Original Article

# Magnetic Resonance Imaging in Acute Optic Neuritis in Singapore

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## Abstract

**Introduction: The Optic Neuritis Treatment Trial (ONTT) has established that the magnetic resonance imaging (MRI) findings at the time of presentation of optic neuritis (ON) is the strongest indicator of the development of multiple sclerosis (MS). Reports from Singapore as well as other Asian countries have indicated that these abnormalities are less frequently encountered compared to that reported by the ONTT. This paper aims to describe systematically the brain MRI as well as the optic nerve abnormalities in patients after an episode of acute optic neuritis. Materials and Methods: Patients who presented with acute optic neuritis were retrieved from our prospective optic neuritis study and their MRI scans were reviewed and graded in accordance with the standardised classification employed in the ONTT. Results: Fifteen of 24 patients had MRI brain and optic nerves performed during the acute episode. In the evaluation of brain abnormalities, 40% were classified as grade 0, 20% grade I, 20% grade II, 6.7% grade III and 13.3% grade IV. Optic nerve abnormalities were observed in 80% of cases. At study entry, 10 patients had idiopathic (monosymptomatic) ON, 3 had multiple sclerosis (MS), one each with infective and autoimmune optic neuritis, respectively. The single patient who developed MS at study completion presented with grade II brain abnormalities at the initial MRI. For those with idiopathic ON, our study revealed a higher percentage of grade 0-I brain changes as well as a lower lesion load compared to the ONTT. Lesion load and grade was also lower in anterior optic neuritis compared with retrobulbar disease. Conclusion: Our study revealed a lower percentage of grade II-IV brain MRI abnormalities as well as less lesion load in idiopathic ON compared to the ONTT. This may be related to the lower prevalence of MS in our predominantly Asian population. As diagnostic tests and understanding of neuromyelitis optica or Devic's disease improves, we may see more patients being diagnosed with this condition, which may also explain our findings. Our data also showed that MRI grade and lesion load in cases of anterior ON was lower than for retrobulbar disease. MRI in ON has an essential role in characterising the disease, evaluating for associated brain lesions, and assessing prognosis in retrobulbar disease but may be less useful in anterior disease.**

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**Key words: Multiple sclerosis, Optic nerve enhancement, Periventricular plaques**

## Introduction

Optic neuritis (ON) is an inflammatory, demyelinating condition affecting the optic nerves. In Western populations, ON is frequently associated with multiple sclerosis (MS).[1] The optic neuritis treatment trial (ONTT)[2] has provided seminal data on the natural history of optic neuritis as well as the high and low risk profiles for the eventual development of MS.[3] At 15-year follow-up, they reiterated their finding that brain magnetic resonance imaging (MRI) abnormalities at the time of an optic neuritis attack is a strong predictor of the 15-year risk of MS.[4] For patients who had no brain MRI lesions at baseline, the risk of developing MS was 25% compared to 72% in patients with 1 or more lesions.

Conversion rate to multiple sclerosis is much lower in Singapore and other Asian countries compared to figures in the West.[5] Our local rate is 9.1% at 4 years,[6] comparable to figures from Taiwan[5] (14.3% in 5 years) and Japan[7] (8.3% in 5.3 years), which are lower compared to figures from

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Table 1. Distribution of Magnetic Resonance Imaging for Patients with Optic Neuritis

| Classification of Changes on Brain Magnetic Resonance Images |
|---|
| Grade 0 |
| Normal |
| Grade I |
| A. 4 or more lesions, all non-ovoid, non-periventricular |
| B. 3 lesions, all non-ovoid, non-periventricular |
| C. 2 lesions, both non-ovoid, non-periventricular |
| D. 1 lesion, non-ovoid, non-periventricular |
| E. 1 lesion, non-ovoid, non-periventricular, plus 1 or more punctuate lesion |
| F. 2 or more punctuate lesions only |
| G. 1 punctate lesion |
| Grade II |
| A. 2 lesions, 1 periventricular |
| B. 1 lesions, periventricular |
| C. 1 lesion, ovoid, non-periventricular |
| D. 1 lesion, ovoid and periventricular |
| Grade III |
| A. 3 lesions only, 1 periventricular |
| B. 2 lesions only, both periventricular |
| C. 2 lesions only, none periventricular, both ovoid |
| D. 2 lesions only, none periventricular, 1 ovoid |
| E. 2 lesions only, 1 periventricular and ovoid |
| F. 2 lesions only, 1 periventricular and 1 ovoid |
| Grade IV |
| A. 4 or more lesions, at least 1 periventricular |
| B. 3 lesions only, at least 2 periventricular |
| C. 3 or more lesions, none periventricular, at least 2 ovoid |
| D. 2 lesions only, 1 periventricular and 1 large brainstem |
| E. 3 or more lesions, 1 periventricular and ovoid |
| F. 3 or more lesions, 1 ovoid |
| G. 3 or more lesions, 1 periventricular amd 1 ovoid |

