Corticosteroids do not prevent optic nerve atrophy following optic neuritis
S J Hickman, R Kapoor, S J Jones, D R Altmann, G T Plant, D H Miller

METHODS
The design, conduct and clinical results of the trial have been reported previously. Briefly, 66 patients with a first episode of acute unilateral optic neuritis within 30 days of onset were enrolled into the study. The median duration of symptoms before randomisation was eight days (range 1–30). Six of the patients had clinically definite MS, another 14 had clinically probable MS, and the rest had clinically isolated optic neuritis. Their optic nerves were imaged with a short tau inversion recovery (STIR) sequence (TR 2500 ms, TE 40 ms, TI 175 ms, matrix 256×128, field of view 16 cm×16 cm, 2 excitations, 5 mm contiguous slices) and were then randomised to receive either 1 g/day IVMP for three days or intravenous saline. Reimaging was performed six months later. In addition, at six months, a detailed clinical assessment was performed including Snellen visual acuity, contrast sensitivity using the Pelli-Robson chart, Humphrey visual field examination, and colour vision using the Farnsworth-Munsell 100 (FM 100) Hue test. Normal values were taken to be a visual acuity of 6/6 or better, contrast sensitivity of 1.65 or better, Humphrey mean deviation of –3 dB or higher, and the total error score of the FM 100 of less than 110.

RESULTS
Table 1 gives measurement reproducibility results. At baseline optic nerve mean area was 18.4 (SD 3.8) mm² in diseased optic nerves and 17.8 (SD 3.6) mm² in healthy optic nerves (n = 45). The estimated geometric mean ratio (diseased nerve area:healthy nerve area) was 1.035 (95% CI 0.96 to 1.11; p = 0.33). At baseline, high signal was present in the measurement area in 36/45 patients. The presence of a lesion did not affect the ratio; however, the degree of swelling increased by 7.3% (95% CI 3.3% to 11.7%; p = 0.001) for each slice that a high signal lesion was visible on.

Abbreviations: IVMP, intravenous methylprednisolone; MRI, magnetic resonance imaging; MS, multiple sclerosis; NO, nitric oxide; STIR, short tau inversion recovery; VEP, visual evoked potentials

SHORT REPORT
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Corticosteroids shorten the period of functional impairment following relapses in optic neuritis and multiple sclerosis (MS); however they have not, thus far, been shown to affect the final level of function compared with placebo. There has been recent interest in the use of corticosteroids as neuroprotective agents by their effect of decreasing nitric oxide (NO) production by mononuclear cells. NO is toxic to axons in vitro. Pulsed corticosteroid treatment has been reported to reduce the development of cerebral atrophy, a putative marker of neuronal loss, over a five year period in relapsing remitting MS. Optic nerve atrophy has been shown to develop following optic neuritis. This study assesses whether a single course of intravenous methylprednisolone (IVMP) during an attack of acute optic neuritis prevents the development of optic nerve atrophy following optic neuritis. Magnetic resonance imaging (MRI) data from a recent randomised placebo controlled trial of IVMP in acute optic neuritis were retrospectively evaluated.

RESULTS
Table 1 gives measurement reproducibility results. At baseline optic nerve mean area was 18.4 (SD 3.8) mm² in diseased optic nerves and 17.8 (SD 3.6) mm² in healthy optic nerves (n = 45). The estimated geometric mean ratio (diseased nerve area:healthy nerve area) was 1.035 (95% CI 0.96 to 1.11; p = 0.33). At baseline, high signal was present in the measurement area in 36/45 patients. The presence of a lesion did not affect the ratio; however, the degree of swelling increased by 7.3% (95% CI 3.3% to 11.7%; p = 0.001) for each slice that a high signal lesion was visible on.
After six months optic nerve mean area was 16.4 (SD 3.8) mm² in diseased optic nerves and 17.4 (SD 3.5) mm² in healthy optic nerves (n = 59) (fig 1). The estimated geometric mean ratio (diseased nerve area:healthy nerve area) was 0.93 (95% CI 0.87 to 0.99; p = 0.02). A lesion was present in 56/59 patients in the orbital portion measured at this time point. Neither the lesion length at baseline or six months correlated with the degree of atrophy. There was no evidence of association between any of the clinical and VEP variables and six month diseased nerve area.

