A serial MRI study following optic nerve mean area in acute optic neuritis

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Summary
This study assessed optic nerve mean area on serial MRI in a cohort of patients with a first episode of acute unilateral optic neuritis to assess the effects of a single acute inflammatory demyelinating lesion. Twenty-nine patients with a median delay from onset of visual symptoms of 13 days (range 7–24 days) were recruited. After a clinical examination and visual evoked potential (VEP) measurement, each patient had their optic nerves imaged with a coronal fat-saturated short echo fast fluid-attenuated inversion recovery sequence. Twenty-one patients had serial examinations after 2, 4, 8, 12, 26 and 52 weeks. In addition, 32 control subjects had their optic nerves imaged up to three times. The mean cross-sectional area of the intra-orbital portion of each optic nerve was calculated by a blinded observer using a computer-assisted contouring technique. At baseline, the mean area of diseased optic nerves was 16.1 mm² compared with 13.4 mm² for healthy contralateral optic nerves (20.1% higher, \(P<0.0001\)) and 13.6 mm² for controls (18.4% higher, \(P=0.0003\)). The diseased optic nerve mean area declined over time, from initial swelling to later atrophy. The mean decline at 52 weeks was \(-0.00051\) mm²/day (95% confidence interval \(-0.0038\) to \(-0.00051\)). At 52 weeks, the mean area of diseased optic nerves was 11.3 mm² compared with 12.8 mm² for healthy contralateral optic nerves (11.7% lower, \(P=0.032\)) and 13.1 mm² for controls (13.7% lower, \(P=0.008\)). The 52 week diseased optic nerve mean area was not significantly affected by the baseline mean area. There was an association between baseline optic nerve mean area and logMAR visual acuity \((r_S = 0.46, P = 0.012)\) and visual field mean deviation \((r_S = -0.55, P = 0.002)\), but there was no evidence of an association between 1 year mean area and visual outcome. There was no evidence of association between baseline, rates of decline or 1 year diseased optic nerve mean areas and any of the baseline, 1 year or time-averaged VEP variables. The present study shows a consistent pattern of changes associated with individual inflammatory demyelinating lesions in the optic nerve. Acutely, there was swelling, consistent with the presence of acute inflammation, which was related to visual impairment. Over the longer term, there was loss of tissue. The lack of association between 1 year optic nerve mean area and visual outcome may reflect a mild loss of tissue, redundancy or remodelling of function.

Keywords: optic neuritis; MRI; atrophy; multiple sclerosis; disability

Abbreviations: ETDRS = early treatment diabetic retinopathy study; FSE = fast spin echo; MTR = magnetization transfer ratio; sTE fFLAIR = fat-saturated short echo fast fluid-attenuated inversion recovery; VEP = visual evoked potential

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Introduction

The major event in relapsing–remitting multiple sclerosis is the acute relapse. The majority of patients with multiple sclerosis present with such an event. Most early relapses are followed by complete or near complete recovery; however, an individual relapse can result in significant permanent disability (Lublin et al., 2003). Study of the effects of individual lesions responsible for a relapse, from the acute phase onwards, may help in improving understanding of the pathophysiological mechanisms of recovery or its failure to occur. This may make prediction of the prognosis for recovery from a relapse better and could provide a means of monitoring treatment effects in future therapeutic trials of novel agents in acute multiple sclerosis relapses. Unfortunately, in the brain and spinal cord, it has been difficult to identify reliably the lesion that is responsible for the symptoms of an individual relapse (Behan et al., 2000), and most new brain and spinal cord lesions which are apparent on MRI are clinically silent (Thorpe et al., 1996; Miller et al., 1998).

