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67	Schedule	Received	30 June 2006
68		Revised	20 September 2006
69		Accepted	12 October 2006

70 Abstract

The purpose of the study was to examine the brain and the visual pathway of patients with non-arteritic anterior ischaemic optic neuropathy (NAION) by using conventional MRI (cMRI) and volumetric magnetisation transfer imaging (MTI). Thirty NAION patients, aged 67.5 ± 8.14 years, and 28 age- and gender-matched controls were studied. MTI was used to measure the magnetisation transfer ratio (MTR) of the chiasm and for MTR histograms of the brain. The presence of areas of white matter hyperintensity (WMH) was evaluated on fluid-attenuated inversion recovery (FLAIR) images. Area of the optic nerves (ONs) and volume of the chiasm were assessed, as were coronal short-tau inversion recovery (STIR) and MTI images, respectively. More areas of WMH were

		observed in patients (total 419; mean 14.4; SD 19) than in controls (total 127; mean 4.7; SD 5.7), *P* < 0.001. Area (in square millimetres) of the affected ONs, volume(in cubic millimetres) and MTR (in percent) of the chiasm (10.7 ± 4.6), (75.8 ± 20.2), (56.4 ± 6.5), respectively, were lower in patients than in controls (13.6 ± 4.3), (158.2 ± 75.3) (62.1 ± 6.2), respectively, *P* < 0.05. Mean MTR of brain histograms was lower in patients (53.0 ± 8.0) than in controls (58.0 ± 5.6), *P* < 0.05. NAION is characterised by decreased ON and chiasmatic size. The low MTR of the chiasm and brain associated with increased areas of WMH may be suggestive of demyelination and axonal damage due to generalised cerebral vascular disease.
71	Keywords separated by ' - '	Magnetic resonance imaging - Non-arteritic anterior ischaemic optic neuropathy - Visual pathway - Magnetisation transfer ratio
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Eur Radiol
DOI 10.1007/s00330-006-0506-9

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Non-arteritic anterior ischaemic optic neuropathy: evaluation of the brain and optic pathway by conventional MRI and magnetisation transfer imaging

Received: 30 June 2006
Revised: 20 September 2006
Accepted: 12 October 2006

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Abstract The purpose of the study was to examine the brain and the visual pathway of patients with non-arteritic anterior ischaemic optic neuropathy (NAION) by using conventional MRI (cMRI) and volumetric magnetisation transfer imaging (MTI). Thirty NAION patients, aged 67.5±8.14 years, and 28 age- and gender-matched controls were studied. MTI was used to measure the magnetisation transfer ratio (MTR) of the chiasm and for MTR histograms of the brain. The presence of areas of white matter hyperintensity (WMH) was evaluated on fluid-attenuated inversion recovery (FLAIR) images. Area of the optic nerves (ONs) and volume of the chiasm were assessed, as were coronal short-tau inversion recovery (STIR) and MTI images, respectively. More areas of WMH were observed in patients (total 419; mean 14.4; SD 19) than in controls (total 127; mean 4.7; SD 5.7), $P<0.001$. Area (in square millimetres) of the affected ONs, volume(in cubic millimetres) and MTR (in percent) of the chiasm (10.7±4.6), (75.8±20.2), (56.4±6.5), respectively, were lower in patients than in controls (13.6±4.3), (158.2±75.3) (62.1±6.2), respectively, $P<0.05$. Mean MTR of brain histograms was lower in patients (53.0±8.0) than in controls (58.0±5.6), $P<0.05$. NAION is characterised by decreased ON and chiasmatic size. The low MTR of the chiasm and brain associated with increased areas of WMH may be suggestive of demyelination and axonal damage due to generalised cerebral vascular disease.

Keywords Magnetic resonance imaging · Non-arteritic anterior ischaemic optic neuropathy · Visual pathway · Magnetisation transfer ratio

Introduction

Non-arteritic anterior ischaemic optic neuropathy (NAION) refers to the development of an idiopathic ischaemic process in the anterior portion of the optic nerve [1, 2]. NAION typically presents in patients older than 50 years, as a sudden onset of unilateral painless visual loss [1, 2]. Sequential involvement of the second eye has been reported in 15% of cases, and simultaneous bilateral NAION may occur after surgical procedures (e.g. cardiopulmonary bypass) [2]. Painful onset (ocular pain or headache) has been reported in 10% of NAION patients [2]. A risk factor that has been consistently associated with NAION is a crowded optic disk, characterised by a small cup-to-disk ratio or absence of the cup [1–3]. Other risk factors are conditions leading to hypovolaemia and systemic hypotension [2, 4]. The pathogenesis of NAION is unknown, but most histopathological studies support the concept of vasculopathic occlusion in the territory of the short posterior ciliary arteries, and an increased incidence of cerebrovascular disease has been reported in these patients [5, 6]. There are few MRI studies, with small series evaluating the brain of NAION patients for areas of white matter hyperintensity (WMH) [7, 8]. Areas of WMH are increasingly common with advancing age; nevertheless, a significantly higher number of such areas has been reported in diseases predisposing to obliterative microangiopathy [9, 10]. Magnetisation transfer imaging (MTI), has been

