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Pegylated Interferon Alpha–Associated Optic Neuropathy

Kathleen T. Berg, BS, Bruce Nelson, MD, Andrew R. Harrison, MD, Linda K. McLoon, PhD, and Michael S. Lee, MD

Department of Ophthalmology, University of Minnesota (KTB, ARH, LKM, MSL), Minneapolis, Minnesota; and Merit Care, Fargo, North Dakota

Abstract

A 52-year-old man with chronic hepatitis C presented with painless, bilateral, simultaneous non-arteritic anterior ischemic optic neuropathy (NAION) and peripheral neuropathy. Symptoms began 19 weeks after starting peginterferon alpha-2a. The peripheral neuropathy and vision of the right eye improved, but the vision of the left eye worsened after stopping interferon. We identified 23 additional cases of NAION during interferon alpha therapy. At least 12 of these patients suffered bilateral NAION. Patients lost vision 1–40 weeks after initiating therapy. Of 21 eyes that had documented initial and follow-up acuities, 8 improved, 1 worsened, and the rest remained stable. One patient had a painful peripheral neuropathy. Treatment with interferon alpha may result in NAION. Discontinuation of therapy deserves consideration after weighing individual risks and benefits.

Interferon alpha is a complex glycoprotein with anti-proliferative, antiviral, and immunomodulatory activity (1). Pegylated interferons have a covalently attached 40 kDa branched chain polyethylene glycol moiety, which improves drug absorption and prolongs the half-life from 4 to 22–60 hours (2), allowing for less frequent injections and improved patient compliance. The 2 forms of pegylated interferon alpha currently approved for the treatment of chronic hepatitis C (CHC) are peginterferon alpha-2a and peginterferon alpha-2b. While peginterferon alpha-2b has a larger volume of distribution and more effective renal clearance than peginterferon alpha-2a (3), studies have found no difference in either the sustained virological response or adverse event incidence between the 2 medications in the treatment of CHC (4).

The most common adverse events associated with interferon alpha therapy are flu-like symptoms, leukopenia, thrombocytopenia, depression, and thyroid disorders (5). Cases of peripheral neuropathy have also been documented (6–10). Several prospective studies have linked interferon alpha therapy with a high incidence of retinopathy, demonstrated by the presence of cotton wool spots and hemorrhage (11–19), although these changes are often asymptomatic (12,16). Other documented ocular complications of interferon alpha therapy include transient blurred vision (20), increased intraocular pressure (21), neovascular glaucoma (22), retinal detachment (5), and orbital and intraocular hemorrhage leading to enucleation (21,23). Nonarteritic anterior ischemic optic neuropathy (NAION) is a relatively rarely reported complication of interferon alpha therapy (15,24–40).

We present a case of NAION following treatment of CHC with peginterferon alpha-2a and review the literature for other documented cases of NAION following interferon alpha therapy.

CASE REPORT

A 52-year-old man with a history of CHC developed painless progressive vision loss in his right eye. He did not detect visual loss in the left eye. He also noted new onset numbness and tingling in both hands and feet. He denied symptoms suggestive of giant cell arteritis. His medical history included migraine headache, cervical radiculopathy, depression, anxiety disorder, and insomnia. Nineteen weeks prior to ophthalmic evaluation, he began treatment for CHC with peginterferon alpha-2a 180 µg/week and ribavirin 1000 mg/day. Other medications included filgrastim, albuterol, eletriptan hydrobromide, hydromorphone, fluticasone and salmeterol, bupropion, clonazepam, omeprazole, zolpidem, prochlorperazine, and tizanidine.

Two days later, examination revealed vision of 20/25 in each eye. Pupils were 3 mm bilaterally with a right relative afferent pupillary defect (RAPD). The patient correctly identified all of the Ishihara color plates with each eye. Fundus examination demonstrated bilateral optic disc edema (Fig. 1) with a normal appearance to each retina. Fundus photographs from 2003 revealed a cup-to-disc ratio of 0.1:0.2. Visual field testing demonstrated inferior field loss in the right eye and no abnormality in the left eye (Fig. 2).

Contrast-enhanced MRI of the brain and orbits showed no optic nerve or intracranial abnormalities. Lumbar puncture demonstrated a normal opening pressure, with normal protein and glucose levels; no white blood cells; and 32 red blood cells. Hemogram showed mild pancytopenia with a white blood cell count of 1800 cells per microliter, platelet count of 110 000 cells per microliter, and hemoglobin of 13 g/dL. A comprehensive metabolic panel showed no abnormalities. Antinuclear antibody, angiotensin-converting enzyme, rapid plasma regain, and neuromyelitis optica (NMO) IgG testing were all negative.

