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Optic Neuritis – Keys to Differentiating the Typical Presentation from Atypical Causes

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Optic neuritis (ON), an acute inflammatory disorder of the optic nerve, is often the presenting sign of multiple sclerosis (MS). It is most commonly seen in young Caucasian women. The primary objective in the initial patient evaluation is to differentiate typical ON – ie, ON associated with demyelination –from a symptom set that suggests an atypical presentation requiring additional investigations. This issue of *Ophthalmology Rounds* outlines the epidemiology and pathophysiology of ON, and findings of the Optic Neuritis Treatment Trial, on which current diagnostic and management strategies depend. A short summary of MS and its connection with ON is also presented.

Case 1

A 29-year-old Caucasian woman presents with a 4-day history of gradually worsening blurry vision in the right eye and seeing bright lights in a dark room. There is discomfort/pain around the right eye, worse when she is looking to the left. She is otherwise healthy and has never had any medical problems. On examination, the vision is 20/60 and 20/20; there is a right afferent pupillary defect, and fundoscopy does not reveal any abnormalities. There is generalized depression on Humphrey visual field testing in the right eye and the field in the left eye is normal.

Case 2

A 43-year-old African-American woman presents with the blurred vision in the right eye that has been worsening for the past week. She denies any pain in/around the eye. The patient is healthy except for a similar episode in the right eye approximately 3 months ago; she was treated with high-dose intravenous (IV) steroids and her the vision improved to baseline less than a week after completion of the course of steroids. On examination, vision is light perception in the right eye and 20/20 in the left, there is a dense right afferent pupillary defect, and the right optic nerve is very slightly pale temporally. On formal visual fields, there is central scotoma in the right eye and the field is normal in the left eye.

Upon completion of this article, readers should be able to identify the key differences in these 2 cases and to understand how these differences would alter their management/treatment strategies.

Optic neuritis (ON) is an acute inflammatory disorder of the optic nerve. It is most often caused by demyelination; thus, the term used to describe it is "acute idiopathic demyelinating optic neuritis." ON associated with demyelination is often referred to as "typical ON." The main objective of the clinician encountering a patient with optic neuritis is to determine whether the optic neuritis is typical, in which case no further testing is necessary to make the diagnosis, or atypical, in which case other testing should be considered.

Clinical Presentation

The classical picture of typical ON is a unilateral, subacute, painful loss of vision without accompanying systemic or neurological symptoms. Vision loss typically occurs

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over days to weeks, and usually reaches its peak at about 2 weeks.

Epidemiology

ON typically affects young adults ranging from 18–45 years of age, with a mean age of 30–35 years and a strong female predominance. There is significant worldwide variation in the prevalence and presentation of ON and multiple sclerosis (MS), of which ON is often the first clinical manifestation. In the United States, the annual incidence of optic neuritis is about 5 per 100 000 population, with a prevalence of about 115 per 100 000.[1] It is more common in regions more distant from the equator,[2,3] with Canada having one of the highest prevalence in the world. ON affects Caucasians almost 3 times more commonly than Asians or Africans.[4,5]

Some studies have shown that those who migrate before puberty take on the incidence of MS in the area to which they migrate.[6,7] This suggests that environmental factors play an important role in addition to genetics. Some studies have also suggested that factors such as infectious etiologies,[8,9] reduced sun exposure at higher latitude,[10,11] and vitamin D deficiency[12,13] may play a role in the pathogenesis.

ON in children is very different from the typical ON seen in adults.[14-17] Demyelinating ON associated with MS is less common in children than in adults; in children, ON is often related to a post-infectious demyelination. Children often present with bilateral ON at onset and more profound visual loss as compared to adults.

Pathophysiology

ON is an immune-mediated disorder involving demyelination and inflammation.[18,19] Some currently unidentified initial trigger leads to abnormalities in the blood-brain barrier (BBB), which subsequently allows the entry of activated T cells into the central nervous system (CNS).[19,20] These T cells then attack myelin and release cytokines and other inflammatory mediators, leading to demyelination, axonal degeneration, and neuronal cell death.

