



Distinctive retinal nerve fibre layer and vascular changes in neuromyelitis optica following optic neuritis

A J Green and B A C Cree

J Neurol Neurosurg Psychiatry 2009 80: 1002-1005 originally published online May 21, 2009

doi: 10.1136/jnp.2008.166207

Updated information and services can be found at:

<http://jnp.bmj.com/content/80/9/1002.full.html>

These include:

References

This article cites 23 articles, 9 of which can be accessed free at:

<http://jnp.bmj.com/content/80/9/1002.full.html#ref-list-1>

Article cited in:

<http://jnp.bmj.com/content/80/9/1002.full.html#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

- [Cranial nerves](#) (456 articles)
- [Ophthalmology](#) (722 articles)
- [Neuromuscular disease](#) (1110 articles)
- [Peripheral nerve disease](#) (553 articles)
- [Immunology \(including allergy\)](#) (1572 articles)
- [Multiple sclerosis](#) (751 articles)
- [Injury](#) (428 articles)
- [Neurological injury](#) (348 articles)
- [Radiology](#) (1525 articles)
- [Radiology \(diagnostics\)](#) (1142 articles)
- [Trauma](#) (429 articles)
- [Trauma CNS / PNS](#) (348 articles)

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>

Distinctive retinal nerve fibre layer and vascular changes in neuromyelitis optica following optic neuritis

A J Green, B A C Cree

► A supplementary table is published online only at <http://jnnp.bmj.com/content/vol80/issue9>

Multiple Sclerosis Center, Department of Neurology, University of California San Francisco, San Francisco, California, USA

Correspondence to: Dr A J Green, 350 Parnassus Ave Suite 908, San Francisco, CA 94117, USA; agreen@ucsf.edu

Received 24 October 2008
Revised 23 March 2009
Accepted 4 April 2009
Published Online First
21 May 2009

ABSTRACT

Patients and methods: This is a cross sectional study comparing the retinal features of optic neuritis (ON) between 20 multiple sclerosis (MS) and 16 neuromyelitis optica (NMO) patients with a history of ON (visual acuity at time of attack >20/100) matched for age and gender using optical coherence tomography (OCT) and fundoscopy.

Results: Compared with MS, NMO patients often had: (1) vascular changes, including attenuation of the peripapillary vascular tree (3/40 MS eyes, 22/32 NMO eyes; $p = 0.001$) and focal arteriolar narrowing (0/40 MS eyes and 9/32 NMO eyes; $p < 0.0001$), (2) a lower average nerve fibre layer (NFL) thickness (59.2 μm compared with 82.0 μm in MS; $p = 0.004$) and (3) nearly twice the NFL thinning after controlling for final visual acuity (32.1 vs 17.6 μm ; $p = 0.004$). Patients with NMO had more severe and diffuse axonal injury of the NFL compared with MS.

Conclusion: These NFL and fundoscopic findings suggest that some of the injury seen in NMO may be vascularly mediated. These inner retinal vascular changes are reminiscent of blood vessel wall thickening previously reported in the optic nerve and spinal cord at autopsy. If the retinal changes share a common pathology to those in the spinal cord and optic nerve, these observations suggest that vascular changes may be detectable during life.

Neuromyelitis optica (NMO) is a CNS demyelinating disease characterised by relatively selective injury to the optic nerve and spinal cord.^{1–3} Given its generally recurrent and aggressive course, distinguishing NMO from multiple sclerosis (MS) in patients presenting with optic neuritis (ON) is important. Previous reports have not described clear ophthalmic differences between ON in NMO and MS.^{4–6} We present evidence that NMO ON includes distinct vascular and retinal nerve fibre layer (NFL) changes on ophthalmoscopy and optical coherence tomography (OCT). These findings may be diagnostically useful and could have implications for understanding NMO pathogenesis.

METHODS

This was a cross sectional study of 16 NMO and 20 MS patients selected for persistent visual deficits after ON who were matched for: prior ON history (visual acuity nadir of at least 20/100), gender and age. NMO and MS patients with known ophthalmological disease (eg, glaucoma, cataract) and ON within the previous 3 months were excluded. This

study received institutional review board approval and written informed consent was obtained from each subject in accordance with the Declaration of Helsinki.