Optic neuritis provides an attractive model to study the effects of relapses in multiple sclerosis. It is a frequent manifestation of multiple sclerosis and has been regarded as a forme fruste of the disease (Ebers, 1985). The natural history of acute optic neuritis mirrors that of an acute multiple sclerosis relapse elsewhere in the CNS, and the response to corticosteroid therapy is the same (Brusaferri and Candelise, 2000). There are also accurate and reproducible tests of visual function across a spectrum of different parameters (Beck, 1998) and it is possible to measure the latency and amplitude of the visual evoked response which give information about the integrity of the visual conducting pathways (Halliday et al., 1972). Finally, MRI, with appropriate fat saturation techniques, enables the symptomatic lesion in optic neuritis to be visualized (Gass et al., 1996) and, unlike elsewhere in the brain and spinal cord, the clinically relevant affected white matter tract (in this instance the optic nerve) can be delineated relatively easily.

MRI allows in vivo study of the evolution of multiple sclerosis. Measurements of CNS atrophy are used increasingly to monitor disease progression in both natural history studies and therapeutic trials (Miller et al., 2002). Atrophy of tissue in multiple sclerosis could potentially result from both demyelination and axonal loss. However, axons contribute almost twice as much to the bulk of white matter as myelin (Miller et al., 2002), and axonal loss would seem likely to be the more important determinant of atrophy. There have been many studies of brain and spinal cord atrophy in multiple sclerosis using MRI. These measures are of either the whole brain or a representative part, for example brain lateral ventricle volume or spinal cord area at C2/3 (Miller et al., 2002). They tend to represent the global effects of disease rather than the effect of lesions on a single pathway. The latter could, in principle, be assessed in the optic nerve. We previously have described a reproducible technique to measure orbital optic nerve mean cross-sectional area using a fat-saturated short echo fast fluid-attenuated inversion recovery (sTE fFLAIR) sequence which removes the high signal from both orbital fat and CSF in the sheath of the optic nerve (Hickman et al., 2001). Optic nerve atrophy was demonstrated following optic neuritis and the degree of atrophy related to time since onset of the illness. Serial follow-up in a subgroup of patients demonstrated ongoing atrophy some years following the acute event in many of the patients. Poor baseline visual acuity ($P = 0.02$), decreased visual evoked potential (VEP) amplitudes ($r_S = 0.65$, $P = 0.02$) and increased latencies ($r_S = -0.61$, $P = 0.04$) were associated with the degree of atrophy (Hickman et al., 2002). Recently, Inglese et al. (2002) imaged 30 patients with multiple sclerosis who had had a previous episode of optic neuritis. Optic nerve atrophy was demonstrated in eyes previously affected by optic neuritis, and optic nerve volume correlated modestly with both visual acuity ($r_S = 0.39$, $P = 0.01$) and VEP latency ($r_S = -0.31$, $P = 0.05$). An earlier study using short tau inversion recovery (STIR) imaging demonstrated optic nerve swelling in acute optic neuritis with atrophy on imaging after a mean follow-up of 465 days (Youl et al., 1996).

Although atrophy measures are widely used to monitor the course of multiple sclerosis, the mechanisms of progressive atrophy and axonal loss are not well understood. One potential mechanism for the development of ongoing atrophy is Wallerian degeneration due to axonal damage in focal multiple sclerosis lesions. This may result from inflammatory and post-inflammatory mechanisms. Axonal transection and loss has been shown to occur in acute inflammatory multiple sclerosis lesions (Ferguson et al., 1997; Trapp et al., 1998). However, axons are potentially vulnerable for a long time, perhaps months or years, in the post-inflammatory lesion if there is persistent demyelination and/or exposure to excitatory neurotoxic molecules including nitric oxide and glutamate (Smith and McDonald, 1999). In the brain and spinal cord, measures of atrophy, in general, correlate only modestly with lesion load measures, but it is difficult to explore the relationship between atrophy and lesions in these regions because it is not possible to study the effects of individual lesions within their relevant fibre tract (Miller et al., 2002). Optic neuritis offers a unique opportunity to investigate individual inflammatory lesions and the consequences that they have for tissue volume loss.

