COMTROVERSIES IN PATHOGENESIS OF NEURONAL DAMAGE IN GLAUCOMA

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Topics of Controversy

1. Which is damaged first?
   • Apoptosis of RGC SOMA
   • Axonal transport blockade of RGC AXONS

2. What triggers damage?
   • A neuroinflammation
   • An ischemic insult
   • A biomechanical insult

3. CSF pressure & translaminar pressure difference
   • A real pathogenetic factor? or
   • An illusion?

4. CNS changes in glaucoma:
   • Come first (descending degeneration)?
   • Come second (ascending degeneration)?

5. Human genome & glaucoma inheritance
   • Where are we now?
   • Where are we going?
WHICH IS DAMAGED FIRST?

Apoptosis of Retinal ganglion cell Soma

OR

Axoplasmic flow blockade of RGC axons

Apoptosis of Retinal ganglion cell bodies (soma)

- RGC loss: 0.4%/yr with ageing
- In glaucoma, up to 4% loss/yr
- RGC death in glaucoma occurs predominantly through APOPTOSIS
- A programmed cell death, autonomous process (cell suicide), genetically controlled, requires energy

The cell receives an order to die
↓
DNA FRAGMENTATION
↓
CHROMATIN CONDENSATION
↓
Electron-dense Pyknotic nuclei
↓
(Apoptotic bodies)
↓
AUTOPHAGIC DEGENERATION

**What initiates RGC death in glaucoma?**

**Overexcitation by excitatory amino acids**
- **Glutamate** overstimulates **NMDA receptors** and activate nitric oxide synthase → intracellular influx of Ca++ → stimulate RGC death via activation of several apoptotic pathways → **Apoptosis** → subsequent RGC axonal degeneration
- **Role of Ca channel blockers in glaucoma**

**Loss of neurotrophic support**
- **Block of transport** of materials within the axons to RGC body → neurotrophic deprivation (especially **Brain-derived neurotrophic factor, BDNF**) → loss of trophic substances from the brain to the RGC for normal survival → **induction of apoptosis** “retrograde degeneration of RGC”

- [Calcins DJ. Prog Retin Eye Res 2012;31:702-9](#)
- [Kuribayashi J et al. Brain Res 2010;1362:133-40](#)

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**RGC AXONAL TRANSPORT**

**AXOPLAZMIC FLOW**

- Intracellular movement of molecules and organelles along the axons in an energy-dependant manner
- **Orthograde (antegrade) flow** (eye to brain, RGC to LGN)
  - Carries mitochondria, proteins, lipids, autophagosomes, and synaptic vesicles containing neurotransmitter
- **Retrograde flow** (brain to eye, LGN to RGC)
  - Recycles materials back to RGC
  - Provides trophic substances from the brain to the RGC for normal survival

WHAT BLOCKS AXOPLASMIC TRANSPORT (FLOW)?

- **High IOP** ➤ distortion of laminar beams (esp at the poles with large pores) ➤ **mechanical injury to axons** ➤ block orthograde & retrograde flow

| Ischemia of ONH & tissue hypoxia | ➤ mitochondrial injury ➤ **decrease energy for axoplasmic flow** ➤ Axonal transport blockade and accumulation of organelles near lamina |

Retinal ganglion cell axons (green) in the optic nerve only partially transport dyes out of the retina (red) even at early stages in glaucoma


The mechanism driving axonal transport may be sensitive to **translamina pressure gradient** and may not be able to overcome increasing hydrostatic pressure gradient (high IOP or low CSFP)

WHAT TRIGGERS DAMAGE?

