Curr Treat Options Neurol (2015) 17:328
DOI 10.1007/s11940-014-0328-z

Multiple Sclerosis and Related Disorders (P Villoslada, Section Editor)

Treatment of Acute Optic Neuritis and Vision Complaints in Multiple Sclerosis

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Published online: 18 November 2014

This article is part of the Topical Collection on *Multiple Sclerosis and Related Disorders*

Keywords Multiple sclerosis · Neuro-ophthalmology · Ocular symptoms · Treatment · Optic neuritis · Efferent symptoms

Opinion statement

Multiple sclerosis is an autoimmune demyelinating disorder of the nervous system, in which almost all patients develop some degree of visual impairment during the disease. Optic neuritis is the most common and known visual affection and may be the initial clinical disease manifestation, but visual complaints can have a wide variety of presentations and some of them can lead to clinical confusion. Most symptoms are the result of acute injury and subsequent axonal loss in the afferent and efferent visual pathway, but others may be consequences of treatments. Currently, we can tell the functional and anatomical damage caused by multiple sclerosis by visual function test, measurement of eye movements, electrophysiological testing, optical coherence tomography, and magnetic resonance imaging. The purpose of this review is to describe the afferent and efferent visual symptoms associated with multiple sclerosis or multiple sclerosis treatment, and review the current and future therapeutic options available for them.

Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) with a variable clinical course and different manifestations. Visual symptoms are highly frequent; indeed, optic neuritis (ON) is the initial manifestation in about 20 % of cases of MS [1]. The disease could affect both the afferent and efferent visual pathway causing a wide range of visual symptoms.

Visual pathway is a system made of a chain of four neurons connecting the retina to visual cortex. The anterior visual pathway is made of photoreceptor cells, bipolar cells, and retinal ganglion cells,

and modulated by horizontal cells. Axons from retinal ganglion cells form the retinal nerve fiber layer, the optic nerve, the chiasm, and optic tracts that connect with lateral geniculate nucleus. From lateral geniculate nucleus emerge the optic radiations and finally the visual cortex. The interaction between those structures on the acute and chronic damage determine the highly visual dysfunction of patients with ON and MS [2].

Despite the diversity, neuro-ophthalmological manifestations can be divided between afferent or efferent symptoms (Table 1).

Clinical course and treatment

Afferent manifestations

Optic neuritis

ON is an inflammation of the optic nerve attributable to many causes. Differential diagnosis is varied and treatment and prognosis depend on the cause. The typical clinical form consists of subacute unilateral painful visual loss, mostly in a young healthy female, followed by spontaneous improvement over several months. Most cases of acute demyelinating ON occur in women (two-thirds) and typically develop in patients between ages 20 and 40 years [3].

ON is monocular in its typical clinical presentation and in 10 % of cases, symptoms may occur in both eyes [4]. Bilateral optic neuritis is relatively uncommon and should suggest other cause of optic neuropathy.

The two most common symptoms of ON are vision loss and ocular pain. Vision loss could be from mild to no light perception and typically develops over a period of hours to days, peaking within 1 to 2 weeks. Ocular pain occurs in 92 % of patients and worsens with eye movement [3].

Other common visual symptoms and signs include relative afferent pupillary defect (RAPD), visual field defect characterized as general depression (the most common field defect), central or cecocentral scotoma, normal optic disk, or mild swelling of the disk, and photopsias by 30 % of patients in the Optic Neuritis Treatment Trial (ONTT) [3], and dyscromatopsia out of proportion to the visual loss.

Other signs of ocular inflammation may be observed in funduscopic or slit lamp examination like periphlebitis retinae, uveitis, cells in the anterior chamber, and/or pars planitis, but are relatively uncommon.

Table 1. Neuro-ophtalmological manifestations of MS

Afferent	Efferent
Optic neuritis	Internuclear ophtalmoplegia
Pulfrich phenomenon [a]	Cranial nerve palsy
Uhthoff phenomenon [a]	Nystagmus
Retrogeniculate visual field defects secondary to visual pathway demyelination	Saccadic dysmetria
	Ocular convergence spasm
	Other efferent visual pathway lesions

ON optic neuritis
[a]ON related

Treatment

Improvement of the visual disability and decreasing the possibility to the progression to MS are the two main goals of acute ON treatment. Most of the visual symptoms of acute ON improve in a few weeks, and treatment should be considered in patients with significant visual disability.