proven to be superior to conventional MRI (cMRI) in detecting and quantifying subtle central nervous system (CNS) changes, especially those affecting white matter [11–14]. Magnetisation transfer ratio (MTR) quantifies the phenomenon of magnetisation transfer, and reduction of this parameter is thought to represent axonal and myelin loss in multiple sclerosis and periventricular leukomalacia [12–14]. Serial MTI has been used for the evaluation of acute optic neuritis, and changes in the MTR, consistent with demyelination and remyelination processes, have been found [15]. Histopathological data from NAION patients and experimentally induced anterior optic nerve ischaemia have demonstrated, throughout the optic nerve, apoptosis of the retinal ganglion cells and oligodendrocytes associated with axonal demyelination and Wallerian degeneration [5, 16]. To the best of our knowledge there are no studies evaluating by MTI the optic pathway and the brain of patients with NAION.

The purpose of the study was to assess the degree of optic nerve damage in NAION and to investigate the presence of macroscopic and microscopic abnormalities of the brain and chiasm in this disease, by using cMRI and MTI.

Patients and methods

Thirty patients with NAION and 28 age- and gender-matched controls were enrolled in the study. There were 16 women and 14 men, aged from 51 years to 86 years (mean age 67.5 years; SD 8.14 years). The disease duration was 1–123 months (mean 25.21 months; SD 26.67 months). Six of the 30 patients had NAION bilaterally. Patients were excluded from the study if they had a history of (1) autoimmune vasculitis, (2) multiple sclerosis (3) herpes virus infection and (4) temporal vasculitis. Each patient underwent a complete ophthalmological examination. Clinical disease variables included: (1) visual acuity, (2) funduscopic appearance, (3) visual fields and (4) presence of uncontrolled hypertension (blood pressure > 140/90 mmHg), nocturnal hypotension or diabetes mellitus.

All MR examinations were performed on the same 1.5 T MR unit (Gyroscan ACS NT; Philips Medical Systems, Best, The Netherlands) using a head coil, a field of view of 24 cm and an acquisition matrix of 256×256 pixels. Subjects were asked to close their eyes and avoid any deliberate eye movements during image acquisition. Sequences were: axial and coronal short -tau inversion recovery (STIR) (TR/2,650 ms, TE/90 ms), slice thickness 3 mm, intersection gap 0.3 mm, three excitations; axial turbo-spin echo, T2-weighted (TR/3,000 ms, TE/90 ms), slice thickness 6 mm, intersection gap 0.6 mm; and sagittal and axial fluid-attenuated inversion recovery (FLAIR) (TR/6,300 ms, TE/90 ms, TI/2,150 ms), slice thickness 5 mm, intersection gap 0.5 mm. To study the magnetisation transfer (MT) phenomenon, we performed a three-dimensional gradient-echo sequence (TR/32 ms, TE/8 ms, flip angle 6°), slice thickness 2 mm, interslice gap 0 mm, without and with the application of an MT binomial prepulse (1-2-1) applied on resonance. The MT sequences were performed in the axial plane (parallel to the intercommisural line) and in the coronal plane (perpendicular to the optic chiasm). Two radiologists (A.K.Z. and I. T.), who were unaware of the clinical status of the patients and the controls, evaluated all MR examinations in concert. The presence and the number of areas of white matter hyperintensity (WMH) were evaluated on axial FLAIR images. The areas of WMH were counted, and the longest diameter was measured (Fig. 1). Area and volume of the retrobulbar optic nerve and of the optic chiasm were measured on STIR and MTI images, respectively, using the ANALYZE 4.0 software (Biomedical Imaging Resource, Mayo Clinic, Minn., USA). Areas were outlined with a method previously described by using the "Auto Trace" function [17]. The measured areas were multiplied by the slice thickness to determine the volume of the outlined structures. This process was repeated for all slices, and the volume of the optic chiasm was computed by summation of the corresponding volumes of all slices.