- A neuroinflammation
- An ischemic insult
- A biomechanical insult

OR

OR
The Glial Tissue & Neuro-inflammation in Glaucoma

- A trigger (high IOP, injury)
- Receptor activation on astrocytes & microglia cells
- Activation of proinflammatory mediators (cytokines, complement pathway, tissue necrosis factor, ...)
- Up-regulation of adhesion molecules on endothelium
- Transendothelial migration of monocytes into the ONH
- Inflammatory reaction & astrogliosis
- May be a mediator of RGC & axon damage in glaucoma

Ocular Ischemia & Glaucoma

- Reduced Ocular blood flow & Perfusion Pressure
- Recurrent mild ischemic injury to RGCs
- Tissue hypoxia
- Oxidative stress (release of H$_2$O$_2$ & other reactive oxygen species)
- Mitochondrial dysfunction
- Impede axonal transport with BDNF depletion
- Apoptosis of RGCs soma
- Anterograde degeneration of RGC axons & higher visual pathways
- NMMA-induced Apoptosis of RGCs soma

- Excitotoxicity (increased sensitivity to glutamate & excessive stimulation of NMDA receptors)
- Increased influx of intracellular Ca$^+$
- Stimulate Ca$^+$ dependent enzymes
ONH BIOMECHANICS: STRESS & STRAIN

PRESSURE EFFECTS (STRESS/FORCES)  STRUCTURE GEOMETRY & MATERIAL PROPERTIES (STRAIN EFFECTS)

IOP magnitude/fluctuation
Perfusion pressure/fluctuation
CSF pressure/fluctuation (TLPD)
Tissue pressure in ON
Orbital (atmospheric) pressure

Retinal ganglion cells
RGC axons
Scleral canal & peripapillary sclera
ONH vasculature
ONH astrocytes & glial tissue
Lamina cribrosa architecture & extracellular matrix

* Burgoyne CF, Downs JC. Premise and prediction—How optic nerve head biomechanics underlies the susceptibility and clinical behavior of the aged optic nerve head? J Glaucoma 2008;17:318-28

GLAUCOMATOUS OPTIC NEUROPATHY

Neuronal damage (RGC axons and soma)

Thinning of RNFL & Ganglion cell complex
Atrophy of neuroretinal rim and prelaminar cupping

ONH Excavation

Posterior deformation of LC & Laminar cupping
IOP-DRIVEN ALTERATIONS OF LC (REMODELING)

**DURING EARLY STAGES**
- IOP elevation/fluctuation, (TLCP Gradient (IOP/CSF))
- Less rigid sclera causes scleral canal expansion
- Stretching & tightening of lamina cribrosa beams
- Resist posterior deformation & Generate strain within laminar beams
- Activation of LC cells & astrocytes

**DURING CHRONIC STAGES**
- Posterior deformation & outward migration of LC (LAMINAR CUPPING)
- Load bearing capacity of LC is exceeded
- IOP-related stress focused only on LC (the weak spot in sclera)
- More rigid sclera prevents scleral canal expansion
- Increase ECM production & thickening of LC to maintain load-bearing condition of laminar beams

A real pathogenetic factor
Or
An illusion?

THE CSF & TRANSLAMINAR PRESSURE DIFFERENCE

CSF PRESSURE & TRANS-LAMINAR PRESSURE DIFFERENCE

- A pressure gradient across the LC between intraocular space with a higher IOP and retrobulbar tissue pressure including a lower CSF Pressure
- Abnormal TLPD influences axoplasmic flow of RGC axons
- Correlation of 3 pressures (IOP, CSFP, BP) may suggest a systematic mechanism simultaneously influencing all three of them

- Jonas JB. Role of cerebrospinal fluid pressure in the pathogenesis of glaucoma Acta Ophthalmol 2011;89:505-514
Translamina Pressure Difference:
CLINICAL OBSERVATIONS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>IOP</th>
<th>CSFP</th>
<th>TLPD</th>
<th>PATHOLOGICAL FINDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT-POAG</td>
<td>High</td>
<td>Normal</td>
<td>High</td>
<td>Posterior laminar deformation</td>
</tr>
<tr>
<td>LT-POAG</td>
<td>Normal</td>
<td>Low</td>
<td>High</td>
<td>Posterior laminar deformation</td>
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<tr>
<td>Ocular hypertension</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>No change</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Normal</td>
<td>Very high</td>
<td>Very low</td>
<td>Anterior laminar deformation</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>High</td>
<td>High</td>
<td>No change</td>
<td>No deformation</td>
</tr>
<tr>
<td>Arterial Hypotension</td>
<td>Normal</td>
<td>Low</td>
<td>High</td>
<td>Posterior laminar deformation</td>
</tr>
</tbody>
</table>