Steroids

The most common treatment for ON is intravenous steroids. In the seminal study for ON, the Optic Neuritis Treatment Trial (ONTT), patients were randomized to oral prednisone (1 mg/kg per day) for 14 days, intravenous methylprednisolone (250 mg four times per day for 3 days) followed by oral prednisone (1 mg/kg per day) for 11 days, or placebo for 14 days [3]. Intravenous methylprednisolone accelerated the recovery of visual function and reduced the risk of conversion to MS the first 2 years but there was no difference in 1-year visual outcomes. The oral prednisone arm had high risk of recurrence of optic neuritis and higher conversion to MS at 10 years [5]. The current recommendation is to treat ON with intravenous methylprednisolone, although mild cases or cases with low risk of MS conversion [based on magnetic resonance imaging (MRI)] may not benefit for this treatment.

Immunoglobulin

Two randomized trials studied the use of intravenous immunoglobulin (IVIG) in 55 and 68 patients with ON [6, 7]. Neither study found a difference in visual outcomes, MRI, and development of demyelinating disease at 6 months [7].

Plasmapheresis

One trial with 10 patients with severe ON after failure of steroids therapy underwent plasma exchange between 11 and 73 days after presentation [8]. Seven patients responded with improvements in visual acuity, but two of them did not improve.

Immunomodulators

In the last few years, the decision to start immonomodulatory therapy for patients with MS has been advanced to patients with ON as the first relapse to prevent or delay subsequent MS. The use of beta interferon or glatiramer acetate is supported by evidence in randomized trials.

Interferon beta 1a

In the Early Treatment of Multiple Sclerosis Study (ETOMS), 308 patients with a first clinical demyelinating event (98 optic neuritis) and high-risk lesions on MRI were randomized to interferon beta-1a subcutaneously or to placebo [9]. In the treatment branch, less patients developed MS (34 % vs 45 %) and the time between demyelinanting events was significantly longer (569 vs 252 days).
The Controlled High-Risk Avonex MS Prevention Study (CHAMPS) was a randomized, placebo-controlled trial of 383 patients (192 with ON) with

high-risk lesions in MRI, comparing early treatment with interferon beta-1a, 30 μg intramuscularly each week vs placebo. The use of interferon beta-1a reduced the risk of developing MS at 3 years (35 % vs 50 %) [10].
In the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT trial), 487 patients presenting with a clinically isolated syndrome (80 with ON) and at least two lesions in brain MRI were randomized to receive 250 μg interferon-1b subcutaneously or placebo [11]. The use of interferon-1b reduced the risk of developing MS from 45 % to 28 % at 2 years.

Glatiramer acetate

In order to assess the effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study trial), a randomized, double-blind, placebo-controlled trial, 481 patients presenting with a unifocal clinically isolated syndrome and two or more lesions in brain MRI were randomized to receive either 20 mg subcutaneously or placebo [12]. There was a relative 45 % reduction in risk of conversion to MS at 3 years of follow-up.

Investigational treatments

The functional impairment in ON is not only due to demyelination; visual dysfunction is mainly related to neuroaxonal loss and corticosteroids do not prevent axonal loss. For this reason, current research efforts are focused on finding neuroprotective drugs with improved long-term outcomes. There are several trials testing different drugs aimed at recovering visual function in patients with ON (Table 2), which could provide beneficial results in a near future.

The Pulfrich phenomenon

The *Pulfrich* phenomenon is a three-dimensional illusion in which a moving object viewed binocularly appears to travel in an elliptical orbit when the object is moving in a lineal way. It is due to a delay in visual transmission between both eyes. The symptoms can be difficult to describe but could be clinically relevant [13].

Treatment

Patients may use a tinted spectacle or contact lens over the normal eye. When symmetrical velocity in visual transmissions is attained, the symptoms disappear [14].

Uhthoff phenomenon

Uhthoff phenomenon is a transient visual blurring secondary to several triggers in patients with ON. The most common triggers are exercise and temperature increase (eg, fever), but patients describe visual alterations with emotional events, menstruation, light changes, smoking, and temperature changes [15].