This study focuses on a cohort of patients recruited prospectively with their first episode of acute optic neuritis. The key aims of the present study are: (i) to quantify the changes in size (measured as the optic nerve cross-sectional area) seen due to an individual acute inflammatory demyelinating lesion within its fibre tract, previously observed to be swollen acutely and atrophied chronically; (ii) to determine the time course of atrophy developing as a result of individual lesions; (iii) to explore if any of the acute imaging, clinical or electrophysiological measures may help in predicting the likelihood of optic nerve atrophy developing: identifying such factors may help in selecting
patients where therapies to prevent atrophy are most needed; and (iv) to determine whether the extent of early swelling or later atrophy is related to clinical, imaging or electrophysiological measures.

**Patients and methods**

**Patients**

Twenty-nine patients with their first episode of acute unilateral optic neuritis (10 males, 19 females, median age 30 years, range 19–53) were recruited from the Neuro-ophthalmology clinic, Moorfields Hospital, London. The median delay from onset of visual symptoms to the first examination was 13 days (range 7–24 days). Three of the patients had clinically definite multiple sclerosis, five had clinically probable multiple sclerosis and 21 had clinically isolated optic neuritis (Poser et al., 1983). All of the patients were examined acutely and then 21 were followed-up after 2, 4, 8, 12, 26 and 52 weeks (with some missing time points for some of the patients). Ethical approval was obtained for the study from the joint ethics committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery; informed consent in writing was obtained from each subject, in accordance with the Declaration of Helsinki.

**Methods**

MRI was performed on a Signa 1.5 T imager (General Electric, Milwaukee, WI). The patients’ optic nerves were imaged with the sTE fFLAIR sequence [coronal-oblique, repetition time (TR) = 2740 ms, echo time (TE) = 16 ms, inversion time (TI) = 1072 ms, number of excitations (NEX) 6, echo train length (ETL) 6, matrix size 512 × 384, 24 × 18 cm field of view, in-plane resolution 0.47 × 0.47 mm, 16 × 3 mm interleaved contiguous slices, acquisition time 13.5 min] and a fat-saturated dual echo fast spin echo (FSE) sequence (coronal–oblique, TR 2300 ms, TEF 58/145 ms, ETL 8, NEX 2, 512 × 384 matrix, 24 × 18 cm field of view, in-plane resolution 0.47 × 0.47 mm, 16 × 3 mm interleaved contiguous slices, 11 min acquisition time).

In addition, 24 of the patients had their optic nerves imaged at baseline before and after intravenous administration of 0.3 mmol/kg dimeglumine gadopentate (double-dose gadolinium) with a coronal–oblique fat-saturated T1-weighted spin echo sequence (TR 600 ms, TE 20 ms, one excitation, 256 × 192 matrix, 24 × 18 cm field of view, in-plane resolution 0.94 × 0.94 mm, 16 × 3 mm interleaved contiguous slices, acquisition time 3 min). An experienced radiologist (K.A.M.), blinded to the lesion side and severity of visual loss, identified and measured the length of lesions on FSE images and any enhancing optic nerve lesions on the post-gadolinium T1-weighted images. Serial imaging following triple-dose gadolinium was performed on 15 of the patients after 2, 4, 8 and 12 weeks until enhancement was deemed to have ceased. The duration of enhancement was noted.

Thirty-two control subjects (14 male, 18 female, median age 31 years, range 21–58) were also imaged. Ten of the controls were imaged once, six were imaged twice and 16 were imaged on three separate occasions spread out over the course of 1 year.

A quadrature birdcage head coil was used as both transmitter and receiver coil. Subjects were asked to close their eyes and avoid any deliberate eye movements during image acquisition. Between imaging sessions, care was taken to reposition the imaging field of view accurately. In particular, the line from the anterior commissure to the posterior commissure on sagittal localizer images was used to ensure that the subjects’ head angles were the same at each session (Hickman et al., 2002).