Punctate lesion: smaller than 3 mm

Lesion: larger than 3 mm

Large lesions: 20 mm or larger

the United States[8] (30% at 5 years) and Sweden[9] (36% in 6 years). It has also been established that ON in Asian populations differ significantly from that in the West, in presenting with a higher incidence of optic disc swelling and haemorrhage and less pain.[6] Data from Singapore[10], Taiwan[5] and Japan[11] have shown a lower prevalence of brain MRI abnormalities in ON compared to figures from the ONTT.[12] However, there was no standardised grading system used in all of the studies from Asia to allow comparison with the ONTT. This paper aims to describe systematically the MRI findings in the brain and optic nerve(s), in patients after an episode of acute optic neuritis.

## Materials and Methods

The Singapore Neuro-Ophthalmology Study Group (SNOSG) was a prospective, population based investigation of neuro-ophthalmology cases (old and new) seen between September 2002 and June 2004 in our public hospital subspecialty clinics at Tan Tock Seng Hospital (TTSH), Singapore National Eye Centre (SNEC), National University Hospital (NUH) and Changi General Hospital (CGH). Patients were in most instances referred from general ophthalmology clinics either on the same day for urgent cases, or given an appointment for the next available specialty clinic.

Each case was classified and coded according to the International Classification of Diseases 9th Revision Clinical Modification (ICD-9) into the following subgroups:

a) Optic neuritis, unspecified

b) Anterior optic neuritis or papillitis

c) Retrobulbar optic neuritis

Our study included only patients seen at TTSH and CGH. The research was conducted according to the Declaration of Helsinki and ethics approval from the respective Ethics Review Boards was obtained. Of the combined 24 patients from these 2 hospitals, 15 patients who had MRI of the brain and optic nerves at presentation were finally recruited for this study.

All MRI studies were performed on clinical 1.5 Tesla MR imaging systems with quadrature transmit-receive headcoils, using the standard protocols at the 2 hospitals. Imaging of the optic nerves included axial and coronal thin section T1 weighted spin-echo sequences before and after intravenous dimeglumine gadopentetate contrast administration, with additional fat-saturation applied after intravenous contrast administration (axial: TR/TE/FA 500/8/80, 3 mm thickness, no gap, matrix 256x192, FOV 20x20 cm, 2 excitations; coronal: TR/TE/FA 620/13/80, 3 mm thickness, no gap, matrix 256x192, FOV 22x17 cm, 2 excitations). Other scan sequences included coronal short tau inversion recovery (STIR) sequence of the optic nerves (TR/TE/FA 3500/46/90, 3 mm thickness, no gap, matrix 256x192, FOV 18x18cm, 1 excitation); whole brain axial T2 weighted fast spin-echo sequence (TR/TE/FA 6300/127/90, 5 mm thickness, 1 mm gap, matrix 320x320, FOV 24x24 cm, 1.5 excitations); coronal whole brain fluid attenuated inversion recovery (FLAIR) sequence (TR/TE/FA 10000/124/90, 5 mm thickness, 1 mm gap, matrix 256x192, FOV 24x24 cm, 1 excitation). The scans were read in consensus by 2 independent neuroradiologists who were masked to any

clinical information about the patients other than the fact that they had ON. Both axial and coronal images were used in the assessment. Documentation of brain lesions followed a methodology similar to that used in the ONTT, with the reader completing a grid that designated each lesion by location (periventricular, peripheral white matter, grey matter, brainstem, cerebellum and corpus callosum) and lesion type (<3mm, 3-20mm and ovoid, 3-20mm and nonovoid, or >20mm). A lesion measuring less than 3mm was classified as punctuate. The brain abnormalities were further classified into grades 0-IV, based on the data entered into the grid. This grading system was identical to that used in the ONTT[12]; grade 0 being a normal scan, grade I having changes not specific for demyelination and grade II to IV having lesions suggestive of demyelination with the severity increasing with increasing grade. In addition, MRI abnormalities in the optic nerve(s) were recorded for laterality, location, swelling and enhancement patterns in these patients. The extraocular muscles and orbit(s) were also reviewed for features of involvement in the process. The data was analysed using Statistical Package for Social Sciences version 11.