Table 2. Current randomized studies for treatment of ON (From clinicaltrail.gov July 21, 2014)

Name	Objective	Treatment	Phase
Amiloride Clinical Trial In Optic Neuritis (ACTION)	Neuroprotection	Amiloride vs placebo	Phase 2
Neuroprotection With Phenytoin in Optic Neuritis	Neuroprotection	Phenytoin vs placebo	Phase 2
Treatment of Optic Neuritis With Erythropoietin (TONE)	Neuroprotection	Erythropoietin vs placebo	Phase 3
Simvastatin Treatment of Patients With Acute Optic Neuritis	Neuroprotection	Simvastatin vs placebo	Phase 3
Ampyra for Optic Neuritis in MS	Neuroprotection	Dalfampridine vs placebo	Phase 3
Fingolimod (FTY720) in Acute Demyelinating Optic Neuritis (ADON)	Neuroprotection	Fingolimod vs placebo	Phase 3
Lipoic Acid as a Treatment for Acute Optic Neuritis	Neuroprotection	Lipoic acid vs placebo	Phase 1
Safety and Efficacy Study of Erythropoietin as add-on Therapy of Methylprednisolone to Treat Acute Optic Neuritis	Neuroprotection	Erythropoietin vs placebo	Phase 2
215ON201 BIIB033 In Acute Optic Neuritis (AON) (RENEW)	Myelin Regeneration	BIIB033 (anti-Lingo antibody) vs placebo	Phase 2
Optic Neuritis Recovery After Oral or IV Corticosteroids	Neuroprotection	Oral prednisone vs methylprednisolone	Phase 3
Effect of Vitamin D on Retinal Changes in Patient With Optic Neuritis by Optic Coherence Tomography	Neuroprotection	Vitamin D vs placebo	Phase 2
A Phase IV Trial of Neuroprotection With ACTH in Acute Optic Neuritis (ACTHAR)	Neuroprotection	Acthar gel * vs methylprednisolone	Phase 4

This phenomenon is attributable to nerve conduction block of demyelinated axons in such situations [16].

Treatment

There is no effective treatment available. In patients with significant symptoms, especially before exercise, it may be useful to take a cool shower or put iced gel packs over the eyes to avoid transitory visual impairment [17••].

Retrogeniculate visual pathway demyelination

Retrogeniculate demyelination may occur anywhere on the posterior visual pathway. Transient or persistent visual field defects can be noticed by patients [18, 19].

Treatment

Intravenous corticosteroids may be used when the symptoms are due to new relapses of MS. Chronic visual field defects cannot be improved, but patients must be advised about driving problems or other limitations because of the restriction in the visual field [20].

Efferent manifestations

Internuclear ophthalmoplegia

Internuclear ophthalmoplegia (INO) is an ipsilateral adduction deficit with nystagmus in the contralateral eye and preserved vergence [21]. It is the most common efferent defect in MS[22]. INO is caused by a lesion in the medial longitudinal fasciculus (MLF) located in the brainstem. Patients describe transient blurry vision, oscilloscopia, or diplopia. Occasionally, patients may have additional features such as vertical misalignment or vergence dysfunction secondary to damage on structures adjacent to the MLF [23]. INO is a chronic defect most times, and at 6 months, full recovery is only 23 % [24]. Bilateral INO manifests as a large angle exotropia (wall-eyed bilateral INO) .

Treatment

INO may improve with IV steroids such as other demyelinating events [25]. Some patients may require prism glasses or strabismus surgery [24].

Saccadic dysmetria

Saccadic dysmetria is one of the most common ocular movement abnormalities in patients with MS [26]. Saccadic dysmetria may occur after demyelinating lesions in the cerebellum or brainstem and is characterized by hypermetric or hypometric saccades.

Treatment

Saccadic dysmetria may improve with IV steroids, but there is no specific effective treatment available [25].

Cranial nerve palsies

MS could affect oculomotor nerves, and the most common nerve affected is the sixth nerve because of its longest course. Symptoms are determined by the affected nerve and are usually transient, but sometimes deficit may not entirely resolve. The involvement of the third nerve is unusual; the fourth nerve is rarely affected.

Treatment

Patients may use stick-on prism or eye patches when the symptoms start. Patients with persistent misalignments may use prim glasses [24]. Botulinum toxin or surgery may be useful in selected cases.