Investigations

Much of our knowledge about ON is derived from the findings of the Optic Neuritis Treatment Trial (ONTT), which is described in greater detail in the next section.[21-23] The diagnosis of typical ON is a clinical one and in the presence of a typical clinical scenario, laboratory tests, lumbar puncture, and neuroimaging are not required for diagnosis.

Baseline visual-field testing is recommended for comparison when following clinical improvement over time. The actual pattern of visual-field defect (VFD) is of limited value in diagnosis, as ON can have any pattern of nerve fibre bundle-related VFD. Recently, ocular coherence tomography (OCT) has been demonstrated to show that retinal nerve fibre layer thinning is correlated with impaired visual function,[24,25] and can be used to monitor progression of axonal loss in patients with MS and ON.

The ONTT found that magnetic resonance imaging (MRI) of the brain has a prognostic role in ON: the 15-year risk of developing MS in patients who have no lesions on baseline MRI is 25%, whereas the risk rises to 72% in the presence of ≥1 lesions.[22] Thus, MRI is the single best predictor for development of MS in patients with ON. It is important to note that the diagnosis of clinically definite MS does not necessarily predict poor overall clinical outcome, as many patients diagnosed with MS have an indolent course and their disease-associated disability is low. We also learned from ONNT that patients presenting with ON as their first manifestation of MS tend to have relatively low risk of disability and their overall prognosis is favourable.[26]

In the absence of lesions on MRI, the following features were found to be associated with low risk of developing MS: male sex, optic disc swelling, atypical features at presentation, no light perception vision, no pain, severe optic disc edema, peripupillary hemorrhages, retinal exudates.[27]

Atypical features suggesting a possible alternative diagnosis and the need for further laboratory testing are described in Table 1.[2]

The Optic Neuritis Treatment Trial (ONTT)

The ONTT was a multicentre, prospective, randomized, placebo-controlled clinical trial, with a 15-year follow-up period. A total of 454 subjects were enrolled, with inclusion criteria of:

- Age 18-46 years
- Unilateral ON
- Visual symptoms of ≤8 days' duration
- Relative afferent pupil defect and VFD in affected eye

Of note: as there were no subjects enrolled who were younger than 18 or older than 46 years of age, interpolating the ONTT findings to patients not in this age group should be done with caution.

Subjects were randomized to one of the following:

- IV methylprednisolone 250 mg q6h for 3 days followed by oral prednisone 1 mg/kg/day for 11 days
- oral prednisone 1 mg/kg/day for 14 days
- oral placebo for 14 days

More than three-quarters (77%) of subjects were women, and 85% were Caucasian. Mean age was 32±7 years. One of the objectives of the trial was to determine the natural history of visual impairment in patients with ON.[28,29]

According to findings in the ONTT, the typical course of ON (as previously stated) usually consists of vision worsening over the first 4 days to 2 weeks. Then visual recovery usually starts, peaks at about 1 month, and continues for 1 year. Final visual acuity and visual fields improve to almost baseline levels in most

Table 1: Atypical features of optic neuritis

- Age of onset <15 or >45 years old
- Progressive visual loss over >2 weeks
- Simultaneous bilateral vision loss
- No light perception vision
- Absence of periocular pain (present in only 7% of patients in the ONTT)
- Lack of substantial visual recovery within 3 month
- Visual decline after withdrawal of corticosteroids
- Severe optic disc edema, disc hemorrhage (present in <5 % of patient in the ONTT), macular star
- Contributory systemic diagnoses
  - Sarcoidosis
  - Rheumatological disorders
  - Immune-compromised state
  - Underlying infection
  - Cancer
- Atypical imaging features (eg, dural enhancement)

ONTT = Optic Neuritis Treatment Trial

patients. The ONTT reported at 15-year follow-up visual acuity of ≥20/20 in 72% of eyes affected with ON, and visual acuity of ≥20/40 in 96%. Only 1% had visual acuity of ≤20/200 in both eyes.

