The optic nerve as a 5th location for dissemination in space for multiple sclerosis criteria: a role for optical coherence tomography

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Disclosures

<u>Funding</u>: The NIHR BRC at Moorfields Eye Hospital supported AP, NGS, PAK, PTK, PJF, and PJP. This analysis was supported by the Eranda Foundation via the International Glaucoma Association, UCL ORS & GRS programmes. PJF received support from the Richard Desmond Charitable Trust, via Fight for Sight, London. The MS Centre Amsterdam is supported by the Stichting MS Research.

<u>Conflict of interests</u>: AP reports personal fees from Novartis, Heidelberg Engenieering, Zeiss, grants from Novartis, outside the submitted work; and AP is part of the steering committee of the OCTiMS study which is sponsored by Novartis. AP is part of the steering committee of Angio-OCT which is sponsored by Zeiss. He does not receive honorary as part of these activities. PAK reports personal fees from Allergan, personal fees from Topcon, personal fees from Heidelberg Engineering, personal fees from Haag-Streit, personal fees from Novartis, personal fees from Bayer, personal fees from Optos, personal fees from DeepMind, grants from National Institute for Health Research (NIHR), outside the submitted work.

CR reports employment by Topcon Healthcare Solutions Inc., outside submitted work. NGS has nothing to disclose. PJF reports personal fees from Allergan, Carl Zeiss, Google/DeepMind and Santen, a grant from Alcon, outside the submitted work; PJP reports grants from Topcon Inc, outside the submitted work.

Background

- The diagnosis of MS is based on a combination of clinical and para-clinical tests
- The potential contribution of OCT has been recognised
- We tested the feasibility of OCT measures of retinal asymmetry as a diagnostic test for MS at the community level

Methods

- n=502,656 UK participants aged 40–69 years
- Retinal spectral domain OCT in n=78,505
- Calculate inter-eye difference from n=72,120
 - Percentage (IEPD) as %
 - [–] Absolute (IEAD) as μm
- Calculate diagnostic value of IEPD/IEAD for MS for a range of scenarios using the Receiver Operator Characteristics (ROC) Area under the Curve (AUC)

Cohort

| | All controls | MS |
|------------------|--------------|------------|
| Ν | 71,939 | 144 |
| Age (years) | 56.67 ±8.05 | 55.20±7.82 |
| Female sex | 38633 (54%) | 110 (74%) |
| Optic Neuritis | 0 (0%) | 0 (0%) |
| mGCIPL OD [µm] | 72.36±6.28 | 67.21±7.04 |
| mGCIPL OS [µm] | 72.45±6.23 | 67.65±7.05 |
| IEPD mGCIPL [%] | 2.76±3.56 | 6.51±6.23 |
| IEAD mGCIPL [µm] | 2.03±2.63 | 4.62±4.62 |

Data also calculated for RNFL and GCC, but of lesser statistical relevance because of lower AUC. See next slide.

The mGCIPL is best

| Inter-eye Difference | AUC | 95% | CI | P-value | P-value |
|----------------------|--------|--------|--------|------------------|------------------|
| IEPD mGCIPL | 0.7110 | 0.6646 | 0.7575 | <u>reference</u> | 0.318 |
| IEAD mGCIPL | 0.7075 | 0.6621 | 0.7529 | 0.318 | <u>reference</u> |
| IEPD mGCC | 0.6483 | 0.5979 | 0.6987 | 0.0073 | 0.011 |
| IEAD mGCC | 0.6419 | 0.5925 | 0.6912 | 0.003 | 0.0043 |
| IEPD mRNFL | 0.5948 | 0.5451 | 0.6445 | <.0001 | <.0001 |
| IEAD mRNFL | 0.5859 | 0.5383 | 0.6334 | <.0001 | <.0001 |