Both peginterferon alpha-2a and ribavirin were discontinued. The patient received intravenous solumedrol 500 mg followed by oral prednisone 40 mg, which was tapered over the next 8 days. When examined 4 weeks later, he reported a 4-day decline in vision in his previously asymptomatic left eye and some improvement in his right eye. Visual acuity was 20/20 in the right eye and 20/60 in the left eye. He saw 8/8 Ishihara color plates with the right eye and 3/8 with the left eye, and there was no evidence of a RAPD. The right optic nerve showed early segmental atrophy while the left optic nerve swelling had worsened. Visual field testing demonstrated slight progression of the inferior arcuate scotoma in the right eye and a new defect in the left eye (Fig. 3). The patient noted almost complete resolution of his paresthesias.

DISCUSSION

Our patient suffered bilateral simultaneous NAION in the setting of peginterferon alpha-2a treatment. Spontaneous, bilateral, simultaneous NAION is rare and typically suggests a systemic disorder or toxicity. While it is conceivable that the interferon therapy was unrelated, this seems unlikely since this case has similar findings to previous reports. In addition, our patient had bilateral paresthesias of the hands and feet, a known side effect of pegylated interferon alpha. With discontinuation of therapy, he noted near total resolution of this symptom, strongly suggestive of a systemic toxic effect of his interferon therapy.

We are aware of 23 additional cases of NAION in the setting of interferon alpha therapy (Table 1). Eleven patients experienced bilateral NAION. One probable case of NAION

following interferon alpha-2b therapy for CHC (45) and one following interferon alpha-2a therapy for acute hepatitis C (47) were omitted from this compilation because the abstracts were not available in English. All other reported patients suffered visual loss between 1 and 40 weeks after initiating therapy. Thirteen cases received combination therapy with ribavirin and interferon alpha. Of these 13 patients, 6 experienced bilateral visual loss. Four patients suffered NAION while taking interferon alpha-2a and 7 while taking interferon alpha-2b. Eleven reports only described treatment as “interferon alpha” therapy. Of these 11 patients, 4 experienced bilateral optic nerve involvement. There was one documented case of NAION following therapy with natural (nonrecombinant) interferon alpha. Of the 17 cases that provided follow-up information, 9 described improvement in signs and symptoms following cessation of interferon alpha, and one showed symptomatic improvement without the withdrawal of therapy. One patient developed painful polyneuropathy in addition to NAION (37).

How interferon causes NAION is currently unknown. Sugano et al (44) studied patients who developed retinopathy while taking interferon alpha (49). They discovered abnormally high levels of circulating activated plasma complement 5 (C5a), an intravascular aggregator of granulocytes. High C5a levels may disrupt blood flow in the retinal circulation, leading to retinal capillary infarction, cotton wool spot formation, and hemorrhage (48,49). Guyer et al (16) proposed that therapy with interferon alpha may cause autoantibody formation and immune complex deposition, with resultant lymphocyte infiltration and inflammation of vessels, leading to retinal ischemia. Nishiwaki et al (50) used a rat model to demonstrate that interferon alpha causes leukocyte activation and adherence to vascular endothelium. The mechanisms proposed for interferon alpha-associated retinopathy could also underlie the development of NAION, with involvement of the posterior ciliary arterial circulation, leading to optic nerve ischemia (26).

It is unlikely that the coadministration of ribavirin contributes directly to the development of NAION, as the only known ocular complication of ribavirin therapy is conjunctivitis. Presumably, this occurs from topical irritation of the conjunctiva, as conjunctivitis only follows aerosol administration (51).

Hepatitis C virus (HCV) has been linked to various immunologic abnormalities, including cryoglobulinemia, arteritis, and thrombocytopenia (52). It appears unlikely that the virus itself was the cause of NAION in our patient, as there was no evidence of systemic vasculitis. While our patient did have thrombocytopenia, Hayasaka et al (13) found no association between thrombocytopenia and ocular complications in patients with CHC receiving interferon therapy. Additionally, development of NAION due directly to HCV infection is extremely rare, with only 2 cases documented (53,54).

Our patient had a preexisting small cup-to-disc ratio, a proposed risk factor in the development of NAION (42). One previous report of unilateral NAION associated with pegylated interferon noted a small optic disc in the fellow eye with crowding and absence of cupping (32). Two other cases of bilateral NAION documented absence of physiologic cupping in the fellow eye prior to second eye involvement (26). It is conceivable that a small cup-to-disc ratio may increase the risk of NAION in patients receiving interferon alpha.