At each visit, the patients were examined. Best visual acuity was measured (unaided, with appropriate spectacle correction or with pinhole correction) using a retro-illuminated early treatment diabetic retinopathy study (ETDRS) chart and recorded as the 4 m logMAR acuity (Ferris et al., 1982). When no letters could be correctly identified, a score of 1.7 was assigned (Optic Neuritis Study Group, 1991). The central 30° of the visual field was analysed using the 30-2 program on the Humphrey field analyser (Allergan-Humphrey Inc., San Leandro, CA). Wide-angle lenses were used to correct refractive errors where necessary. The overall field mean deviation was compared with a reference field derived from control data provided by the manufacturer. A mean deviation of −35 dB was assigned when vision was too poor to attempt the test (Kupersmith et al., 2002). The above two parameters were chosen because they give continuously variable measures that are amenable to statistical analysis.

In addition, at baseline, 4, 12 and 52 weeks, whole-field and central-field pattern-reversal VEPs were measured on each patient (Brusa et al., 2001).

The sTE fFLAIR images were displayed on Unix workstations (Sun Microsystems, Mountain View, CA) using the DispImage display tool (Plummer, 1992). The mean cross-sectional area of the intra-orbital portion of each optic nerve was calculated by an experienced observer blinded to image identity and acquisition order. Analysis of the images was performed on five consecutive 3 mm slices anteriorly from the orbital apex, using a computer-assisted contouring technique as previously described (Hickman et al., 2001). The measurements were repeated from all of the controls’ baseline imaging and 20 of the patients’ images selected at random so that the measurement reproducibility could be calculated.

One patient had bilateral recurrence of optic neuritis after 12 weeks and two patients had recurrences in their previously healthy contralateral optic nerves, one patient at both 12 and 52 weeks and one patient at 26 weeks. The respective data from these time points and after have been discarded.

**Statistical methods**

To assess measurement reproducibility, the within- and between-subject SDs [and hence coefficient of variation
(CV) and intraclass correlation coefficient (ICC) were obtained from random effects one-way analysis of variance (Bland and Altman, 1996).

Paired t tests were used to assess differences between diseased and healthy contralateral optic nerve mean areas at fixed time points. Two-sample t tests were used for the comparison between diseased and control optic nerve mean areas both at fixed time points and for ‘time-averaged’ values (mean for each patient over available time points). For controls, the average of their left and right optic nerve mean areas was used throughout. Variation in healthy nerve area over time was examined using random intercept and fixed slope regression models (Goldstein, 2000) with linear term in time (there was no evidence that random slopes improved fit). Patient indicator \( \times \) time interaction terms were used to assess patient versus control differences in gradients over time.

Patient-specific baseline and 1 year rates of decline and eventual levels of diseased optic nerve area were estimated by fitting exponential models in time (Snedecor and Cochran, 1989) for each patient. The exponential model used captures features of the trajectory by means of three estimated parameters: \( \alpha, \beta \) and \( \gamma \):

\[
y_{ij} = \alpha_j + \beta_j \exp(-\gamma_j \text{time}_ij) + \epsilon_{ij} \sim N(0, \sigma^2)
\]

where \( y_{ij} \) is the area variable for the \( i \)th assessment of the \( j \)th subject, and \( \text{time}_ij \) is the time from onset at the \( i \)th assessment of subject \( j \); \( \epsilon_{ij} \) is the error term, assumed normally distributed with mean 0, variance \( \sigma^2 \). The interpretation of the estimated parameters is: \( \alpha_j \) is the asymptote, or estimated ‘eventual’ atrophy level, for subject \( j \), and the product \(-\beta_j \gamma_j\) is the estimated gradient of decline of area at baseline. Since this type of non-linear model is difficult to fit in a multilevel context, the model was fitted for each subject separately giving subject-specific estimates for the three parameters, in particular, subject-specific eventual atrophy levels, and initial change in mean area gradients; these were then summarized and used in conventional regression models to investigate whether specified baseline variables were associated with these trajectory characteristics. Subjects with too few data points to generate estimates for the three parameters were automatically excluded from the analysis; but, additionally, any fitted subjects with data not available at >300 days were set a missing ‘asymptote’ parameter, though they still contributed information on early gradient through the other two parameters.