Cumulative comorbidities matter

Cumulative comorbidities





Healthy controls and disease conditions

Forest plot of relevant confounders

| | (A) The mGCIPL | L IEPD as a su | pportive | e paraclinical te | est for MS | | | |
|-------------------------|--------------------|-----------------|----------|-------------------|------------|-------|---------|------|
| Characteristic | No.of Patients (%) | | (| Odds Ratio Plot | | (|)r (95% | CI) |
| Subgroup | CountPct | | | | | | | |
| Overall | 72083 (100%) | | | ├──■ ─┤ | | 1.13 | 1.1 | 1.16 |
| Age (years) | | | | | | | | |
| <=65 | 61668 (86%) | | | _ +=-1 | | 1.14 | 1.12 | 1.17 |
| >05 Gender | 10448 (14%) | E CONTRACTOR OF | | | | 1.05 | 0.94 | 1.17 |
| Female | 38720 (54%) | | | ∎ | | 1.13 | 1.11 | 1.16 |
| Male | 33357 (46%) | | | · · · | 4 | 1.14 | 1.09 | 1.19 |
| Ethnicity | | | | | | | | |
| Nonwhite | 5823 (8.1%) | | | | | 1.11 | 0.97 | 1.27 |
| White | 65814 (91%) | | | ┝─╋─┤ | | 1.13 | 1.11 | 1.16 |
| >170 | 30343 (42%) | | | | | 1 16 | 1 12 | 12 |
| <=170 | 41294 (58%) | | | ⊢ _ | i. | 1.12 | 1.09 | 1.16 |
| BMI | | | | | | | | |
| >25 | 45875 (65%) | | | ∎ | | 1.13 | 1.09 | 1.17 |
| <=25 | 24394 (35%) | | | ∎ | | 1.14 | 1.1 | 1.17 |
| Alcohol | 12245 (500() | | | | | 4 4 7 | | 1 22 |
| yes | 13245 (50%) | | | | | 1.17 | 1.11 | 1.23 |
| Smoker | 13030 (30 %) | | | | | 1.1 | 1.04 | 1.17 |
| yes | 42768 (60%) | | | ⊢-∎ | | 1.14 | 1.11 | 1.17 |
| no | 28914 (40%) | | | ÷ | | 1.22 | 1.08 | 1.17 |
| Diabetes mellitus | | | | | | | | |
| yes | 3685 (5.1%) | | | | | 1.09 | 0.98 | 1.2 |
| no Eva Diagona | 68001 (95%) | | _ | | | 1.14 | 1.11 | 1.16 |
| ves | 1759 (2.4%) | | | _ | | 1 04 | 0.95 | 1 14 |
| no | 70324 (98%) | | ' I I | | | 1.14 | 1.11 | 1.16 |
| Visual acuity [log MAR] | . , | | | | | | | |
| <=0 | 34343 (56%) | | | .⊢ . | 4 | 1.15 | 1.11 | 1.19 |
| >0 | 27230 (44%) | | | | | 1.14 | 1.1 | 1.17 |
| IOP [mmHg] | 21540 (45%) | | | | | 1 1 2 | 1.00 | 1 17 |
| <16 | 38490 (55%) | | | | | 1.12 | 1.00 | 1.17 |
| Glasses | 30430 (3370) | | | | | 1.14 | | 1.17 |
| yes | 61074 (100%) | | | ∎ | | 1.14 | 1.12 | 1.17 |
| anisometropia | 11542 (16%) | | | ⊢ | | 1.1 | 1.04 | 1.16 |
| | _ | T T | | | 1 1 | | | |
| | C | 0.8 0.9 | 1.0 | 1.1 | 1.2 1.3 | OR | LI | UI |
| | | | MC | moro likoly | | | | |
| | | | 1113 | | | | | |