## Results

In our study cohort, all MRI studies of the brain and optic nerves were performed within 6 weeks after acute presentation (range, 7 to 45 days). The mean age of the patients was 34.6 years (range, 13 to 53). There were 9 females and 6 males. Table 1 and 2 show the classification system used for MRI brain abnormalities and clinical and magnetic resonance imaging features of our patients, respectively. Figure 1 is an illustrative case from our series. Optic neuritis was bilateral in 4 patients and unilateral in 10 (5 right-sided and 5 left-sided). Optic neuritis was idiopathic (monosymptomatic) in 10 patients. Five patients had an underlying cause: 3 were due to MS, 1 had an infective cause (syphilis), and 1 had an inflammatory/autoimmune (steroid dependent) cause.

Table 2 shows the brain MRI characteristics of the patients. Six patients (40%) were graded as normal (grade 0), 3 (20%) grade I, 3 (20%) grade II, 1 (6.7%) grade III and 2 (13.3%) grade IV. Amongst those with idiopathic (monosymptomatic) ON at study entry (n = 10), 5 were grade 0, 2 were grade I, 1 was grade II, 1 was grade III and 1 was grade IV. When we look at the number of lesions present, 7 of 10 had no lesion, a single patient each had 1, 3 had greater than 10 lesions. Of the 3 patients with lesions on MRI, the patient with 3 lesions developed MS during the 4 years of follow-up, the one with a single lesion had anterior disease while the patient with grade IV MRI abnormalities (>10 lesions) had retrobulbar disease (no MS as yet).

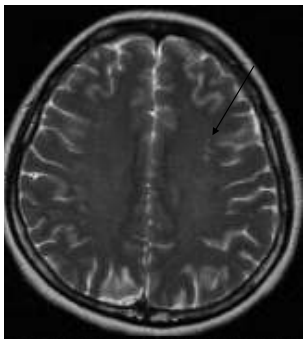


Fig. 1a.

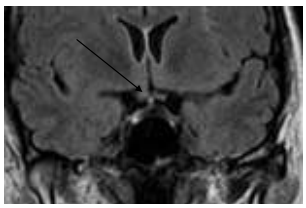
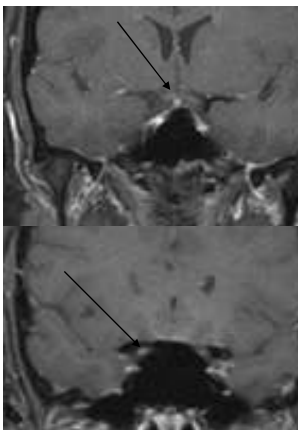


Fig. 1b.



Figs. 1c-d.

Fig. 1. Initial scans of a 36-year-old female with clinical right optic neuritis. (a) Axial T2W image shows multiple punctate peripheral white matter lesions. (b) Coronal FLAIR image shows pre-chiasmatic right optic nerve swelling, with (c) enhancement seen on the corresponding post-contrast fat-saturated T1W scan, and (d) more anteriorly at the right orbital apex.

The 3 patients known to have MS were classified singly in grade I (8 lesions), grade II (1 lesion) and IV (>10 lesions). Of note, none of these patients had punctate brain parenchymal lesions and the patient with grade I abnormalities had 8 lesions in the peripheral white matter. The only patient to convert to MS in the 4-year period had changes in grade II (3 lesions), none of which were punctate (mentioned above). The single patient with steroid dependent optic neuropathy had a normal brain MRI while the patient with syphilitic optic neuritis had grade II changes (1 lesion) which were periventricular.

The distribution of grades of brain changes in anterior versus retrobulbar ON is shown in Table 3. Most of the patients with anterior ON had grade 0-I changes, while the majority of patients with retrobulbar disease had changes of higher grades II-IV. Lesion load in patients with anterior optic neuritis was also lower compared to retrobulbar disease. In anterior optic neuritis, 8 of 10 patients did not have any lesions, the remaining 2 having only 1 lesion each. For the 5 patients with retrobulbar disease, 1 patient each had a single lesion, 3 lesions and 8 lesions and the remaining 2 had >10 lesions at initial MRI.