Nystagmus

Nystagmus may be asymptomatic, or may cause oscillopsia, blurred vision, or decreased visual acuity. The most common type of nystagmus in MS patients is gaze evoked nystagmus (GEN) because of the inability of the eye to maintain eccentric gaze as a result of a defect in the neural integrator network. Nystagmus occurs in up to 65 % of MS patients [27•] and differs from physiological GEN because it is prolonged and could be associated with other ocular motility alterations.

Acquired pendular nystagmus (APN), with two slow phases and without fast phase, present in patients with significant oscillopsia. Central vestibular nystagmus is also common in MS, but less frequent than GEN.

Treatment

GEN usually does not require treatment. APN can cause severe visual impairment and the key is to be treated with several drugs such as gabapentin, memantine, valproate, and scopolamine [28–31].

Other efferent visual pathway lesions

The supranuclear pathway is a complex and extensive network formed by the cerebellum, medulla, and midbrain. It receives hemisferic input and also involves the semicircular canals, utricle, and saccule. Damage of the supranuclear network can cause skew deviation, horizontal gaze palsy, and dorsal midbrain syndrome.

Treatment

The supranuclear syndrome may improve with IV steroids as with other demyelinating lesions. Patients with significant upgaze paralysis may require bilateral inferior rectus recessions to shift the eyes into primary position [32].

Ocular convergence spasm

Transient neurologic events such as ocular convergence spams are rare but they may be part of MS symptoms and are caused by empathic transmission in demyelinated plaques. Lesions in MLF could cause ocular convergence spasm[33]

Treatment

Ocular convergence spams may improve with IV steroids, but there is no effective treatment available Table 3.

Table 3. Summary of treatments for visual symptoms on MS

Symptoms	Treatment
Afferent	
ON*	Acute ON: methylprednisolone 1 g per d for 3 d. Immunomodulatory therapy for preventing MS conversion and/or activity: Interferon beta-1a (22-44 g/d s.c or 30 µg intramuscularly weekly). Interferon-1b 250 µg daily. Glatiramer acetate 20 mg s.c. daily.
Pulfrich phenomenon	Tinted spectacle or contact lens over the normal eye.
Uhthoff phenomenon	There is no effective treatment available. Cool showers or put iced gel packs over the eyes may be useful.
Retrogeniculate visual pathway demyelination	Methylprednisolone 1 g/d/3 d i.v. for acute episode or MS recurrence.
Efferent	
INO	Methylprednisolone 1 g/d/3 d i.v. for acute episode or MS recurrence. Prism glasses or strabismus surgery on some patients.
Cranial nerve palsy	Temporarily stick-on prism or eye patches. Prims glasses on patients with persistent symptoms.
Nystagmus	GEN: Not treatment. APN: Gabapentin 100 mg tid - 1200 mg tid Memantine 5 mg qd - 10 mg bid Clonazepam 0.5 mg tid - 6.5 mig tid Valproate 10 mg/kg/d - 60 mg/kg/d Scopolamine 1.5 mg transdermal every 3 d
Saccadic dysmetria	There is no effective treatment available. May improve with methylprednisolone 1 g/d/3 d i.v. for acute episode or MS recurrence..
Ocular convergence spasm	There is no effective treatment available. methylprednisolone 1 g/d/3 d i.v. for acute episode or MS recurrence.
Other efferent visual pathway lesions	Methylprednisolone 1 g/d/3 d i.v. for acute episode or MS recurrence. Specific treatments depends of the type of ocular deviation and symptoms.

**ON* optic neuritis

Complications of MS treatments

Steroids

Corticosteroids remain highly relevant in the treatment of ON and MS recurrences. Ocular adverse effects are highly frequent and well-known [34]. The most important and frequent side effects are increase of the intraocular pressure, glaucoma, and cataracts.

Immunoglobulin

Many side effects have been reported regarding the use of immunoglobulin.

Most of them are mild and disappear when the treatment stops. Headache, chills, nausea, and fatigue are the most common side effects. Adverse events are

attributed to fast administration, immune reaction, high volume infusion, and hyperviscosity [35]. There are reports of vascular retinal occlusion associated with hypervicosity syndrome secondary to immunoglobulin infusions [36].