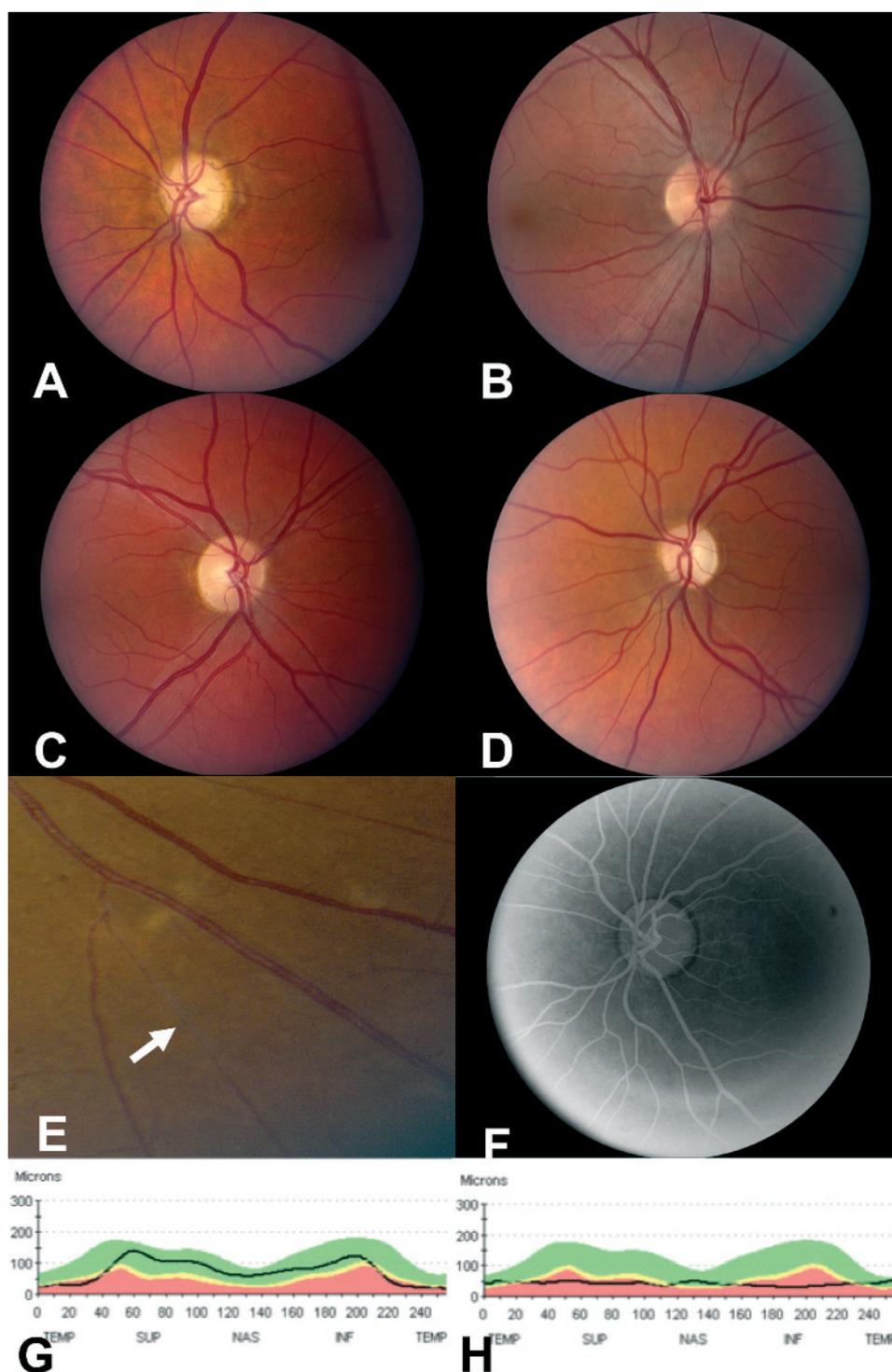
The mean age of the NMO and MS subjects was 41 (11.7) years. Disease duration for MS and NMO subjects was 5.0 and 5.5 years, respectively. A total of 80% of MS subjects and 87% of NMO subjects were women; 75% of MS and 44% of NMO subjects were white; and 69% of NMO subjects were seropositive for anti-aquaporin 4 (AQP4) antibodies. ON occurred in 24 MS and 27 NMO eyes ($p = 0.028$). The final visual acuity (logMAR) of ON affected MS eyes was 0.44 (~20/60, range 0–2) and 0.81 (~20/120, range 0–3) for NMO eyes ($p = 0.056$).