Table 2. Clinical and Magnetic Resonance Imaging Characteristics of Patients at Study Entry

| Patient no. | Anterior (A)/ retrobulbar (R) optic neuritis | Unilateral (U)/ bilateral (B) optic neuritis | Past history of multiple sclerosis (Y/N) | Final diagnosis | No. of brain lesions on MRI* | MRI* grade | Optic nerve involved (Y/N) | Location of optic nerve involvement | Optic nerve swelling (Y/N) | Optic nerve enhancement |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | R | U | Y | Multiple sclerosis | >10 | IVA | Y | Intraconal and prechiasm | Y | Optic nerve and perineural |
| 2 | A | B | N | Syphilitic optic neuritis | 1 | IIB | N | Not applicable | Not applicable | Not applicable |
| 3 | R | U | N | Multiple sclerosis | 3 | IIC | Y | intraconal | Y | Optic nerve |
| 4 | A | B | N | Idiopathic | 0 | IG | N | Not applicable | Not applicable | Not applicable |
| 5 | A | U | N | Idiopathic | 0 | 0 | Y | Intraconal | N | perineural |
| 6 | A | U | N | Steroid dependent optic neuropathy | 0 | 0 | Y | Intraconal | N | Optic nerve |
| 7 | R | U | N | Multiple sclerosis | 8 | IA | Y | prechiasm | Y | Optic nerve |
| 8 | A | U | N | Idiopathic | 0 | 0 | N | Not applicable | Not applicable | Not applicable |
| 9 | A | U | N | Idiopathic | 1 | IIIA | Y | Intraconal and prechiasm | Y | Optic nerve |
| 10 | R | U | Y | Multiple sclerosis | 1 | IIC | Y | Intraconal and prechiasm | Y | No |
| 11 | A | B | N | Idiopathic | 0 | 0 | Y | Intraconal and prechiasm | Y | perineural |
| 12 | A | U | N | Idiopathic | 0 | 0 | Y | Intraconal and prechiasm | Y | Optic nerve and perineural |
| 13 | A | B | N | Idiopathic | 0 | IG | Y | Intraconal and prechiasm | Y | Perineural |
| 14 | R | U | N | Idiopathic | >10 | IVC | Y | Intraconal, prechiasm and chiasm | Y | Optic nerve |
| 15 | A | U | N | Idiopathic | 0 | 0 | Y | Intraconal and prechiasm | Y | Optic nerve and perineural |

*MRI: Magnetic resonance imaging

Table 2 also shows the optic nerve abnormalities detected in our patients. Abnormalities were noted in 12 (80%) patients while none showed involvement of the extraocular muscles and orbit. Majority showed abnormalities in the intraconal (11 patients [91.7%]) and/or prechiasmic (9 patients [75%]) segment of the optic nerve, including those cases with bilateral disease. Optic nerve swelling was noted in 10 (83.3%), nerve enhancement in 8 (66.7%) and perineural enhancement in 6 (50%). Three patients showed both nerve as well as perineural enhancement, while 3 showed isolated perineural without nerve enhancement.

## Discussion

In our study, for the patients with idiopathic (monosymptomatic) optic neuritis, 50% (5/10) had normal brain MRI findings, 20% (2/10) were classified as grade I and 10% (1/10) grade II, III and IV, respectively. In comparison, the ONTT figures were 40.9% normal, 10.8% grade I, 9.1% grade II, 6.7% grade III and 32.5% grade IV. In the previous study by Wang et al in Singapore,[10] of the 21 patients with MRI scans, plaques were seen in only 1 patient. In Taiwan, Lin et al[5] reported "MS negative scans" to be 65.1% of their 43 patients studied. In Japan, Wakakura[11] reported periventricular plaques in 13.6% of their 66 patients, leaving 86.4% with "MS negative scans". Defining "MS positive scans" as those classified from grade II-IV, the proportion of "negative scans" (grade 0 and I) were greater in Asian countries compared with that reported in the ONTT (Singapore 95%,[10] Taiwan 65.1%,[5] Japan 86.4%,[11] ONTT 51.6 %[2]). The percentage of "negative scans" in our study was 70%. Comparing the number of lesions gave similar results as the grade (Table 4).