Treatment

Corticosteroids

The ONTT specifically investigated the role of corticosteroids in patients with ON and it showed that IV steroids speed up the visual recovery by 4–6 weeks, if started within 8 days of onset, but have no lasting benefit.[30] Oral steroids actually increased the risk of recurrence in both the affected and fellow eye, and the effect was still seen at 15 years; thus, the use of oral steroids in ON is contraindicated. IV steroids can be considered for patients who require rapid visual recovery, such as monocular patients, patients with significant bilateral visual loss, and those with an occupational requirement. The typical regimen used today is IV methylprednisolone 1 g daily for 3 days, without the oral taper.[31,32] It is important to inform patients of the common adverse events of high-dose systemic corticosteroids given for a short time, including insomnia, mild mood changes, gastrointestinal upset, and facial flushing.

Disease-modifying agents

Disease-modifying agents increase the time from the initial CIS (in this case, ON) to the onset of the second neurological episode, the frequency of subsequent MS relapses, and the volume of demyelinating lesions on MRI. Currently available disease modifying agents include the immunomodulatory agents interferon β-1a, interferon β-1b, and glatiramer acetate. Interferon β induces an inhibitory effect on the proliferation of leukocytes, antigen presentation, and T-cell migration across the BBB and enhances anti-inflammatory cytokine production. Glatiramer acetate may work as a decoy for the immune system by inducing antigen presenting cells with anti-inflammatory properties and promoting the generation of immunoregulatory T cells that suppress pathogenic T cells.

Several studies have looked at the effect of interferon β-1a and interferon β-1b in patients with CIS, including ON, and at least ≥2 white-matter lesions on brain MRI.

- The Controlled High-Risk Avonex® Multiple Sclerosis Prevention Study (CHAMPS)[33]
- Early Treatment of Multiple Sclerosis (ETOMS) study with interferon β-1a[34]
- Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study.[35]

All of the studies showed that interferon β increases the time interval to CDMS and decreased the lesion load on brain MRI in high-risk patients at 1-5 years.

CHAMPS[33] was a Phase III, multicentre, randomized, double-blind, placebo-controlled clinical trial. The study's objective was to determine whether treatment with interferon β-1a in patients with CIS and ≥2 white-matter lesions on brain MRI reduced the incidence of CDMS. The 383 subjects, recruited over 3 years, were initially treated with IV steroids. They were randomized to weekly intramuscular injection of interferon β-1a or placebo. CHAMPS demonstrated that the cumulative probability of developing CDMS was significantly lower in the interferon β-1a group (35%) than in the placebo (50%) group during 3 years. Interferon β-1a group also had a relative reduction in MRI lesion load compared to placebo.

Despite modestly positive results of these studies, it must be noted that the endpoint of developing CDMS and the volume of lesions on MRI were not correlated with disability or quality of life measures. In addition, patients will need to be on treatment for approximately 6 years to prevent a single relapse.[34] Thus, the decision to start immunomodulatory therapy in patients with ON should be individualized and not all patients should necessarily be placed on treatment.

Conditions Associated with ON

Multiple sclerosis (MS)

MS is an acquired inflammatory demyelinating disease of the CNS, resulting in multiple varied neurological symptoms and signs. In most patients, the disease starts off with the relapsing-remitting course: periodic attacks of demyelination resolve by themselves over time with almost complete restoration of function. However, over time, many patients progress to the secondary progressive form, in which no discreet attacks are identifiable but there is slow progression of

disability over time. CNS lesions are separated in time and space.

Clinically isolated syndrome (CIS) is the first neurological episode of demyelination. Clinically definite MS (CDMS) is defined by the McDonald criteria[36] and is essentially 2 attacks or 2 lesions separated in time or space.

There are many theories as to the initial trigger of MS, including toxins, infectious agents, and primary neurodegeneration. A very old hypothesis that gained renewed attention starting around 2006 is the vascular theory. Italian vascular surgeon Paolo Zamboni proposed that MS is caused by chronic cerebrospinal venous insufficiency, a term used to describe ultrasound-detectable abnormalities in the anatomy and flow of intracerebral and extracerebral veins.[37,38] Zamboni and colleagues hypothesized that MS was caused by impaired venous outflow in the neck, leading to cerebral venous backflow, resulting in deposition of iron in the brain, which triggers an autoimmune reaction.[37] Patients diagnosed with cerebrospinal venous insufficiency underwent catheter-based venography, during which stenoses were treated with balloon angioplasty. The investigators found an increase in rate of relapse-free patients from 27% to 50% post-balloon angioplasty and improvement in quality of life with the MS Functional Composite at 1 year of follow-up in cases of early relapsing-remitting MS. However, no significant changes were observed in patients with secondary progressive or primary progressive MS in an open-label trial of the procedure.[39] This theory has gained momentum through social media, spurring patients to seek treatment outside of traditional care and advocacy groups to push for widespread availability of the balloon angioplasty for areas of vein stenosis.