Best recorded monocular visual acuity, with correction when appropriate, was used for all analyses. Each patient underwent a dilated fundoscopic examination with retinal photographs. The Fast Retinal Nerve Fibre Layer thickness protocol was performed on a Stratus OCT machine (Zeiss, Fremont, California, USA) by a trained technician masked to the patient's diagnosis. Scans were repeated twice and assessed for signal strength and centring. Signal strength scores of 6 or less were not used. Two NMO patients were unable to undergo OCT because of inability to support weight while seated upright.

Optic disc pallor was assessed (absent, sectoral or global) and graded (mild, moderate and severe). Retinal photographs documented retinal vasculature appearance in the peripapillary and mid-periphery retina and were evaluated using modified Atherosclerosis Risk in Communities criteria.⁷ Vascular changes were described as involving arteries, veins or both. Narrowing of all vessels arising from the disc was categorised as global, whereas narrowing of localised vessel or area of vessels leaving the optic disc was categorised as sectoral. Narrowing of the blood column in an arterial branch with obscuration of the vessel lumen was categorised as "frosting". These changes were not described as "sheathing" to avoid confusion with "venous sheathing"^{7,8,9} and "arteriolar sheathing" (ie, thickening of any vessel wall with narrowing).⁷ Retinal changes were confirmed by an examiner masked to the subject's diagnosis (overall agreement between examiners was 88%, kappa = 0.81).

STATA 9.0 (North Fork, Texas, USA) was used for statistical analyses. Logistic analyses were adjusted for clustering by individual, gender, race (white versus non-white), age, history of ON and final visual outcome where appropriate.

Figure 1 Fundus appearance of eyes after optic neuritis in subjects with neuromyelitis optica (NMO) and multiple sclerosis (MS). (A) Left eye from NMO patient showing global attenuation of vessels arising from the optic disc. Visual acuity in this eye was 20/20. Optic disc pallor is graded as global and severe. Only the vein arising from the superior edge of the disc appears normal in size. (B) Right eye from patient with MS. Visual acuity in this eye was 20/20. Optic disc pallor is graded as segmental and mild. Vessels are normal in appearance. Slits are present in both superior and inferior arcuate bundles. (C) Right eye from patient with NMO and sectoral arteriolar narrowing. Visual acuity in this eye was 20/20. Optic disc pallor is graded as segmental and moderate. The arterioles arising from the superior and inferior nasal edge of the disc are narrowed. (D) Left eye from patient with MS with severe global pallor and normal appearing vessels. Visual acuity in this eye is 20/200. (E) Arteriolar frosting noted in the left eye of NMO patient in mid-periphery of retina. Note frosted appearance of arteriolar branch (arrow). Visual acuity was 20/400. (F) Fluorescein angiogram in an NMO patient with arteriolar “frosting” shows no leakage. (G) Pattern of nerve fibre layer (NFL) thinning in typical MS patient; mean NFL thickness = 89 μm . (H) Pattern seen in NMO patient; mean NFL thickness = 55 μm . Note the relative preservation of fibres in the temporal fibres in the NMO case (maculopapillary bundle).



RESULTS

We found that, relative to MS, ON in NMO was associated with: (1) vascular changes involving the arterial blood supply to the inner retina, (2) greater axonal loss and (3) broader topographic patterns of axonal injury.

