Spatial vision in visually asymptomatic subjects at high risk for multiple sclerosis

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Objective: To investigate the state of spatial vision in visually asymptomatic subjects at high risk for multiple sclerosis.

Methods: Fifteen subjects suffering a first neurological episode suggestive of multiple sclerosis in clinical presentation, immunological profile, and magnetic resonance imaging, were examined with a new, sensitive test of spatial vision, rarebit perimetry. None had symptoms or signs of optic neuropathy.

Results: Results of rarebit perimetry were significantly worse than those of 15 age matched normal controls (p=0.01); seven patients (47%) were outside normal limits. One patient only obtained abnormal results in high pass resolution perimetry.

Conclusions: Rarebit perimetry may help to close the sensitivity gap between clinical examinations and neuroimaging.

Advances in neuroimaging have highlighted an extensive involvement of the central nervous system at early stages of multiple sclerosis (MS), even at its very first manifestation. The first bout usually produces clinical signs attributable to a single lesion, most commonly in an optic nerve, in the brain stem cerebellum, or in the spinal cord. However, most of the lesions revealed in neuroimaging reside in the cerebral hemispheres, particularly in the periventricular regions, and are clinically silent. This silence points to the need for better tools for assessing neural function. Accurate assessment has become increasingly important with the advent of new treatment modalities.

When considering what functions and pathways might be best accessible for refined assessment, vision and the visual pathways emerge as good candidates. Strong advantages include the possibility to probe function in small subsets of fibre bundles and the pathways’ wide extension throughout the hemispheres, including the posterior periventricular regions. Although perimetry might seem ideal for the task, standard perimetry actually has a limited ability to detect small degree neural damage. Clinicopathological correlations have shown that neural channel losses must amount to 25% to 50% before standard perimetry returns consistently abnormal results. Experimental studies have revealed similar sensitivity gaps. To meet the need for a more sensitive assessment, a new test principle, rarebit probing, has been developed and shown to have superior sensitivity in one model disorder—that is, chiasmal compression. Rarebit perimetry was used in this study of 15 subjects with a first, non-visual bout of focal, neurological disease. All had immunological and neuroimaging abnormalities predictive of MS.

METHODS

Patients were recruited sequentially from Sahlgren’s Hospital’s emergency neurological service where they had presented with a first neurological episode suggestive of MS. Those who had symptoms and/or signs of acute optic neuritis were excluded. Table 1 summarises key clinical data. Cerebrospinal fluid was assayed for oligoclonal banding. Magnetic resonance imaging (MRI) used a MS protocol.

Age matched normal controls were recruited among healthy blood donors and hospital staff. All subjects underwent a detailed clinical neuro-ophthalmological evaluation, including visual fields by high pass resolution perimetry.

Abbreviations: MS, multiple sclerosis; MRI, magnetic resonance imaging; HRP, high pass resolution perimetry

Table 1 Summary of patient data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Duration weeks</th>
<th>Symptoms</th>
<th>Hit rate (%)</th>
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<tr>
<td>1</td>
<td>22</td>
<td>m</td>
<td>1</td>
<td>sensory: hemi</td>
<td>97</td>
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<tr>
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<td>22</td>
<td>f</td>
<td>1</td>
<td>motor: hemi</td>
<td>95</td>
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<td>24</td>
<td>f</td>
<td>4</td>
<td>motor: legs</td>
<td>86</td>
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<tr>
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<td>m</td>
<td>2</td>
<td>motor: arm</td>
<td>85</td>
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<td>m</td>
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<tr>
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<td>f</td>
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<td>motor: face+arm</td>
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<td>87</td>
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<tr>
<td>10</td>
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<td>1</td>
<td>vertigo</td>
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<tr>
<td>15</td>
<td>49</td>
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<td>1</td>
<td>vertigo, sens arm</td>
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controls (average 6.4 (3.8) times were 0.63 (0.16) s for patients and 0.70 (0.16) for controls, as was the modal number (0). Mean reaction times were 0.70 (0.16) s for patients and 0.70 (0.16) for controls (p=0.31).

RESULTS

Most subjects obtained closely similar results in both eyes. The study concentrates on the results from the first tested eye, to exclude inter-eye dependencies and any training effects.