Confidence intervals (CIs) and \( P \)-values for these estimates were obtained using a non-parametric bias-corrected bootstrap with 1000 replicates (Carpenter and Bithell, 2000). Figures 3 and 4 were generated using exponential models fitted to all patient data.

Linear regression was used to investigate associations at fixed time points between atrophy and other quantitative variables (VEP and visual acuity), and between time-averaged variables. Where normality of residuals could not be assumed, bootstrap CIs and corresponding \( P \)-values were obtained; where outliers were present, Spearman rank coefficients are reported.

All analyses were carried out in Stata 7.0 (Stata Corporation, College Station, TX), except for random slopes models which were examined in MLwiN 1.10 (Centre for Multilevel Modelling, Institute of Education, London, UK).

**Results**

Measurement reproducibility figures are given in Table 1.

### Control optic nerves

At baseline, the mean area of control optic nerves was 13.6 mm\(^2\) (SD 1.8). There were no significant differences between right or left optic nerves or in optic nerve mean area between males and females. The control mean area at 52 weeks was 13.1 mm\(^2\) (SD 1.8) to give a time-averaged mean of 13.5 mm\(^2\) (SD 1.6) and gradient of change of \(-0.001\) mm\(^2\)/day (95% CI \(-0.003\) to 0.001; \( P = 0.36 \)). As expected, there was no evidence of a systematic change in mean area from controls according to the date of acquisition. These data provide quality assurance that disease effects, observed over the same time period, were real and not artefactual.

### Patients’ healthy contralateral optic nerves

At baseline, the mean area of the healthy contralateral optic nerves was 13.4 mm\(^2\) (SD 2.0). There was no evidence of change in area over time (gradient = \(-0.00072\) mm\(^2\)/day, 95% CI \(-0.0029\) to 0.0015; \( P = 0.52 \)) (Fig. 1). There was also no evidence of any difference in time-averaged values between the patients’ healthy contralateral optic nerves (mean 13.15 mm\(^2\), SD 1.0) and control optic nerves (13.5 mm\(^2\), difference 0.35 mm\(^2\) (95% CI 0.3–1.0; \( P = 0.32 \)). The mean area after 52 weeks was 12.8 mm\(^2\) (SD 1.5).

### Patients’ diseased optic nerves

At baseline, the mean area of diseased optic nerves was 16.1 mm\(^2\) (SD 3.1), 20.1% higher than the healthy contralateral optic nerves.

### Table 1 Measurement reproducibility for the different subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (mm(^2))</th>
<th>Within-subject SD</th>
<th>95% reference range(^a)</th>
<th>CV (%)</th>
<th>Reliability coefficient (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>13.5</td>
<td>0.55</td>
<td>±1.07</td>
<td>4.0%</td>
<td>0.90 (0.84–0.97)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diseased optic nerves</td>
<td>13.6</td>
<td>0.65</td>
<td>±1.26</td>
<td>4.8%</td>
<td>0.96 (0.93–0.99)</td>
</tr>
<tr>
<td>Healthy optic nerves</td>
<td>12.7</td>
<td>0.67</td>
<td>±1.31</td>
<td>5.3%</td>
<td>0.84 (0.70–0.97)</td>
</tr>
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</table>

\(^a\)1.96 × within-subject SD; 95% of measurements are expected to lie within this range of the true value, if the variable is approximately normally distributed. \(^b\)Intraclass correlation coefficient (ICC): the proportion of total variance due to between-subject variation. Under assumptions which are plausible here, one minus this value is the proportion of variation due to measurement error. CV = coefficient of variation.
nerves (mean difference = 2.7 mm², 95% CI 1.8–3.7; 
\( P < 0.0001 \) for hypothesis of zero difference) and 18.4% 
higher than control optic nerves (mean difference = 2.5 mm², 
95% CI 1.2–3.8; \( P = 0.0003 \)).