Three overlapping patterns of arteriolar changes were observed in NMO patients. The most prominent and common pattern was attenuation of arterioles in the peripapillary retina often with accompanying venous (fig 1A). Narrowing of arterioles was severe enough in many cases to give the vessel wall a thickened appearance. Sometimes, the peripapillary

vascular attenuation was sectoral and, in these cases, appeared more prominent in arterioles compared with veins (fig 1B), a pattern sometimes observed after ischaemic optic neuropathy. Collectively, these changes (fig 1A, 1B) were seen in 22 of 32 eyes from patients with NMO but in only three of 40 eyes of patients with MS ($p = 0.001$). These patterns occurred in MS only when severe papillitis accompanied ON. MS eyes more commonly showed classic segmental (frequently temporal) disc atrophy, with or without slits, in the arcuate bundles but with normal appearing vessels (fig 1C). Venous sheathing was not seen in the MS eyes.^{8,9} In MS cases with pronounced disc

Table 1 Fundoscopic and optical coherence tomography differences between optic neuritis in neuromyelitis optica and multiple sclerosis

	NMO	MS	Unadjusted	Adjusted
Arteriolar changes (n = eyes)	22/32	3/40	0.0001	0.001
Arteriolar frosting (n = eyes)	9/32	0/40	0.0024	<0.0001
NFL thickness (μm) (mean (SD))	59.2 (16.2)	82.0 (17.6)	<0.0001	0.004
M:T ratio (mean (SD))	2.67 (0.70)	3.38 (0.78)	0.011	0.026

Two sided Fisher's exact p values are reported for the unadjusted analyses. Adjusted analyses used multivariable models adjusting for race, final visual acuity, sex and age. Average values are only reported for eyes with a history of optic neuritis. All analyses include clustering adjustment (two eyes from each patient).

MS, multiple sclerosis; M:T ratio, the ratio of the maximum NFL thickness in the arcuate bundles to the average temporal quadrant NFL thickness; NFL, mean nerve fibre thickness; NMO, neuromyelitis optica.

atrophy, vascular changes were not observed suggesting that the vascular changes common in NMO were not dependent on the severity of ON (fig 1D).

A second less common pattern observed in NMO demonstrated more selective and focal arteriolar "frosting" in vessels at a distance greater than two disc diameters from the disc edge (fig 1E). This was seen in 9/32 NMO eyes and was never seen in MS eyes ($p < 0.0001$). In a single case examined, leakage of fluorescein was not observed from these "frosted" vessels (fig 1F). An association between anti-AQP4 autoantibodies and retinal vascular changes was not found ($p = 0.279$) although the cohort size was too small to detect a modest correlation.

Despite adjusting for gender, age, race and final visual outcome, NFL thinning in NMO was more diffuse and severe than in MS (table 1). In MS, ON reduced the NFL thickness by 17.6 μm and by 32.1 μm in NMO. As previously reported,^{10 11} NFL thinning in MS ON was predominantly temporal (fig 1G). In contrast, NFL thinning in NMO involved all quadrants and sometimes preserved axons mediating central vision (fig 1H and supplementary fig 1 available online).

Although NFL thinning is generally more severe in NMO, the extent of thinning in the temporal quadrant (which corresponds to the fibres forming the maculopapillary bundle) is equivalent in NMO and MS (see supplementary fig 1C online). Therefore, the average lower total NFL thickness scores in NMO appear to be related to more profound injury in arcuate and nasal fibres than in MS.

DISCUSSION

We reported previously unrecognised ophthalmological features that help distinguish ON of NMO from MS including: (1) attenuation of the peripapillary vascular tree, (2) focal arteriolar narrowing sometimes associated with obscuration of the vessel lumen, (3) approximately twofold thinning of the NFL and (4) diffuse thinning of the NFL rather than concentrated maculopapillary bundle thinning. These findings could serve as predictors of disease state following severe ON (visual acuity $< 20/100$). Moreover, the vascular changes seen on fundoscopy can be readily evaluated by a trained examiner and the inter-examiner correlation was excellent (overall agreement 88%, kappa = 0.81). Because both vascular changes and extent of retinal NFL thinning are correlated with NMO, the cross sectional nature of this study cannot resolve whether the reported vascular changes precede or occur independently from retinal NFL thinning. Prospective studies are needed to confirm and extend these observations.