A recent meta-analysis commissioned by the Canadian Institutes of Health Research of all currently published studies found that chronic cerebrospinal venous insufficiency was more frequent among those with MS than healthy controls.[40] However, the meta-analysis could not differentiate between causation versus association, and the studies analyzed in the meta-analysis had considerable unexplained variation in results and strength of association. Similar findings were obtained by a systemic review from a United Kingdom group.[41] Some studies have suggested that chronic cerebrospinal venous insufficiency may be a consequence of MS, with inverse correlation to the duration of MS.[42]

Eye findings in MS

Beside ON, fairly common ocular symptoms of MS include intermediate uveitis and retinal periphlebitis. When the brainstem is involved, internuclear ophthalmoplegia, nystagmus, and ocular motor nerve palsies can be seen. Hemianopic VFDs can be found as well, albeit rarely, resulting from the demyelinating lesions affecting visual pathways behind the chiasm.

MS and ON

ON is the initial presenting sign of MS in 20% of patients. One-half of MS patients have experienced ON at some point. Almost all MS patients have evidence of subclinical ON.

New treatment modalities for MS

Several therapies utilizing antibodies directed against different receptors playing a role in the pathogenesis of MS have shown tremendous promise in the treatment of primary progressive MS.

Natalizumab, a humanized monoclonal antibody directed against integrin (cell adhesion molecule responsible for the migration of the lymphocytes from the blood vessels), has been shown in recent trials to decrease the rate of relapses but most importantly to decrease the progression of disability.[43]

Fingolimod is a ligand that binds and downregulates the receptors on the surface of lymphocytes responsible for their migration from lymph nodes to serum. Several well-conducted trials demonstrated that fingolimod improved the relapse rate, the risk of disability progression, and lesion load on MRI in patients with MS.[44] One of the important adverse events of fingolimod with which ophthalmologists should be familiar is development of cystoid macular edema. The product monograph recommends the performance of an ophthalmic evaluation 3-4 months after fingolimod is initiated, as well as whenever any patient taking the agent complains of visual disturbances.[45]

Neuromyelitis optica (NMO)

NMO, also known as Devic disease, has been recognized as a distinct inflammatory demyelinating disease consisting of ON in combination with longitudinally extensive transverse myelitis.[46] The median age of onset is in the fourth decade and is about 10 years later than MS.[47] There appears to be a higher prevalence of NMO among non-Caucasian populations.[46]

NMO is a rare B-cell-mediated disease associated with the presence of a specific serum NMO immunoglobulin G autoantibody. This autoantibody targets the cellular membrane water channel aquaporin-4, which is found primarily in the optic nerves, spinal cord, hypothalamus and periventricular tissues.[48] As NMO is a B-cell disease, its pathophysiology mimics vasculitis rather than MS.

It is important to distinguish NMO from MS, as NMO has much poorer prognosis with increased frequency of relapse, higher chance of permanent visual loss, higher chance of permanent paralysis of the limbs.[49] The treatment of NMO is also different, requiring sustained immunosuppression.[46] NMO should be suspected in atypical ON (usually poor visual recovery), in patients with transverse myelitis, and in patients with bilateral simultaneous or sequential ON shortly after the first episode, especially if the brain MRI is not diagnostic for MS.

Conclusions

Acute demyelinating ON can occur in isolation or be associated with MS. ON is often the first presenting symptom of MS. Fortunately, the rate of disability in patients with multiple sclerosis whose initial presenting manifestation was ON is low. Typical ON (unilateral, subacute, painful loss of vision without systemic or neurological symptoms) is a clinical diagnosis and does not require investigations. MRI helps predict the prognosis (risk of development of CDMS) and can help the decision-making process in initiating immunomodulatory therapy. Although it is important to diagnose typical ON, it is more important to identify those patients with atypical ON where different treatments might be needed to prevent irreversible visual loss, such as NMO.