The diseased optic nerve mean area declined over time, 
from initial swelling to later atrophy (Figs 2 and 3 for mean 
area, and Fig. 4 for ratio of diseased : healthy optic nerve mean 
area). This decline was well described by an exponential 
curve with median (interquartile range) parameter values: 
\( \alpha = 11.06 \) (9.63–12.94), \( \beta = 10.69 \) (7.14–13.56) and \( \gamma = 0.03 \) 
(0.01–0.04). The data were therefore modelled as such during 
the subsequent analyses. The median gradient of decline in 
mean area at baseline (reported as median due to three out-
liers) was \(-0.26 \text{ mm}^2/\text{day} \) (95% CI \(-0.35 \) to \(-0.05 \)).

At 52 weeks, the mean area of diseased optic nerves was 
11.3 mm² (SD 2.2), 11.7% lower than the healthy contralateral 
optic nerves (mean difference = \(-1.5, 95\% \text{ CI } \(-0.1 \) to \(-2.8; 
\( P = 0.032 \)) and 13.7% lower than the control optic nerves (mean 
difference = \(-1.8, 95\% \text{ CI } \(-0.5 \) to \(-3.2; \ P = 0.008 \)).

Significant ongoing decrease in mean area was still 
apparent after 1 year. The mean gradient at 365 days was 
\(-0.0018 \text{ mm}^2/\text{day} \) (95% CI \(-0.0038 \) to \(-0.00051; \ P < 0.01 
for difference from hypothesis of zero gradient).

There was no evidence of association between baseline dis-
eased optic nerve area and outcome optic nerve area or with rate 
of decline of optic nerve area at either baseline or 1 year.

**Associations with vision**

Higher baseline diseased optic nerve mean area was correlated 
with worse baseline logMAR visual acuity (\( r_S = 0.46, 
\( P = 0.012 \)) and with lower baseline visual field mean deviation 
(\( r_S = -0.55, P = 0.002 \)). However, at 52 weeks, there was no 
direct evidence of association between vision scores and diseased 
optic nerve mean area. There was also no evidence of association 
between vision scores at 1 year and either baseline or 1 year 
gradients of decrease in diseased optic nerve mean area.

**Associations with VEP parameters**

There was no evidence of association between baseline, rates 
of decline or 1 year diseased optic nerve mean areas and any 
of the baseline, 1 year or time-averaged VEP variables.
Associations with high signal lesion lengths

The median baseline gadolinium-enhanced lesion length was 30 mm (range 0–39) and the median duration of enhancement was 63.5 days (range 0–113). There was a relationship between degree of diseased optic nerve swelling at baseline and the length of the initial enhancing lesion. The baseline diseased optic nerve mean area was 0.2 mm\(^2\) (95% CI 0.08–0.3; \(P = 0.001\)) higher for every additional 1 mm of gadolinium-enhanced lesion length. However, there was no association between baseline lesion length and initial or 1 year rate of decline of optic nerve mean area, or 1 year optic nerve mean area.

There was borderline evidence that the initial rate of decline in diseased optic nerve mean area was related to the length of time for which enhancement was detected, but not the 1 year rate of decline: the baseline gradient of decline was less steep by 3.5 mm\(^2\)/day for each day for which enhancement was detected (95% CI 0.00099–8.40; \(P = 0.05\)).

The median baseline lesion length on FSE images was 21 mm (range 9–39). There was no evidence of association between baseline lesion lengths on FSE images and baseline diseased optic nerve mean area or initial rates of decline of diseased optic nerve mean area. There was borderline evidence that the 1 year rate of decline in diseased optic nerve mean area (in those patients where this calculation was possible) was less steep in the shortest quartile (\(n = 4\) patients) of baseline lesion length than in patients with longer lesions (\(n = 14\)) by 0.0019 mm\(^2\)/day (95% bootstrap CI 8.6 \(\times\) 10\(^{-5}\) – 0.0044; \(P = 0.045\)).