MTR of the chiasm was evaluated by the region-of-interest (ROI) method. Care was taken to avoid the partial volume effect of cerebrospinal fluid (CSF) when we were defining the ROIs. The MTR was calculated as: MTR=

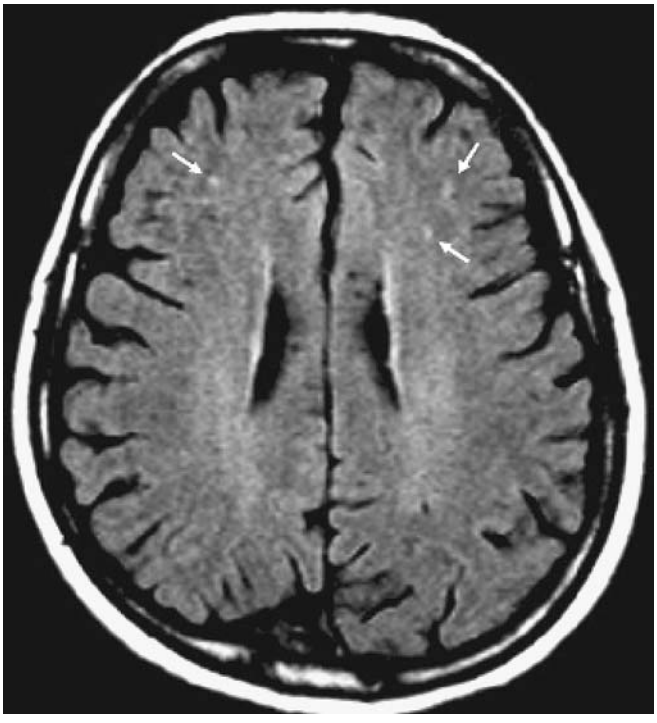

Fig. 1 A 56-year-old female patient with non-arteritic anterior ischaemic optic neuropathy: FLAIR (TR 6,300/TE 120/TI 2,150 ms) axial MR image of the brain shows areas of white matter hyperintensity (*white arrows*)

(Sio−SIm)/SIo×100 (%), where SIm refers to the signal intensity from an image acquired with an MT prepulse and SIo to the signal intensity from the image acquired without an MT prepulse.

Segmentation was performed with a home-made software package developed by the IPAN group (http://www.cs.uoi.gr/~ipan), as follows: image data [in digital imaging and communications in medicine (DICOM) format] were accessed and read and a (binary) mask was created. MTR images were obtained by calculating the MTR for every voxel. These MTR images were segmented automatically by a method previously described [18]. We observed that no separate cluster for WMH could be obtained, and the number of clusters that best captured the spatial distribution of intracranial brain tissue (IBT), and CSF was 2. The cluster with the high level of pixel intensity values represented CSF, and the cluster with the low level of pixel intensity values represented IBT. MTR histograms were created. To allow comparison of histograms resulting from heads with different intracranial volumes, we corrected the MTR histograms by dividing the individual bins by the total number of intracranial voxels. From MTR histograms we derived the mean MTR value (mMTR); the peak height (H); the kurtosis which indicated the peakness of the histogram; the skewness which indicated the shouldering of the histogram.

Statistical analysis

Statistical analysis was performed with SPSS base 14 for Windows. The normality of distribution of the parameters was assessed by the Kolmogorov–Smirnov test. The Mann–Whitney U test was used to study differences in the number of areas of WMH between patients and controls. The unpaired two-tailed Student's *t*-test was used to study differences in the area of the optic nerve, the volume and MTR of the chiasm, and the brain histogram parameters between patients and controls. The Pearson correlation coefficient was used to study the relationship between MRI and clinical parameters. A P value less than 0.05 was considered statistically significant.

Results

A significantly higher number of WMH areas was observed in patients (total 419; mean 14.4; SD 19) than in controls (total 127; mean 4.7; SD 5.7), $P<0.001$. There were no confluent or patchy areas of WMH, and their longest diameter was <2 mm. mMTR of the brain histograms was significantly lower in patients (53.0±8.0) than in controls (58.0±5.6), $P<0.05$ (Fig. 2). Area (in square millimetres) of the affected ON and volume (in cubic millimetres) and MTR (in percent) of the chiasm (10.7±4.6), (75.8±20.2), (56.4±6.5), respectively, were