Interferon beta 1a

There is evidence of several but uncommon ocular adverse effects associated with interferon-alpha therapy, such as decreased vision, ocular pain, macular edema, and vascular occlusion. In regards to interferon-beta therapy, about 7 % 13 % of patients present with mild visual alterations [37, 38].

Glatiramer acetate

There is no evidence of ocular adverse reactions. Significant adverse reactions in clinical trials (>10 %) where chest pain, vasodilatation, skin rash, and immediate hypersensitivity [39, 40].

Fingolimod

Fingolimod is the first oral drug approved for treatment of MS by the Food and Drug Administration (FDA). Patients treated with fingolimod are at risk of developing macular edema (about 0.4 %), but patients with retinal diseases like diabetic retinopathy, previous uveitis, or retinal vascular disorders have a higher risk (around 20 %) [41, 42].

Natalizumab

Natalizumab has been linked to progressive multifocal leukoencephalopathy (PML) in patients exposed previously to JC virus. It is a rare complication associated that the fact that because of its preference for the posterior brain, it can produce visual impairment [43].

Conclusions

Visual symptoms associated with MS may appear at disease onset or any time during the course of MS. The symptoms are varied in presentation and severity. The correct identification of symptoms would allow clinicians to avoid the use of unnecessary tests and ensure the best treatment for patients. With the development of technologies (optical coherent tomography, MRI), it is now possible to recognize the damage associated with MS, the functional consequences, and to measure treatment response. Moreover, better knowledge of the biological basis of CNS damage would allow the development of new therapies preventing axonal and neuronal damage, reducing subsequent neuronal loss, and promoting axonal remyelination, which will translate to better function maintenance.

Compliance with Ethics Guidelines

Conflict of Interest
Ruben Torres-Torres and Bernardo F. Sanchez-Dalmau declare no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Foroozan R, Buono LM, Savino PJ, Sergott RC. Acute demyelinating optic neuritis. Curr Opin Ophthalmol. 2002;13(6):375–80.
2. Martínez-Lapiscina E, Sanchez-Dalmau B, Fraga-Pumar E, Ortiz-Perez S, Tercero-Uribe A, Torres-Torres R, et al. The visual pathway as a model to understand brain damage in multiple sclerosis. Mult Scler. 2014.
3. Optic Neuritis Study Group. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Arch Ophthalmol. 1991;109(12):1673.
4. de la Cruz J, Kupersmith MJ. Clinical profile of simultaneous bilateral optic neuritis in adults. Br J Ophthalmol. 2006;90(5):551.
5. Beck RW, Gal RL, Bhatti MT, Brodsky MC, Buckley EG, Chrousos GA, et al. Visual function more than 10 years after optic neuritis: experience of the optic neuritis treatment trial. Am J Ophthalmol. 2004;137(1):77–83.
6. Noseworthy JH, O'Brien PC, Petterson TM, et al. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. Neurology. 2001;56:1514.
7. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology. 2005;64:804.
8. Ruprecht K, Klinker E, Dintelmann T, et al. Plasma exchange for severe optic neuritis: treatment of 10 patients. Neurology. 2004;63:1081.
9. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet. 2001;357:1576.
10. CHAMPS Study Group. Interferon beta-1a for optic neuritis patients at high risk for multiple sclerosis. Am J Ophthalmol. 2001;132:463.
11. 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;67:1242.
12. Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1503.
13. Heron G, Thompson KJ, Dutton GN. The symptomatic Pulfrich phenomenon can be successfully managed with a coloured lens in front of the good eye—a long-term follow-up study. Eye (Lond). 2007;21:1469–72.
14. McGowan G, Ahmed TY, Heron G, Diaper C. The Pulfrich phenomenon; clumsiness and collisions which can be ameliorated. Pract Neurol. 2011;11(3):173–6.
15. Perkin GD, Rose FC. Uhthoff's syndrome. Br J Ophthalmol. 1976;60(1):60–3.
16. Davis SL, Frohman TC, Crandall CG, et al. Modelling Uhthoff's phenomenon in MS patients with internuclear ophthalmoparesis. Neurology. 2008;70(13 pt 2):1098Y1106.
17. •• Rae-Grant AD. Unusual symptoms and syndromes in multiple sclerosis. CONTINUUM Lifelong Learn Neurol. 2013;19(4):992–1006.