IV steroids speed up visual recovery by about one month if started within 8 days of onset, but have no other lasting benefit. Oral steroids increase risk of recurrence in affected and fellow eye, even 15 years later. Immunomodulatory agents have been shown to reduce the risk of developing CDMS and MRI lesion number, but it is not known how this is correlated with disability or quality of life.

Cases (continued)

Case 1

The patient in this vignette presents with a typical clinical scenario seen in demyelinating optic neuritis, thus no additional tests are necessary in diagnosing acute idiopathic demyelinating optic neuritis. The treatment approach should be based on the findings of ONTT: the patient should be offered a choice of receiving high-dose IV prednisolone to hasten visual recovery. The role of MRI (to help prognosticate the chances of developing clinically definite MS) should be discussed with the patient. The patient should be reassured that even if a diagnosis of clinically definite MS is made in the future, the prognosis in terms of disability is likely to be favourable.

Case 2

This case should prompt the recognition of features not typical of demyelinating optic neuritis: absence of pain on eye movements (only 7% of patients in ONTT did not have pain on eye movements), and visual acuity of light perception (vision of light perception or worse was present in only 6% of patients in ONTT). Quick improvement of vision after steroid administration and rapid worsening on steroid withdrawal (so-called "steroid-sensitive optic neuropathy") is not a feature of idiopathic demyelinating optic neuritis. All of these atypical findings should prompt further investigations/referrals.

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References

1. Rodriguez M, Siva A, Cross SA, et al. Optic neuritis: a population-based study on Olmsted County, Minnesota. *Neurology.* 1995;45(2):244-250.
2. Shams PN, Plant GT. Optic neuritis: a review. *Int MS J.* 2009;16(3):82-89.
3. Kurtzke JF. Optic neuritis or multiple sclerosis. *Arch Neurol.* 1985;42(7):704-710.
4. Phillips PH, Newman NJ, Lynn MJ. Optic neuritis in African Americans. *Arch Neurol.* 1998;55(2):186-192.
5. Bhigjee AI, Moodley K, Ramkissoon K. Multiple sclerosis in KwaZulu Natal, South Africa: an epidemiological and clinical study. *Mult Scler.* 2007;13(9):1095-1099.
6. Kurtzke JF. Multiple sclerosis among immigrants. *Br Med J.* 1976;1(6024):1527-1528.
7. Dean G, Elian M. Age at immigration to England of Asian and Caribbean immigrants and the risk of developing multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1997;63(5):565-568.
8. Allen L, Brankin B. Pathogenesis of multiple sclerosis – the immune diathesis and the role of viruses. *J Neuropathol Exp Neurol.* 1993;52(2):95-105.
9. Power C, Antony JM, Ellestad KK, *et al.* The human microbiome in multiple sclerosis: pathogenic or protective constituents? *Can J Neurol Sci.* 2010;37(Suppl 2):S24-S33.
10. Cabre P. Environmental changes and epidemiology of multiple sclerosis in the French West Indies. *J Neurol Sci.* 2009;286(1-2):58-61.
11. Cabre P, Signate A, Olindo S, et al. Role of return migration in the emergence of multiple sclerosis in the French West Indies. *Brain.* 2005;128(12):2899-2910.
12. Zhang X, Wang W, Wei W, et al. Etiological profile of presumptive optic neuritis in China. *J Clin Neurosci.* 2008;15(12):1346-1349.
13. Lim SA, Goh KY, Tow S, et al. The pattern of ON as seen in Singapore differs from that reported in Caucasian studies and from the seminal Optic Neuritis Treatment Trial. *Singapore Med J.* 2008;49(9):667-671.
14. Boomer JA, Siatkowski RM. Optic neuritis in adults and children. *Semin Ophthalmol.* 2003;18(4):174-180.
15. Brady KM, Brar AS, Lee AG, et al. Optic neuritis in children: clinical features and visual outcomes. *J AAPOS.* 1999;3(2):98-103.
16. Morales DS, Siatkowski RM, Howard CW, et al. Optic neuritis in children. *J Pediatr Ophthalmol Strabismus.* 2000;37(5):254-259.
17. Lucchinetti CF, Kiers L, O'Duffy A, et al. Risk factors for developing multiple sclerosis after childhood optic neuritis. *Neurology.* 1997;49(5):1413-1418.