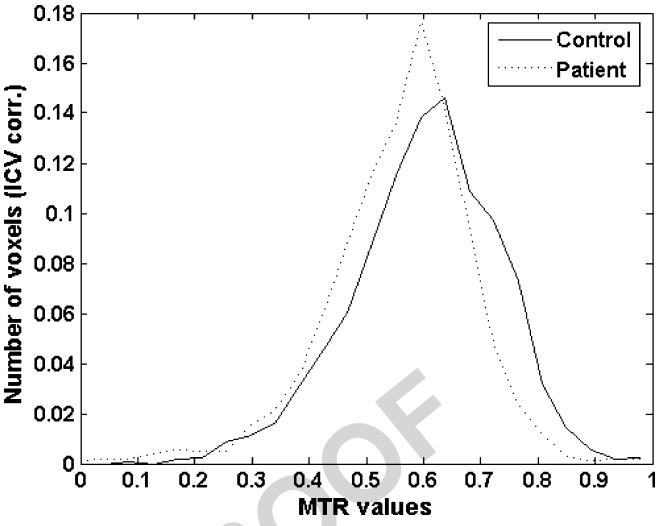

Fig. 2 Magnetisation transfer histogram (MTR) after correction for intracranial volume (*ICV*) in patients and controls. The scale of the y-axis is arbitrary and reflects the corrected (*corr.*) number of voxels

significantly lower in patients than in controls (13.6±4.3), (158.2±75.3) (62.1±6.2), respectively, $P<0.05$ (Fig. 3). Area of the unaffected optic nerve was not significantly different in patients (12.8±4.4) compared with controls (13.6±4.3) (Fig. 4). There was no correlation between area of the optic nerve, volume and MTR of the chiasm, brain histogram parameters and visual acuity or visual field abnormalities. None of the patients had diabetes mellitus or uncontrolled hypertension. Sixteen patients were treated for arterial hypertension by angiotensin-converting enzyme.

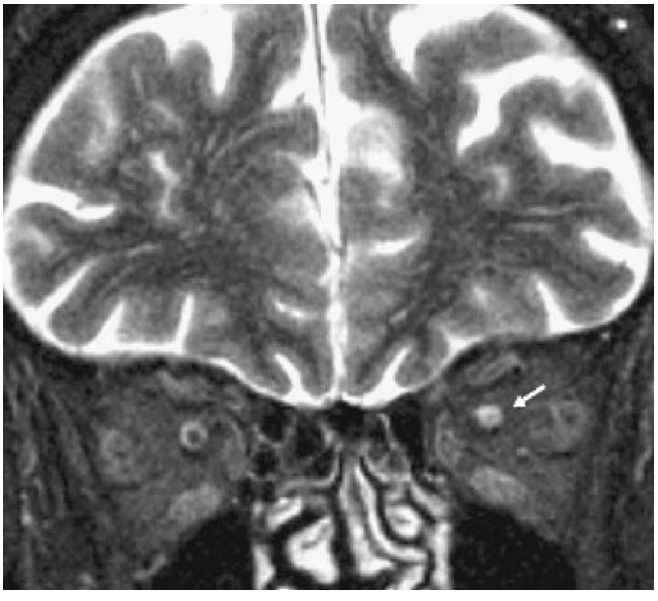

Fig. 3 A 73-year-old male patient with non-arteritic anterior ischaemic optic neuropathy: STIR (TR/2,650 ms, TE/90 ms) coronal brain MR image shows atrophy of the left optic nerve (*white arrow*)

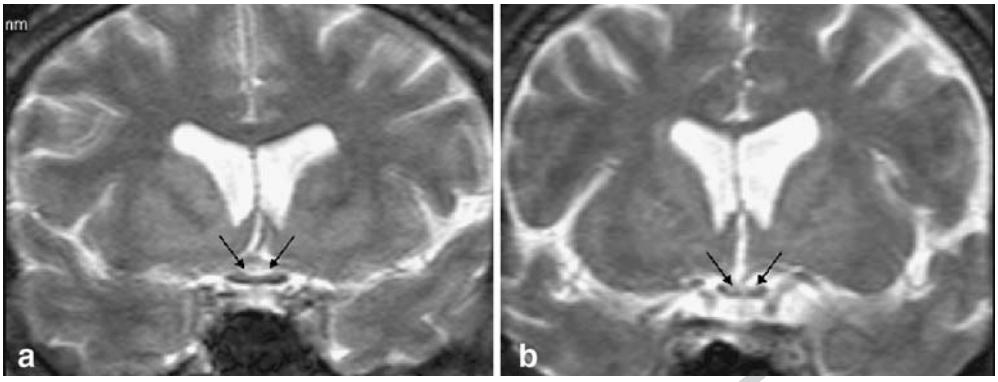

Fig. 4 Coronal 3D-gradient echo scans (TR/32 TE/8 flip angle 80) with the application of magnetization transfer prepulse: **a**) Control male 57-years old with normal chiasm (*black arrows*), **b**) Patient female 56-years old with atrophic chiasm (*black arrows*)