The very latest and most comprehensive review of unusual symptoms and síndromes. in MS; essential reading

18. Keltner JL, Johnson CA, Spurr JO, et al. Baseline visual field profile of optic neuritis: the experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Arch Ophthalmol. 1993;111:231–4.
19. Plant GT, Kermode AG, Turano G, et al. Symptomatic retrochiasmal lesions in multiple sclerosis: clinical features, visual evoked potentials, and magnetic resonance imaging. Neurology. 1992;42:68–76.
20. Francis CE. Visual issues in multiple sclerosis. Phys Med Rehabil Clin N Am. 2013;24(4):687–702.
21. Zee DS. Internuclear ophthalmoplegia: pathophysiology and diagnosis. Baillieres Clin Neurol. 1992;1:455–70.

22. Frohman EM, Frohman TC, O'Suilleabhain P, et al. Quantitative oculographic characterisation of internuclear ophthalmoparesis in multiple sclerosis: the versional dysconjugacy index Z score. J Neurol Neurosurg Psychiatry. 2002;73:51–5.
23. Serra A, Derwenskus J, Downey DL, et al. Role of eye movement examination and subjective visual vertical in clinical evaluation of multiple sclerosis. J Neurol. 2003;250:569–75.
24. Bolanos I, Lozano D, Cantu C. Internuclear ophthalmoplegia: causes and long-term follow-up in 65 patients. Acta Neurol Scand. 2004;110:161–5.
25. Frohman EM, Frohman TC, Zee DS, McColl R, Galetta S. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol. 2005;4(2):111–21.
26. Niestroy A, Rucker JC, Leigh RJ. Neuro-ophthalmologic aspects of multiple sclerosis: using eye movements as a clinical and experimental tool. Clin Ophthalmol. 2007;I(3):267–72.
27.• Graves J, Balcer LJ. Eye disorders in patients with multiple sclerosis: natural history and management. Clin Ophthalmol. 2010;4:1409–22.
A full update of the visual manifestations of multiple sclerosis and its management. Recommended reading
28. Averbuch-Heller L, Tusa RJ, Fuhry L, et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. Ann Neurol. 1997;41:818–25.
29. Starck M, Albrecht H, Pollman W, et al. Drug therapy for acquired pendular nystagmus in multiple sclerosis. J Neurol. 1997;244:9–16.
30. Rucker JC. Current treatment of nystagmus. Curr Treat Options Neurol. 2005;7:69–77.
31. Leigh RJ, Tomsak RL. Drug treatments for eye movement disorders. J Neurol Neurosurg Psychiatry. 2003;74:1–4.
32. Buckley EG, Holgado S. Surgical treatment of upgaze palsy in Parinaud's syndrome. J AAPOS. 2004;8:249–53.
33. Postert T, McMonagle U, Buttner T, et al. Paroxysmal convergence spasm in multiple sclerosis. Acta Neurol Scand. 1996;94(1):35–7.
34. Renfro L, Snow JS. Ocular effects of topical and systemic steroids. Dermatol Clin. 1992;10(3):505–12.
35. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin. Clin Rev Allerg Immunol. 2005;29(3):173–84.
36. Oh KT, Boldt HC, Danis RP. Iatrogenic central retinal vein occlusion and hyperviscosity associated with high-dose intravenous immunoglobulin administration. Am J Ophthalmol. 1997;124(3):416–8.
37. Rubio JE, Charles S. Interferon-associated combined branch retinal artery and central retinal vein obstruction. Retina. 2003;23:546–8.
38. Tokai R, Ikeda T, Miyaura T, Sato K. Interferon-associated retinopathy and cystoid macular edema. Arch Ophthalmol. 2001;119:1077–9.
39. Cohen JA, Rovaris M, Goodman AD, et al. Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS. Neurology. 2007;68(12):939–44.
40. Comi G, Filippi M, Wolinsky JS, et al. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. Ann Neurol. 2001;49(3):290–7.
41. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362:402–15.
42. Highlights of prescribing information: Gilenya (fingolimod) capsules. Novartis. 2012.
43. Clifford DB, DeLuca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9(4):438–46.