Discussion

By prospectively studying a cohort of patients with acute optic neuritis using detailed clinical tests, VEPs and MRI with the sTE fFLAIR sequence and a computer-assisted contouring technique to segment the optic nerves, it has been possible to extend our previous observations that optic nerve atrophy occurs following optic neuritis, and may continue to develop over several years (Hickman et al., 2001, 2002). The measurement CV figures for optic nerve area were of the order of 5%; however, the ICC figures of \(\sim 0.9\) suggest that the technique is reproducible, with 90% of the variability due to inter-subject variability and only 10% due to measurement error (see Table 1). The reproducibility is not as good as for atrophy studies in the brain or spinal cord, reflecting the small size of the optic nerves and the greater potential for movement artefact. Higher resolution sequences or higher field imagers may help in future studies, although the former would be at the expense of increasing the acquisition time (Barker, 2000). At present, the sTE fFLAIR sequence presents the best compromise between high resolution and an acceptable acquisition time.

This study confirms, quantitatively, that optic nerve swelling occurs in acute optic neuritis, followed by the development of optic nerve atrophy over time. The results suggest an average increase in optic nerve mean area at baseline of \(\sim 20\%\). Optic nerve swelling on MRI previously had been thought to be a rare occurrence in acute optic neuritis and if swelling was present then it was recommended that a glioma or meningioma should be suspected (Cornblath and Quint, 1997). The present study is in agreement with other studies (Youl et al., 1996; Kapoor et al., 1998) which suggest that optic nerve swelling is actually common in acute optic neuritis. This swelling is probably due to acute inflammation with inflammatory cell infiltrates and vasogenic oedema. The observations that the amount of swelling was related to the lesion length on the gadolinium-enhanced images and the less steep decline in optic nerve mean area with increasing duration of enhancement support this conclusion, since the gadolinium enhancement has been shown to correlate with pathological features of inflammation in multiple sclerosis (Katz et al., 1993; Bruck et al., 1997). This study also supports the previous observation that acute inflammation causes impairment of vision (Youl et al., 1991), with an association between the extent of acute optic nerve swelling and the degree of visual impairment in the acute phase. However, the lack of relationship between early swelling and later visual outcome suggests that the extent of swelling per se does not indicate the severity of the inflammatory process with respect to its potential to cause permanent structural damage and axonal loss.

The data show that diseased optic nerve mean area declined from initial swelling to later atrophy. An exponential model provided a good fit for this change. The initial steep decline in mean area occurred at the time of most rapid recovery in vision, probably due to the resolution of vasogenic oedema which was responsible for optic nerve swelling and conduction block in relatively normal axons within the optic nerve (Youl et al., 1991, 1996). After 1 year, significant and continuing optic nerve atrophy had occurred in the diseased optic nerves. There are two potential mechanisms for this continuing atrophy. First, there is Wallerian degeneration of axons that were previously transected in the acute inflammatory lesion (Trapp et al., 1998); this process and the associated clearance of myelin debris probably takes place over a number of months. Secondly, there is later axonal death in persistently demyelinated axons (Scolding and Franklin, 1998), these being more vulnerable than myelinated axons.

The lack of association between the optic nerve mean area and visual impairment after 1 year could reflect the fact that few patients had substantial visual impairment and that the overall extent of tissue loss was small (mean decrease in area 12%). It is probable that the remaining axonal fibres are sufficient to enable restoration of vision once the phase of conduction block during acute inflammation has passed. There may be redundancy in the number of axons required to maintain vision, hence large numbers may need to be lost to be clinically significant. Frisén and Quigley (1984) obtained nerve fibre counts from the temporal quadrants of optic nerves with optic atrophy. The temporal quadrant was measured as it was felt that this portion of the nerve was most likely to subserve foveal vision. This was compared with the visual
acuity to give an indication of the functional fraction of neural channels. This produced a parabolic relationship and the suggestion that normal (Snellen 6/6) vision can remain despite the loss of 40% of the neural substrate. Visual acuity of 6/15 seemed possible with 10% remaining of the neural substrate, and 6/60 with only 1%. The recovery and/or retention of function despite continued axonal dysfunction or loss within the optic nerve may also be as a consequence of plasticity and functional remodelling within the visual system and higher centres, perhaps by utilizing the redundant capacity. Werring et al. (2000) observed extra-occipital activation on functional MRI using periodic monocular 8 Hz photic stimulation in seven patients with optic neuritis who had recovered back to normal visual acuity (Snellen 6/6 or better). Whilst this study demonstrated that altered cortical responses occur following optic neuritis, their functional significance in contributing to recovery of vision currently is unknown.