The 15 control subjects presented overall mean (SD) hit rates of 96.6% (2.0). Missed presentations occurred mostly in the blindspot area and along major retinal vessels (angiotoscotaoma). A lower normal limit was defined from these results as the mean—1.96×SD—that is, 92.7%. None of the normal subjects fell outside this limit. Term times averaged 5 min 4 s.

The 15 patients were examined a median two weeks (range 1–16) after debut of sympotms, at a mean age of 31 (8) years. All had oligoclonal banding in their cerebrospinal fluid. The median number of intracranial MS-like lesions in MRI was 5 (range 0–10); the median number of hemispheric lesions was 2 (0–9). The patients showed a larger range of overall mean hit rates than did the controls (fig 1). The group mean equalled 92.0 (5.9)% and was significantly different from that of the controls (p=0.01). Seven patients (47%) fell outside the individual control limits. Mean hit rate in the blindspot area was only 12%, attesting to good fixation. For the controls, the same statistic equalled 24%; the difference was not significant (p=0.12). The median number of test errors was the same (1) for both groups, as was the modal number (0). Mean reaction times were 0.63 (0.16) s for patients and 0.70 (0.16) s for controls (p=0.31).

One single patient had a focal yet asymptomatic defect in rarebit perimetry, a homonymous upper quadratnt depression. The other patients presented apparently randomly distributed losses, of low degrees. There was no central field preponderance, either in individual maps or when averaging across subects. Averages across locations were tightly correlated with those of the controls (r=0.974). However, there were a somewhat larger number of locations where two or more presentations (out of 10) were missed among patients compared with controls (average 6.4 (3.8) v 2.6 (1.8); p=0.01).

Apart from the patient with a homonymous field defect, there were no statistically significant correlations between the rarebit results and the numbers or distribution of macroscopic lesions in MRI.

The results of HRP threshold perimetry were less striking. The instrument automatically provides a number of quantitative indices. An effective capacity index aims to assess spatial density of functional neural channels, relative to normals. Mean effective capacity for controls equalled 105 (17.3)% and for patients 97.7 (21.9)% (p=0.32). Again deriving normal limits from the control subjects, only one patient fell outside HRP normal limits.

DISCUSSION

For a plausible diagnosis of early stage demyelinating disease, this study relies heavily on recent advances in neuroimaging technology. Previous reports on spatial vision in visually asymptomatic MS patients have had to focus on later stages.4,5 There seems to exist only one closely comparable study. Lycke and coworkers6 used HRP to illuminate spatial vision in patients selected on the basis of exactly the same criteria and from the same geographical area. These authors reported a 57% prevalence of HRP results outside normal limits. However, the number of patients was small (7) and the observed prevalence might be fortuitously high. There were no statistically significant differences between previous studies and this study with respect to duration of symptoms, disability (expressed as scores on the Expanded Disability Status Scale), or mean number of MRI lesions. Hence, pooling should provide a better estimate of the true prevalence of HRP abnormality. Pooling indicated a 23% prevalence of HRP abnormality—that is, one half of the prevalence found by rarebit perimetry.

Several studies have aimed to illuminate early involvement of the visual pathways in demyelinating disease by another approach—that is, selecting subjects with unilateral optic neuritis and studying the fellow eye. Many previous studies
depended on perimetric techniques that are now obsolete. Studies using modern, computer assisted perimetry have identified some abnormality in many fellow eyes. The Optic Neuritis Treatment Trial (ONTT) is the most representative by virtue of its size (448 subjects) and its strict quality controls. Keltner et al reported that 69% of the ONTT fellow eyes showed perimetric abnormalities. These were labelled minimal in 62%. One quarter (26%) of all subjects had moderate or severe fellow eye abnormality. Most of the fellow eyes were found normal at a six month follow up.

Rapid perimetry software

The rapid perimetry software (in Microsoft Windows format) is available free of charge from the author.

REFERENCES

1 CHAMPS Study Group. Baseline MRI characteristics of patients at high risk for multiple sclerosis: results from the CHAMPS trial. Multiple Sclerosis 2002;8:330–8