* Jonas JB. Role of cerebrospinal fluid pressure in the pathogenesis of glaucoma Acta Ophthalmol 2011;89:505-514

TLPD: CLINICAL OBSERVATIONS

- **Limitations of CSF Studies in glaucoma**
  - Invasive nature of CSF pressure measurement (lumbar puncture)
  - It is not clear that the lumber CSFP is directly related to CSFP around the ON in the orbit
  - The role of retrolaminar tissue pressure within the ON which may act as a stable pillar of the LC against IOP even with low CSFP in the subarachnoid space around ON
  - Hospital-based studies may carry the potential of bias of the diseased sample or the control group (nonglaucomatous neurological pts)

* Jonas JB. Role of cerebrospinal fluid pressure in the pathogenesis of glaucoma Acta Ophthalmol 2011;89:505-514
CNS CHANGES IN GLAUCOMA

CNS & GLAUCOMA: A Real Change?

- **Experimental studies**: trans-synaptic degeneration of LGN & V1 after IOP elevation and ON damage
- **Postmortem analysis** for a glaucoma patient revealed correlation of ON damage, VF defects, and pathological changes in ON, LGB, & VC
- **MRI studies** in glaucoma patients revealed reduction in ON diameter, optic chiasm height, height & volume of LGN, optic radiation & visual cortex,

**GLAUCOMA AS A NEURODEGENERATIVE DISEASE**

- **Similarities between glaucoma & ND diseases (Alzheimer & Parkinson’s):**
  - **Selective loss of specific neuron population:**
    - Alzheimer: loss of hippocampal & cortical neurons → memory & cognitive disorder
    - Parkinson’s: loss of nigrostriatal dopaminergic neurons → movement disorder
    - Glaucoma: loss of RGC neurons & axons → loss of visual functions
  - **Mode of disease spread** by trans-synaptic degeneration in both ND disorders & glaucoma
  - **Common mechanism of cell injury & death (apoptosis)**


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**Are brain changes in glaucoma precede or follow RGC degeneration?**

Where are we now?
And
Where are we going?

HUMAN GENOME & GLAUCOMA INHERITANCE

IS GLAUCOMA AN INHERITED DISORDER?

- Strong familial association in many types of glaucoma
- High prevalence of certain types of glaucoma among certain ethnic groups:
  - POAG in black population
  - PACG in East Asian, Alaska
  - PDS & PG in white Caucasian
  - Congenital glaucoma in Middle East
- Evident heritability of some parameters associated with glaucoma: high IOP, large cup/disc ratio, steroid responsiveness
- Some forms inherited as mendelian dominant or recessive traits (JOAG)
- Mapping of glaucoma associated genes: JOAG, POAG, PCG, Rieger's syndrome
Advantages of molecular genetic studies

- Understanding disease pathophysiology from its root cause
- Development of diagnostic tests of the disease based on genetic mutations
- Development of pharmacologic or gene therapy treatment that target the affected gene
- Prevention of disease development may be possible through gene replacement therapy

Gene Therapy for Glaucoma

Gene Editing For POAG Proves Successful in Mice

It has implications for persons with mutations in the myocilin gene which have been reported in 4% of POAG patients, most notably juvenile.

FDA Approves the first true GENE therapy, LUXTURNA for an inherited retinal disorder of RPE 65 gene (Jan 2018)
Conclusions

- Glaucoma is a multifactorial disease with multiple contributing factors to its pathogenesis
- Glaucomatous optic neuropathy at optic nerve head is the hallmark of the disease
- Optic nerve head excavation and retinal ganglion cell and axon atrophy are the main characteristic features of glaucomatous optic neuropathy
- Excavation (cupping) comprises two components: prelaminar cupping (loss of neural tissues) and laminar cupping (posterior deformation of lamina cribrosa)
- All mechanisms of glaucomatous injury of ONH are inseparably intertwined

Thank You for your kind attention

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