The cause of the vascular changes described in NMO is unclear. Some component of the vascular attenuation may be secondary to reduced metabolic demand with inner retinal

atrophy. However, MS cases with severe inner retinal atrophy and global disc pallor but normal vessel appearance—as evidenced in fig 1D (global RNFL = 55 μm)—argue against this explanation. Global attenuation of the vascular tree could also be caused by prior optic disc oedema and secondary vascular compromise. Indeed, anecdotes suggest that NMO ON is associated with optic disc oedema.^{12 13} Therefore, vascular injury may be partially mediated by mechanical factors at the optic nerve head. However, previous pathological series described abnormally thickened vessel walls with narrowing of the vessel lumen in the retrobulbar optic nerves and spinal cords of NMO patients.^{4 14–16} Vascular hyalinisation of the spinal cord pathologically distinguishes NMO from MS although the mechanism of hyalinisation is not understood.¹⁶

Several pathological reports commented on the presence of inflammatory cell infiltration into the vessel walls of the optic nerves/chiasm in NMO patients.^{4 14 17} Therefore, some of the arteriolar changes described here, particularly "frosting", may result from direct vascular inflammation. It is possible that anti-AQP4 autoantibodies participate in this process. AQP4 is expressed on the abluminal surface of endothelial cells in unfenestrated capillaries from the CNS, as well as in the astrocytic end feet that supply the tight junction of the blood–brain barrier.¹⁷ AQP4 is known to upregulate in response to injury and is present in the walls of astrocyte associated^{18–20} and inner retinal arterioles.²¹

The observation that all four quadrants of the NFL are thinned in NMO confirms a recent report of global NFL layer thinning in NMO detected by OCT.²² The greater magnitude of average NFL thinning in our series is presumably because only eyes affected by ON were studied. The pattern of global NFL thinning may be causally related to the described vascular changes. Vascularly mediated optic neuropathies such as glaucoma and non-arteritic anterior ischemic optic neuropathy are known to cause injury to the arcuate fibres of the NFL.^{23 24} This is in contrast with MS associated ON where injury is relatively more selective for the maculopapillary bundles.^{10 11} Therefore, the pattern of global NFL thinning is more consistent with a vascular process. We speculate that vasculopathy may play a direct role in tissue injury in NMO. It seems plausible that directly addressing vascular compromise, or disc oedema, might be therapeutically beneficial in NMO.

In summary, we describe a distinct pattern of NFL and vascular injury in NMO compared with MS. Further clinical studies incorporating OCT and fundoscopy could help improve the accuracy and speed with which NMO is diagnosed following ON: a clinically important distinction given the high risk for devastating outcomes and the availability of potentially beneficial treatments.^{25–27}

Acknowledgements: Both authors participated in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, and approval of the manuscript. The authors have nothing to disclose, had full access to the data and take responsibility for the integrity and accuracy of the analysis. We would like to thank Dr William F Hoyt for his assistance in this project.

Funding: This work was in part supported by NIH K23-NS048869 (BACC) and NIH KL2- RR024130 (AJG).

Competing interests: None.

Ethics approval: Ethics committee approval was obtained from the University of California San Francisco.