The degree of initial swelling or acute enhancing lesion length was not associated with the degree of atrophy at 1 year, although there was a suggestion that the patients who had short acute FSE lesions had a decreased rate of continuing development of atrophy after 1 year. The general lack of direct association between the baseline imaging findings and later optic nerve atrophy may reflect efficient repair mechanisms to restore structure and function following an acute inflammatory demyelinating episode. Also, simple measures of lesion length may not accurately measure the degree of the initial inflammatory insult.

A sister study showed that mean magnetization transfer ratio (MTRs) in diseased optic nerves declined following an attack of optic neuritis, probably due to demyelination and Wallerian degeneration, reaching a nadir after ~8 months (Hickman et al., 2004). Subsequently, mean MTR increased, although not significantly, up to 1 year, possibly due to the effects of remyelination. More prolonged follow-up will be undertaken and this may help to determine if further remyelination, inferred from increasing mean MTR values and shortening of VEP latencies, confers protection against continuing axonal degeneration, as measured by ongoing atrophy development. If this is the case, then therapies to induce remyelination might be appropriate for neuroprotection.

Two previous studies suggest that in patients seen some years following optic neuritis there is an association between the degree of atrophy and visual impairment (Hickman et al., 2002; Inglese et al., 2002). Although it is hard to compare studies directly, the degree of tissue loss was not much greater than reported in the present study at 1 year. It may be that further episodes of optic neuritis (that could have been asymptomatic) had occurred, leading to more demyelination and conduction block, or that failure of remyelination of the initial lesion with persistent demyelination may have predisposed, over time, to secondary axonal degeneration (Scolding and Franklin, 1998; McGavern et al., 2000). In this case, a small decrease in the number of critical macular axons may affect the ability of the visual system to compensate. The failure to compensate as axonal degeneration slowly but relentlessly occurs is one potential explanation for the development of secondary progression in multiple sclerosis. Although progressive significant visual impairment is unusual in multiple sclerosis, evidence for progressive atrophy of the optic nerve over a long period of time would support the concept that progressive axonal loss may follow acute inflammatory demyelination.

In the brain and spinal cord, measures of atrophy in multiple sclerosis reflect the global effects of the disease, which include both old and new lesions and normal-appearing tissues. Our observation of swelling in the acute inflammatory lesion and atrophy in the more chronic post-inflammatory lesion suggests that the concurrent presence of lesions of differing ages—as is often seen in the brain of patients with relapsing forms of multiple sclerosis—may introduce noise when using the measure of progressive brain atrophy as a surrogate marker of axonal loss. Our observations support the study of optic neuritis as a model for the development of atrophy following inflammatory demyelinating lesions. A further implication of the present study is that disease-modifying therapies for preventing acute inflammation have the potential to decrease the extent of tissue damage and axonal loss in multiple sclerosis. It also suggests that acute treatments during the inflammatory episode which prevent or reduce subsequent tissue loss should be sought. We have reported recently that high dose intravenous methylprednisolone failed to prevent optic nerve atrophy following an attack of optic neuritis, consistent with the lack of long-term functional benefit from the therapy (Hickman et al., 2003). Novel therapies for acute multiple sclerosis relapses are therefore required. In future treatment trials of such agents, inclusion of patients with optic neuritis and the use of combined clinical, electrophysiological and quantitative MRI measures including optic nerve size would be useful in assessing the response to treatment.

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