18. Bar-Or A. The immunology of multiple sclerosis. *Semin Neurol* 2008; 28(1):29-45.
19. Söderström M, Link H, Sun JB, et al. Autoimmune T cell repertoire in optic neuritis and multiple sclerosis: T cell recognizing multiple myelin proteins are accumulated in cerebrospinal fluid. *J Neurol Neurosurg Psychiatry.* 1994;57(5):544-551
20. Brück W, Stadelmann C. Inflammation and degeneration in multiple sclerosis. *Neurol Sci.* 2003;24 Suppl 5:S265-S267.
21. Beck RW, Cleary PA, Trobe JD, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. The Optic Neuritis Study Group. *N Engl J Med.* 1993;329(24): 1764-1769.
22. Beck RW, Arrington J, Murtagh RF, et al. Brain magnetic resonance imaging in acute optic neuritis: experience of the Optic Neuritis Study Group. *Arch Neurol.* 1993;50(8):841-846.
23. The Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. *Arch Neurol.* 2008;65(6):727-732.
24. Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optic coherence tomography. *Ann Neurol.* 2006;59(6):963-969.
25. Trip SA, Schlottmann PG, Jones SJ, et al. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. *Ann Neurol.* 2005;58(3):383-391.
26. Beck RW, Smith CH, Gal RL, et al. Optic Neuritis Study Group. Neurologic impairment 10 years after optic neuritis. *Arch Neurol.* 2004;61(9):1386-1389.
27. Beck RW, Trobe JD, Moke PS, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol.* 2003;121(7):944-949.
28. Optic Neuritis Study Group. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. *Ophthalmology.* 2008;115(6):1079-1082.
29. Beck RW, Cleary PA, Backlund JC, et al. The course of visual recovery after optic neuritis. Experience of the Optic Neuritis Treatment Trial. *Ophthalmology.* 1994;101(11):1771-1778.
30. Beck RW, Cleary PA, Trobe JD, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. The Optic Neuritis Study Group. *N Engl J Med.* 1993;329(24): 1764-1769.
31. Beck RW, Cleary PA, Anderson MM Jr, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med.* 1992;326(9):581-588.
32. Wenning GK, Wiethhölter H, Schnauder G, et al. Recovery of hypothalamic-pituitary-adrenal axis from suppression by short-term, high-dose intravenous prednisolone therapy in patients with MS. *Acta Neurol Scand.* 1994;89(4):270-273.
33. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinatig event in multiple sclerosis. *N Engl J Med.* 2000;343(13):898-904.
34. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet.* 2001;357(9268):1576-1582.
35. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology.* 2006;67(7): 1242-1249.
36. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol.* 2005;58(6):840-846.
37. Zamboni P. The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. *J R Soc Med.* 2006;99(11):589-593.
38. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2009;80(4):392-399.
39. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg.* 2009;50(6):1348-1358.e1-3.
40. Laupacis A, Lillie E, Dueck A, et al. Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis. *CMAJ.* 2011;183(16):E1203-1212.
41. Thapar A, Lane T, Nicholas R, et al. Systemic review of sonographic chronic cerebrospinal venous insufficiency findings in multiple sclerosis. *Phlebology.* 2011; 26(8):319-325.
42. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology.* 2011;77(2):138-144.
43. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing forms of multiple sclerosis. *N Engl J Med.* 2006;354(9):899-910.
44. Kappos L, Radue EW, O'Connor P, et al; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010 ;362(5):387-401.
45. Novartis Pharmaceuticals Canada. Gilenya* (fingolimod) Product Monograph. Date of revision: July 12, 2012.
46. Thornton IL, Rizzo JF, Cestari DM. Neuromyelitis optica: a review. *Semin Ophthalmol.* 2011;26(4-5):337-341.
47. Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology.* 1999;53(5):1107-1114.
48. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485-1489.
49. Pau D, Al Zubidi N, Yalamanchili S, et al. Optic neuritis. *Eye.* 2011;25(7):833-842.

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