REFERENCES

1. **Albutt TC.** On the ophthalmoscopic findings of spinal disease. *Lancet* 1870;**1**:76–8.
2. **Wingerchuk DM,** Hogganville WF, O'Brien PC, *et al.* The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;**53**:1107–14.
3. **Wingerchuk DM,** Lennon VA, Pittock SJ, *et al.* Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;**66**:1485–9.
4. **Beck GM.** A case of diffuse myelitis associated with optic neuritis. *Brain* 1927;**50**.
5. **McKee SH,** McNaughton FL. Neuromyelitis optica: a report of two cases. *Trans Am Ophthalmol Soc* 1937;**35**:125–35.
6. **Merle H,** Olindo S, Bonnan M, *et al.* Natural history of the visual impairment of relapsing neuromyelitis optica. *Ophthalmology* 2007;**114**:810–15.
7. **Hubbard LD,** Brothers RJ, King WN, *et al.* Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology* 1999;**106**:2269–80.
8. **Rucker CW.** Sheathing of the retinal veins in multiple sclerosis. *Proc Staff Meet Mayo Clinic* 1944;**19**.
9. **Birch MK,** Barbosa S, Blumhardt LD, *et al.* Retinal venous sheathing and the blood-retinal barrier in multiple sclerosis. *Arch Ophthalmol* 1996;**114**:34–9.
10. **Parisi V,** Manni G, Spadaro M, *et al.* Correlation between morphological and functional retinal impairment in multiple sclerosis patients. *Invest Ophthalmol Vis Sci* 1999;**40**:2520–7.
11. **Sepulcre J,** Murie-Fernandez M, Salinas-Alaman A, *et al.* Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. *Neurology* 2007;**68**:1488–94.
12. **Gault F.** *De la neuromyéélite optique aiguë* (Doctoral thesis). Lyons: Université de Lyons, 1874.
13. **Stansbury FC.** Neuromyelitis optica; presentation of five cases, with pathologic study, and review of literature. *Arch Ophthalmol* 1949;**42**:292.
14. **Lefkowitz D,** Angelo JN. Neuromyelitis optica with unusual vascular changes. *Arch Neurol* 1984;**41**:1103–5.
15. **Mandler RN,** Davis LE, Jeffery DR, *et al.* Devic's neuromyelitis optica: a clinicopathological study of 8 patients. *Ann Neurol* 1993;**34**:162–8.
16. **Lucchinetti CF,** Mandler RN, McGavern D, *et al.* A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* 2002;**125**:1450–61.
17. **Roemer SF,** Parisi JE, Lennon VA, *et al.* Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. *Brain* 2007;**130**:1194–205.
18. **Aoki-Yoshino K,** Uchihara T, Duyckaerts C, *et al.* Enhanced expression of aquaporin 4 in human brain with inflammatory diseases. *Acta Neuropathol* 2005;**110**:281–8.
19. **Quick AM,** Cipolla MJ. Pregnancy-induced up-regulation of aquaporin-4 protein in brain and its role in eclampsia. *FASEB J* 2005;**19**:170–5.
20. **Papadopoulos MC,** Verkman AS. Aquaporin-4 gene disruption in mice reduces brain swelling and mortality in pneumococcal meningitis. *J Biol Chem* 2005;**280**:13906–12.
21. **Wang A-G,** Yen M-Y, Fann MJ. The expression of aquaporin-4 in the retina and optic nerve. Immunofluorescence staining of human and mouse retina and optic nerve. Presented at the Asian Society of Neuro-Ophthalmology, Taipei, 2008; abstract FP-10.
22. **de Seze J,** Blanc F, Jeanjean L, *et al.* Optical coherence tomography in neuromyelitis optica. *Arch Neurol* 2008;**65**:920–3.
23. **Quigley HA,** Miller NR, Green WR. The pattern of optic nerve fiber loss in anterior ischemic optic neuropathy. *Am J Ophthalmol* 1985;**100**:769–76.
24. **Mok KH,** Lee VW, So KF. Retinal nerve fiber loss pattern in high-tension glaucoma by optical coherence tomography. *J Glaucoma* 2003;**12**:255–9.
25. **Mandler RN,** Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology* 1998;**51**:1219–20.
26. **Weinstock-Guttman B,** Ramanathan M, Lincoff N, *et al.* Study of mitoxantrone for the treatment of recurrent neuromyelitis optica (Devic disease). *Arch Neurol* 2006;**63**:957–63.
27. **Jacob A,** Weinschenker BG, Violich I, *et al.* Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Archiv Neurol* 2008;**65**:1443–8.

Keep up to date: sign up for our alerting services

Find out automatically when an article is published on a specific topic or by a particular author. We can also alert you when an article is cited or if an eLetter or correction is published. You can also choose to be alerted when a new issue is published online [and when we post articles Online First]. Check out the New Content Alerts and Citation tracker from the Online tools section on the home page.