“THE EYES HAVE IT”
A RETROSPECTIVE LONGITUDINAL COHORT STUDY IDENTIFYING POTENTIAL FOR GLAUCOMA TREATMENT AS NEUROPROTECTION FOR ALZHEIMER’S DEMENTIA

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Background

- MSc in Neuroscience at the Institute of Psychiatry, King’s College London between 2008-2010
- MRC Centre for Neurodegeneration Research
- Research undertaken at the Biomedical Research Centre, South London & Maudsley NHS Trust
Introduction

- Growing evidence of associations with AD
- Several studies have demonstrated higher rates of glaucoma in neurodegenerative disease
- It is suggested that similar models of degeneration occur in retinal ganglion cells of glaucoma with neurons of AD – cell death by apoptosis
- Growing opinion that treatment for AD could benefit glaucoma and vice versa
Unpublished data

Robust evidence linking later age of retirement to a delay in the onset of AD


Subset of patients with glaucoma may also have had a causal relationship with a delay in age of onset of AD
Objective

- To investigate whether the main treatments for glaucoma could offer neuroprotection by delaying the age of onset (AOO) in Alzheimer’s Dementia
- Secondary analysis investigated the neuroprotectant properties of common systemic medication subclasses
Method

- Subjects identified from SLaM ePJS database using their new CRIS data analysis tool
- Identifies patients in anonymised form based on keyword searches
- Inclusion criteria:
  - Patients assessed during 2005-2010 & given a diagnosis of AD or mixed AD/VaD
- Exclusion criteria:
  - Diagnosis before 65 years of age
- Cases: AD and on glaucoma treatment
- Controls: AD without glaucoma treatment
Data extracted

- Data from files extracted manually
- DOB, primary diagnosis, date of diagnosis, medications
- AOO of AD was determined by scrutinising timing of symptoms in documentation
- AOO recorded to nearest year
Analysis

- STATA version 10
- Linear regression analysis on identified variables against the recorded AOO of AD
“The cohort effect” (Bowler 1998)

Attempt to compensate for the high correlation between patient Age and AOO of AD (P < 0.001)

- Cohort divided into age ‘bins’
- Regression analysis performed against individual ‘bins’
Baseline results

55 cases & 198 controls from 2859
All suitable glaucoma cases used
Controls randomly selected by computer
Baseline results

At baseline, cases had a higher median age (85.33 vs. 82.84), which appeared to correlate with an older AOO of AD compared to controls.
<table>
<thead>
<tr>
<th>AOO of AD</th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>T</th>
<th>P</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Glaucoma medication</td>
<td>0.9995</td>
<td>0.4279</td>
<td>0.23</td>
<td>0.816</td>
<td>-0.7430 - 0.9429</td>
</tr>
<tr>
<td>Beta-antagonists</td>
<td>0.7156</td>
<td>0.5388</td>
<td>1.33</td>
<td>0.185</td>
<td>-0.3457 - 1.7770</td>
</tr>
<tr>
<td>Prostaglandin analogues</td>
<td>0.0364</td>
<td>0.5388</td>
<td>0.08</td>
<td>0.940</td>
<td>-0.9171 - 0.9901</td>
</tr>
<tr>
<td>Carbonic anhydrase Inhibitors</td>
<td>0.4272</td>
<td>0.8159</td>
<td>0.52</td>
<td>0.601</td>
<td>-1.1799 - 2.0345</td>
</tr>
<tr>
<td>Alpha-agonists</td>
<td>0.0050</td>
<td>1.0555</td>
<td>0.00</td>
<td>0.996</td>
<td>-2.0842 - 2.0741</td>
</tr>
<tr>
<td>Miotics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>0.7803</td>
<td>0.3489</td>
<td>0.22</td>
<td>0.823</td>
<td>-0.6091 - 0.7652</td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>0.7133</td>
<td>0.3776</td>
<td>1.89</td>
<td>0.060</td>
<td>-0.0305 - 1.4573</td>
</tr>
<tr>
<td>Statins</td>
<td>0.2326</td>
<td>0.3901</td>
<td>0.60</td>
<td>0.551</td>
<td>-0.5358 - 1.0012</td>
</tr>
</tbody>
</table>

Final results from data analysis
Supplementary analysis

- **Lupton data:**
  - 3132 patients
  - 46 cases
  - 3086 controls

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<th>P&gt;</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupton et al data</td>
<td>2.5159</td>
<td>0.8861</td>
<td>2.84</td>
<td>0.005</td>
<td>0.7776 - 4.2543</td>
</tr>
<tr>
<td>Combined data</td>
<td>0.9473</td>
<td>0.4931</td>
<td>1.92</td>
<td>0.055</td>
<td>-0.0199 - 1.9146</td>
</tr>
</tbody>
</table>
Discussion

- Although results disappointing, vastly premature to conclude that medications in glaucoma do not have an effect on AD
- Any genuine effect size is likely to be small and would need sizeable samples in a analysis
- **Obvious limitations:**
  - Small study size
  - Data collected retrospectively
  - Huge assumptions on accuracy and record keeping
  - Medication compliance presumed
Interesting points

- Growing evidence and opinion of links between glaucoma, AD & their treatments
- Potential for glaucoma treatments in AD related to their vasodilatory / blood pressure effects alone
  - Forette F et al; Prevention of dementia in a randomised double blind placebo controlled systolic hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352 (9137): 1347-1351
- ? Activation of pro-survival pathways, inhibition of glutamate exitotoxicity, free radical damage & effects on trophic factors
- Potential for existing treatments & novel routes of drug administration in neurodegenerative disease
Acknowledgements

- Drs John Powell & Michelle Lupton (IOP)
- Dr Rob Stewart (SLaM)
- Andrea Fernandes & Matthew Broadbent (SLaM)
- Daniel Stahl (IOP)
References

References

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Osbourne N: recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. Acta Ophthalmol 2009; 4: 450-454


Stewart R et al: the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 2009; 9:51

Summit Medical Group Website: http://media.summitmedicalgroup.com/media/db/relayhealth-images/glauc.jpg


References

“When our eyesight fails!”

Thank you

Questions?
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