with a 74% reduction in death.


NEUROLOGY AND GLAUCOMA

When the RNFL Dies, The Brain Dies
When the Brain Dies, The RNFL Dies
The Optic Nerve is Part of the Brain
Stuff That is Good for the Brain is Also Good For the RNFL

Degeneration of RGC and axons represent a substantial loss of neural activity in the brain as 50% to 60% of the cerebral cortex spread over 40-45 visual areas represent visual function. This RGC degeneration entails downstream caspase and mitochondrial dependent apoptotic cascades resulting in actual loss of cortex.


Grey density reduction occurs in the primary visual cortex in patients with advanced glaucoma.


Measuring the optic nerve diameter at the orbital apex (15 mm behind the eye) shows significant correlation with RNFL loss.


Progressive visual field loss in NTG is associated with silent cerebral infarcts as defined by CT.


CEREBROSPINAL FLUID PRESSURE AND GLAUCOMA

QuickTime™ and a decompressor are needed to see this picture.
ICP is significantly lower in patients with POAG and NTG and higher in those with OHT without glaucoma. Minor differences of IOP have been associated with progression.


Minor differences of IOP have been associated with progression.


Lamina separates two distinctive pressurized zones, IOP 10-21 mm Hg and ICP 5-15 mm Hg. Average IOP is 16 and Average ICP is 12 and the IOP-ICP is called the Trans-laminar pressure.


Alteration of Trans-laminar pressure may bow the lamina creating a pinching of axons. Both intraocular fluid and intracranial fluid are created by carbonic anhydrase reactions and ultrafiltration.

Both IOP and ICP affected by BP.

Both IOP and ICP affected by BP.


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Both IOP and ICP affected by BP.


OTHER Neurological ISSUES

• EXCESSIVE GLUTAMATE FORMATION
  ISSUES INCLUDE:
    – STROKE
    – MIGRAINE
    – CNS TRAUMA
    – EPILEPSY
    – PD, AD, HD
    – HIV DEMENTIA
    – ALS, MS


WHITE MATTER LESIONS

• 1/3 NTG HAD WMLs ON MRI WITH INF VF DEFECTS (Optophthalmology 1985;115:1155, Arch. Ophthalmol. 2004;122)
  477)
• CSVD ANDATHEROMA WITH WML 3X INCIDENCE OF
  STROKE, AND LARGE RET VEIN DIAMETER WITH WML

MIGRAINE OCCURS IN 43% OF WOMEN
AND 18% OF MEN. AURA IN 25%. CNTGS
STATES MIGRAINE WAS RISK FACTOR
FOR PROGRESSION OF GLAUCOMA.
OTHER STUDIES REPORT NO
STATISTICAL RELATIONSHIP.


NEUROLOGICAL DIFFERENTIAL

• NEURO INVESTIGATION FOR FOLLOWING
  ISSUES
    – Young age
    – Sudden vision loss
    – Reduced central vision that is progressive
    – Vertically aligned visual field defects or VF
defects atypical for glaucoma
    – VF defects out of proportion to cupping
    – Eyes with optic atrophy exceeding cupping
    – Atypia


Conclusion???

HORMONES AND GLAUCOMA

IOP was significantly lower in women taking HT than in those who had never taken HT, even after removing other possible influences on IOP. 


Data in a recent study suggest a possible role for declining sex hormone levels in the genesis of primary open angle glaucoma. This study also found that current use of estrogen with progestin was associated with a reduced risk of POAG. 


Suggestions that estrogens are neuroprotective in degenerative disorders and possibly within the retina and in glaucoma. 

ESTROGEN LEVELS MAY HAVE SOME EFFECT ON GLAUCOMA

ESTRADIOL LEVELS 1/2 IN GLAUCOMA VERSUS NORMALS

ESTRADIOL POTENTIATES FLOW, TESTOSTERONE INHIBITS FLOW

RIM STRUCTURE ALTERED DURING MENSTRUAL CYCLE

SUGGESTION THAT FEMALE SEX HORMONES MAY BE PROTECTIVE OF THE OPTIC NERVE.

There are suggestions that “Topical estrogen drops may be a new alternative treatment of glaucoma.” Ozcura F, Aydin S. Med Hypotheses 2007;69:456.

VASCULAR SYSTEM AND GLAUCOMA

Conclusion???
THE DRANCE HEMORRHAGE IS THE DEMON OF GLAUCOMA.

FACT OR FICTION?

OHTS study photo review 84% detection of disc heme, observation gave 16%. Disc heme related to age, CCT, family history and smoking. Presence of heme increased risk of progression by 6X and 13.6% in eyes with previous heme 5.2% without previous heme.

BUT!!!
87% of eyes with disc heme did not progress in the 31 month follow-up.

Kass MA, Heuer DK, Higgenbotham EJ et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypertensive medication delays the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701-713.

Gordon MO, Beiser JA, Brandt JD et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:714-720

Simvastatin significantly protected against the development of progression of visual fields in a cohort of 121 patients with normal tension glaucoma.

WHY?

This Vascular Perfusion Stuff is All over the Place. Logic Dictates it is an Issue, But the Issue is Yet to Be Defined.

VASCULAR PERFUSION IS AN ISSUE. DIFFERENCE OF SYSTOLIC AND DIASTOLIC IOP IS OCULAR PULSE AMPLITUDE (OPA) AND IS LOWER IN PATIENTS WITH POAG AND NTG. AVE OPA IS 2.09 TO 2.8 MM HG

ASSOCIATIONS WITH POAG AND NTG

BLOOD FLOW

- VASCULAR DYSREGULATION
  - ABERRANT AUTOREGULATION
  - POSTURAL INDUCED
  - INCR VF PROGRESSION
  - IMPACTS ON MITOCHONDRIA


BLOOD FLOW

- SVP GONE 46% GLAUCOMA AND PRESENT 98% CONTROLS. (Br J Ophthalmol 2007;91:405, ARVO 2007 Abstract 2879)
- CCT AND INCR IN RVO (ARVO 2007 Abstract 3080/B587)
- GLAUCOMA HAS LOWER OCULAR SURFACE TEMP (Br J Ophthalmol 2007;91:878)

DORZOLAMIDE AS A VASOREGULATOR

- MAY INCREASE BLOOD VELOCITY AND FLOW (Microvasc Res 2006;72:101)
- DOES THIS ALSO LOWER ICP AND ALTER THE TRANS-LAMINAR PRESSURE GRADIENT?
- SHOULD NOT USE IN PATIENTS WITH A DEFECTIVE CORNEAL PUMP (Arch Ophthalmol 2007;125:1345)

SO SHOULD WE LOOK AT WAYS TO IMPROVE BLOOD FLOW???
Conclusion???