Discussion

The retina and the optic nerve are sensitive to ischaemia, and NAION is presumed to result from circulatory insufficiency within the territory of the short posterior ciliary arteries, leading to disruption of the normal nerve architecture and death of retinal ganglion cells (RGCs) [2, 5, 19]. Retrobulbar haemodynamics of NAION patients have been studied with colour Doppler, and decreased peak systolic velocities have been demonstrated in the territory of the central retinal artery and the nasal short posterior ciliary arteries [20]. Furthermore, studies with laser Doppler velocimetry have shown decreased velocities in the capillaries of the optic nerve head [21]. The sequence of events and the mechanisms responsible for anterior ischaemic optic neuropathy (AION) have been experimentally studied by using a *c-fos* transgenic mouse model [16]. *c-Fos* is a stress-response gene that is immediately expressed after ischaemic cellular stress [22]. Experimentally induced AION is characterised by early expression of *c-fos* followed by apoptotic cell death of the RGCs and the oligodendrocytes throughout the ON up to the chiasm [16]. Another important finding of AION is the significant axonal loss in the ON. Axonal loss is thought to result from different mechanisms, such as direct effect of ischaemia, Wallerian degeneration due to RGC death and demyelination due to extensive oligodendrocyte death. According to these experimental data the decreased size of the affected ON and chiasm observed in the NAION patients of the present study may be explained by extensive axonal and oligodendrocyte loss. Moreover, axonal loss and demyelination may be the histopathological substrate explaining the decreased MTR of the optic chiasm. MTI enables semi-quantitative tissue characterisation (MTR) using the phenomenon of saturation transfer between immobile macromolecular protons and the mobile water protons. Macromolecular protons are found in proteins and cellular membranes. The MTR is determined by the field strength and the scanning parameters, but principally by the concentration of macromolecules and the efficacy of interaction between the bound and free pool of protons [23, 24]. MT contrast and MTR of the brain are mainly related to the presence of myelin [11, 12]. The optic nerve and chiasm consist mainly of myelinated fibres derived from the ganglionic cells of the retina [19, 25]. Myelin sheath, which is essential for axonal survival, derives from oligodendrocytes [26]. Because each oligodendrocyte myelinates many axons, death of oligodendrocytes may lead to demyelination and loss of a large number of axons throughout the ON up to the chiasm [26]. RGC death, taking place in the context of NAION, may further contribute to axonal loss through a process of Wallerian degeneration.

Increased numbers of WMH areas have been detected in brain MRI in two previous studies of NAION patients [7, 8]. Cerebral white matter lesions are the most commonly known brain changes associated with aging. Indeed, Areas of WMH have been reported to be frequent in subjects older than 50 years and seem to reflect zones of atrophic perivascular demyelination [9, 27]. Areas of non-confluent WMH are not progressive. In contrast, patchy or confluent WMH areas have been demonstrated to be associated with hypertension and older age. In the present study none of the subjects had uncontrolled hypertension and WMH areas were non-confluent in both patients and controls. Nevertheless, the higher number of WMH areas in patients than in controls may suggest that a mechanism (e.g. microangiopathy) other than aging is responsible for WMH in NAION. Microangiopathy might also be responsible for the lower mean MTR of the brain histograms in patients than in controls. Small but significant age-related reductions of the corpus callosum and frontal white matter MTR have been previously reported to be associated with normal aging [28]. Moreover, significant differences have been reported in the brain histogram parameters, such as mean, median, and peak height between young and older subjects [29]. All these changes are thought to be associated with neuronal shrinkage, demyelination and axonal loss, which,

according to neuropathological studies, take place with advancing age [30]. More pronounced neuronal shrinkage, demyelination and axonal loss might account for the lower mMTR of the brain histograms in NAION patients. Previous studies have demonstrated that the MTR of WMH in elderly people is lower than that of normal white matter but higher than that of demyelinating lesions [31]. In this study, although segmentation did not identify any separate cluster for WMH, their larger number in patients might have influenced the mMTR of the brain histograms.

In the present study a lack of correlation was found between cMRI and MTI measurements and clinical parameters such as visual acuity. This is probably because normal vision can remain, despite the loss of 40% of the neural substrate. Visual acuity of 6/15 seems 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 a consequence of plasticity and functional remodelling within the visual system and higher centres [32].

To conclude, in NAION patients, cMRI and MTI reveal optic nerve and chiasmatic atrophy associated with increased numbers of areas of WMH and low MTR of the chiasm and the brain. The association of these findings may suggest hypoperfusion due to microangiopathy as the underlying cause of NAION.

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