| | (B) The mGCI | PL IEAD | as a su | ipporti | ve paraclir | nical test f | or MS | | | |
|--------------------------------------|-----------------------------|-----------------------------|---------|----------|--|-------------------|-------|--------------|--------------|--------------|
| Characteristic | No.of Patients (%) | %) OddsRatio Plot OR (95% C | | | | | | G CI) | | |
| Subgroup | CountPct | | | | | | | | | |
| Overall | 72083 (100%) | | | | ⊢ | | | 1.13 | 1.1 | 1.16 |
| Age (years) <=65 >65 | 61668 (86%) 10448 (14%) | | F | | _ | ┝╌╋╌┤ | | 1.14 1.05 | 1.12 0.94 | 1.17 1.17 |
| Gender Female Male | 38720 (54%) 33357 (46%) | | | | F | - - | | 1.13 1.14 | 1.11 1.09 | 1.16 1.19 |
| Ethnicity Nonwhite White | 5823 (8.1%) 65814 (91%) | | | - | | | | 1.11 1.13 | 0.97 1.11 | 1.27 1.16 |
| Height [cm] >170 | 30343 (42%) | | | | 1 | | | 1.16 | 1.12 | 1.2 |
| <=170 | 41294 (58%) | | | | | ╉──┤ | | 1.12 | 1.09 | 1.16 |
| >25 <=25 | 45875 (65%) 24394 (35%) | | | | ⊢ ⊢ | ■ ■ | | 1.13 1.14 | 1.09 1.1 | 1.17 1.17 |
| Alcohol yes | 13245 (50%) | | | | F | - | -1 | 1.17 | 1.11 | 1.23 |
| no | 13056 (50%) | | | | | | | 1.1 | 1.04 | 1.17 |
| yes no | 42768 (60%) 28914 (40%) | | | | + بــــــــــــــــــــــــــــــــــــ | | | 1.14 1.22 | 1.11 1.08 | 1.17 1.17 |
| Diabetes mellitus | | | | | | | | | | |
| yes | 3685 (5.1%) 68001 (95%) | | | - H | _ | | | 1.09 1.14 | 0.98 1.11 | 1.2 1.16 |
| Eye Disease | | | | | | | | | | |
| yes no | 1759 (2.4%) 70324 (98%) | | | | | ∎ | | 1.04 1.14 | 0.95 1.11 | 1.14 1.16 |
| Visual acuity [log MAR] <=0 >0 | 34343 (56%) 27230 (44%) | | | | F | (| | 1.15 1.14 | 1.11 | 1.19 1.17 |
| IOP [mmHg] | | | | | | | | | | |
| >= 16 <16 | 31540 (45%) 38490 (55%) | | | | | ∎──┤ ──₩─┤ | | 1.12 1.14 | 1.08 1.11 | 1.17 1.17 |
| Glasses yes anisometropia | 61074 (100%) 11542 (16%) | | | | ⊦∎ | ├ -ब | | 1.14 1.1 | 1.12 1.04 | 1.17 1.16 |
| | | 0.8 | 0.9 | 1 | n 11 | 1 2 | 13 | | | |
| | | 0.0 | 0.5 | MS r | nore likely - | > | 1.5 | 011 | | 01 |
| | | | | 10131 | nore incly - | - | | | | |

Diagnostic sensitivity and specificity of the IEPD/IEAD for MS

| mGCIPL | Cut-off | References | Specificity | Sensitivity | PPV | NPV |
|--------|---------|-----------------------------|-------------|-------------|-------|------|
| IEPD | 20 % | Petzold et al. 2014 | 99.4 | 2.7 | 0.998 | 0.01 |
| IEPD | 4 % | Coric et al. 2017 | 82.8 | 51.7 | 0.6 | 99.9 |
| IEAD | 4 µm | Nolan-Kenney et al. 2019 | 86.8 | 43.5 | 0.7 | 99.9 |

Discussion

- The mGCIPL IEPD / IEAD may be considered as 5th location for dissemination in space for MS (slide 6)
 - in less than 5 comorbidities (slide 7)
 - in absence of confounders (slide 8)
- To be viable, higher sensitivity and specificity levels are needed (slide 9)