The mean area of affected optic nerves at six months in the IVMP group was 15.9 (SD 3.9) mm² (n = 30) compared with 16.9 (SD 3.8) mm² in the placebo group (n = 29). The ratio of six month diseased:six month healthy optic nerve area was 6.8% lower in the IVMP group than in the placebo group (95% CI, 16.1% lower, 3.6% higher, p = 0.19). The ratio of six month diseased nerve area:baseline diseased nerve area was 0.8% lower in the IVMP group than in the placebo group (95% CI 14.8% lower, 15.5% higher, p = 0.92). Neither the MS status nor the duration of symptoms before treatment was instigated affected these ratios.

DISCUSSION
This technique was able to show optic nerve atrophy following optic neuritis with good reproducibility as witnessed by the high reliability coefficients. The area measurements are greater than those produced from sTE fFLAIR images as the measurements from the STIR images include the nerve sheath. Even though the measurements were of the optic nerve–sheath complex, atrophy was still detected after six months. At the time that the images were acquired during the trial, the sTE fFLAIR sequence had not been developed and STIR was the preferred sequence for optic nerve lesion identification.

A study using sTE fFLAIR in a more chronic cohort of optic neuritis patients showed that increasing optic nerve atrophy was associated with worse vision and decreased VEP amplitudes.11 Qualitative assessment of the sTE fFLAIR images from that study suggests that atrophy of the optic nerve sheath occurred as well (SJ Hickman, unpublished observations). The lack of correlation between the clinical outcome measures and optic nerve mean area in the present study may be caused by functional reorganisation in the visual system in the early recovery process,12 potentially achieved by utilising redundant optic nerve capacity.13 This plasticity may fail over time and this may be one explanation for the development of late clinical progression in MS.

There is no evidence from these data that a course of IVMP prevents the short term development of optic nerve atrophy following acute optic neuritis. This is consistent with the lack of long term functional benefit seen as a result of IVMP in both this and other studies.

ACKNOWLEDGEMENTS
We would like to thank all the patients who took part in this study and we acknowledge the help of Dr A Brusa, Dr A Gass, Dr CP Hawkins, Dr R Page, Prof. NW Wood, Prof. DAS Compston, Dr IF Moseley, Prof. WI McDonald, Mr DG MacManus, Miss C Middledlitch, and Mrs M Galton. SJH is supported by The Wellcome Trust. The NMR Research Unit is supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland.

Table 1 Measurement reproducibility for the different subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (mm²)</th>
<th>Within subject SD</th>
<th>95% reference range</th>
<th>CV (°)</th>
<th>Reliability coefficient (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute diseased nerve area</td>
<td>18.4</td>
<td>1.13</td>
<td>± 2.21</td>
<td>6.4</td>
<td>0.92 (0.88 to 0.96)</td>
</tr>
<tr>
<td>Acute healthy nerve area</td>
<td>17.8</td>
<td>1.21</td>
<td>± 2.37</td>
<td>6.8</td>
<td>0.89 (0.84 to 0.94)</td>
</tr>
<tr>
<td>Six month diseased nerve area</td>
<td>16.4</td>
<td>0.76</td>
<td>± 1.49</td>
<td>4.6</td>
<td>0.96 (0.95 to 0.98)</td>
</tr>
<tr>
<td>Six month healthy nerve area</td>
<td>17.4</td>
<td>1.11</td>
<td>± 2.18</td>
<td>6.4</td>
<td>0.91 (0.87 to 0.95)</td>
</tr>
</tbody>
</table>

*1.96 x within subject SD, 95% of measurements are expected to lie within this departure from the true value.
†The proportion of total variance caused by between subject variation. Under assumptions which are plausible here, one minus this value is the proportion of variation caused by measurement error.

CV, coefficient of variation.