Our study had a greater proportion of scans with no lesions. There could be two explanations for these differences. Firstly, this could reflect the lower prevalence of MS in our predominantly Asian population. Presently the neuromyelitis myelitis optica (NMO) antibody has been used to differentiate MS from NMO, which has normal scans at the onset of disease.[13] Singapore has recently started obtaining these tests and future studies will elucidate if we see more NMO compared to MS locally. Secondly, we included bilateral cases in our series (3/9 idiopathic were bilateral). Bilateral simultaneous optic neuritis has been described previously[6,14] to be more common in males, more commonly anterior and not to be associated with neurological dysfunction, although the follow-up period was relatively short in these studies.

These findings also make us question the utility of doing MRI scans in patients with anterior optic neuritis, especially in bilateral cases and in males where the risk of developing MS is lower. At present, more studies need to be done to ascertain the cost-effectiveness of this investigation.

With regards to optic nerve abnormalities on imaging, these were seen in 80% (12/15) of our patients (optic nerve swelling in 83.3%, nerve enhancement in 66.7% and perineural enhancement in 50%). This is markedly different from the previous study by Wang et al[10] where enhancement was present in only 33.3%, while another earlier study by Wakakura et al reported optic nerve swelling in only 30.3% of their cases (83.3% in this series).[11] Compared to these 2 studies, the much higher proportion of abnormal imaging findings in the optic nerves observed in our study is more consistent with that reported by Hickman et al[15] where abnormal optic nerve enhancement was found in 75% of subjects. Both Hickman et al[15] and our study utilised specific imaging protocols optimised for the assessment

Table 3. Distribution of Magnetic Resonance Imaging Abnormalities According to Type of Optic Neuritis

| Classification of MRI changes | Anterior optic neuritis | Retrobulbar optic neuritis |
|---|---|---|
| Grade 0 | 6 | 0 |
| Grade I | 2 | 1 |
| Grade II | 1 | 2 |
| Grade III | 1 | 0 |
| Grade IV | 0 | 2 |
| Total | 10 | 5 |

Table 4. Comparison of Number of Lesions on Brain MRI in Patients with Idiopathic Optic Neuritis

| Lesions on baseline MRI | No. of patients (%) ONTT | No. of patients (%) present study |
|---|---|---|
| Overall | 389 | 10 |
| No lesions | 191 (49.1%) | 7 (70%) |
| 1 lesion | 44 (11.3%) | 1 (10%) |
| 2 lesions | 26 (6.9%) | 0 (0%) |
| ≥3 lesions | 91 (23.4%) | 2 (20%) |

of the optic nerves. Optic nerve changes per se were not studied in the ONTT.

Optic nerve abnormalities may also be seen in atypical cases of optic neuropathy (infiltrative, infective)[16] and further studies may be helpful to determine the significance and clinical utility of these observations, particularly in clinical outcome prognosis.

We did not find any associations between the patient's vision data and their MRI findings. This is similar to the ONTT results which did not find any association between vision or visual recovery and the MRI load, and hence MRI is useful mainly in the prediction of the development of MS.[17]

This study has several limitations. Firstly, ours is an extremely small series and may not be entirely representative of all cases of optic neuritis in Singapore. Secondly, we included all cases of acute optic neuritis (1 infective, 1 steroid dependent and 3 bilateral simultaneous optic neuritis), and hence we are looking at a heterogeneous group of patients. We tried to segregate these groups into idiopathic (monosymptomatic), MS and others to better comprehend the findings. Thirdly, we did not specify the exact time the MRI was performed as an inclusion criteria, although all scans were performed within 6 weeks (range, 7 days to 45 days; mean, 17 days; median and mode, 14 days).

## Conclusion

Our study revealed a higher percentage of grade 0-I brain changes as well as a lower lesion load in idiopathic (monosymptomatic) ON compared to the ONTT. This corroborates with previous studies which showed lower rates of brain MRI abnormalities in Asians compared to the West. This may be related to the lower prevalence of MS in Asian populations. Our data also showed that lesion load and grade in cases of anterior ON was lower than for retrobulbar disease. MRI in ON has a role in characterising the disease, evaluating for associated brain lesions, and assessing prognosis in retrobulbar disease, but may be less useful in anterior disease.

The usefulness of imaging abnormalities of the optic nerve is still not established in the clinical management of ON. With advances in MR imaging techniques, these optic nerve abnormalities are detected more frequently. Further studies may help to determine if these abnormalities are useful in prognostication and/or classification of the optic neuropathies.

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