REFERENCES

Figure 1 Short tau inversion recovery magnetic resonance images showing optic nerve swelling at baseline (left) and optic nerve atrophy after six months (diseased nerve arrowed) in a 27 year old man with right optic neuritis.
HISTORICAL NOTE

The West Riding Lunatic Asylum

“Few subjects in medicine are so intimately connected with the history and philosophy of the human mind as insanity. The reason, where there are so many errors of opinion; and so many prejudices to remove. Derangement of the understanding is generally considered as an effect of an organic lesion of the brain, consequently as incurable; a supposition that is, in a great number of instances, contrary to anatomical fact.” Philippe Pinel, Treatise on Insanity, 1801

Until the second half of the 19th century, the study of the brain and its interplay with the mind was beset by mysticism and confusion. Speculation was rife and constituted little better than a repository for the guesswork of ignorance. In varying degree, both neurology and psychology were culpable. In his book, The metaphysical foundations of modern physical science, EA Burtt described the concept of mind as “a convenient receptacle for the refuse, the chips and whittlings of science, rather than a possible object of scientific knowledge”.

The 19th century hospitals, created for the mentally ill, had two distinct but intertwined functions. The first was to provide a caring place for the treatment of the mentally ill who were commonly spurned by society, receiving brutal and harsh physical treatments and inhumane restraints over many centuries. Pinel had written Treatise on insanity, a revolutionary recipe for more gentle treatment and abolition of widespread brutality for the mentally ill. The second and often neglected function was the analysis of brain function and disease, whose investigation in time was to bear the fruits of the neurological sciences.

The 1842 Licensed Lunatic Asylums Bill proposed a Barristers’ Commission to review the law, and it was recognised that county licensing and visiting were defective. It stated that two legal commissioners should visit and report on county houses supplementary to the county visitors. The House of Commons rejected this proposal and an amended bill became the 1842 Inquiry Act. Two medical and two legal commissioners were added. One of the medical commissioners was a psychiatrist, the other a statistician. They jointly visited and reported on public asylums and licensed houses throughout England and Wales, and in 1844, the commission published a 300 page report with recommendations. The 1845 County Asylums Act compelled every county and borough in England and Wales to provide asylum treatment for all its pauper lunatics.

The West Riding Lunatic Asylum (later, Stanley Royd Hospital) was sited in Wakefield, on East Moor, and Samuel Tuke gave advice about its workings and plans. It opened on 23 November, 1818. William and Mrs Ellis were the superintendents and matrons from 1818 to 1831. It was a large establishment, and was repeatedly expanded. It was under the control of the West Riding Magistrates; and the initial land, buildings, and furniture cost about £100 000. CC Corseil, MD, was an early resident physician and director and often had under his care about 450 lunatics. Henry Maudsley, born in Settle, in the Yorkshire dales, was briefly the director; he was the most esteemed psychiatrist of the day, and founded the Maudsley Hospital. Slater in 1864 noted its expansion: “The asylum is situated about a mile north east of the town. Another building was erected in 1849, which far surpasses the old one, both in size and architecture; the whole combined are calculated to give accommodation to upwards of 1000 patients.”

The hospital had many clinical clerks, clinical assistants, and physicians who attended the sick. By 1 January 1844, there were 433 patients—all paupers. The Stephen Beaumont Museum of Mental Health was in the hospital until it closed in 1995; it was moved to Fieldhead Hospital. It relates the history of the asylum and contains many exhibits. In 1948 a report on Wakefield was made by a medical officer to the new Leeds Regional Hospital Board. It described: “The old gaol-like buildings at Wakefield are gloomy and depressing and the galleries where many patients aimlessly spend so much of their time are deficient in natural lighting. The accommodation can best be described as austere, pre-Dickensian, falling far short of usually acceptable standards.”

A major salmonella outbreak at Stanley Royd Hospital in 1984 led to the deaths of 14 psychogeriatric patients and the infection of nearly 400 others. The hospital closed in 1995. The asylum had enjoyed highest repute founded on care and its renowned researchers. The most eminent were Sir David Ferrier and Sir James Crichton-Browne.

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