Based on the evidence from our patient, as well as from the compiled case reports, we propose that the association between interferon alpha therapy and the development of NAION is “possible,” based on the World Health Organization criteria for establishing causality in adverse drug reactions (Table 2) (<http://www.who-umc.org/DynPage.aspx?id=22682>). The visual changes consistent with NAION occurred within a reasonable time

frame following the start of interferon alpha therapy. The cases reviewed could not be clearly linked to the presence of other diseases, underlying risk factors, or other medications.

While improvement in visual acuity was noted following discontinuation of interferon alpha in 9 of the 23 cases reported in the literature, a large, randomized, prospective study of patients with NAION showed that 43% of untreated eyes with vision of 20/64 or worse gained 3 lines or more of vision at a 6-month follow-up (55). It is also unclear whether continuing therapy with interferon alpha results in progressive visual deterioration. The high frequency of bilateral NAION in cases linked to interferon alpha therapy suggests that presentation in one eye may place the fellow eye at risk, especially in patients with small cup-to-disc ratio. Further study is warranted to identify whether discontinuing therapy diminishes the likelihood of NAION in the fellow eye.

In conclusion, treatment with interferon alpha may lead to the development of NAION. Currently, the decision to continue or discontinue interferon alpha in patients presenting with unilateral NAION should be made on a case-by-case basis until proven therapeutic guidelines are established.

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FIG. 1.
Bilateral optic disc edema is present with a flame hemorrhage (arrow) on the left eye.

FIG. 2.
Initial visual fields show an inferior arcuate defect in the right eye and a normal result in the left eye.

FIG. 3. Four weeks later, visual fields reveal slight progression of field loss in the right eye and an inferior altitudinal defect with central involvement in the left eye.

TABLE 1

Previously reported cases of NAION following treatment with interferon alpha-2a, interferon alpha-2b, or natural interferon alpha

Patient Age, Gender (reference)	Underlying Disease	Medication	Unilateral vs Bilateral	Treatment Duration Prior to NAION	Visual Acuity at Presentation	Visual Acuity After IFN Cessation
54, Female (37)	CHC	IFN alpha-2a, ribavirin, and amantadine	Bilateral	6 months	Unknown	Unknown
68, Female (25)	CHC	IFN alpha-2a and ribavirin	Unilateral	3 weeks	20/50	20/30
61, Female (25)	CHC	IFN alpha-2a and ribavirin	Bilateral	8 weeks	20/100 OU	20/25 OU
71, Male (25)	CHC	IFN alpha-2a and ribavirin	Unilateral	7 months	20/100	20/30
64, Male (24)	CHC	IFN alpha and ribavirin	Unilateral	8 months	20/100	Marked improvement
Unknown (35)	Malignant melanoma	IFN alpha	Unknown	Unknown	Unknown	Unknown
40, Male (26)	RCC	IFN alpha	Bilateral	3 weeks	20/25	Unknown
51, Male (26)	Multiple myeloma	IFN alpha	Bilateral	1 week	20/20 OD; 20/30 OS	20/20 OD; 20/30 OS
70, Male (34)	RCC	IFN alpha	Unilateral	6 weeks	20/80	20/100
72, Male (34)	RCC	IFN alpha	Unilateral	10 months	Counting fingers	Did not return to baseline
Unknown (40)	CHC	IFN alpha and ribavirin	Unknown	Unknown	Unknown	Unknown
64, Male (38)	CHC	IFN alpha	Unilateral	Unknown	20/200	Improved
59, Gender not specified (31)	CHC	IFN alpha	Unknown	8 weeks	Unknown	Unknown
44, Male (15)	CHC	IFN alpha	Bilateral	10 weeks	20/100 OD; 20/200 OS	20/100 OD; 20/200 OS
61, Male (15)	Essential thrombocytosis	IFN alpha	Bilateral	3 months	20/60 OD; 20/80 OS	20/30 OU
46, Male (30)	CHC	IFN alpha-2b and ribavirin	Bilateral	3 weeks	20/400 OD; 20/100 OS	20/80 OU
51, Male (28)	CHC	IFN alpha-2b and ribavirin	Bilateral	3 months	Unknown	Unknown
64, Male (29)	CHC	IFN alpha-2b and ribavirin	Bilateral	6 weeks	Unknown	20/20 OD; 20/200 OS (both worsened)
60, Male (27)	Malignant melanoma	IFN alpha-2b	Bilateral	23 weeks	20/120 OD; 20/400 OS	20/120 OD; 20/400 OS
46, Male (33)	CHC	IFN alpha-2b and ribavirin	Unilateral	Unknown	Unknown	Improved without treatment cessation
55, Female (39)	CHC	IFN alpha-2b and ribavirin	Bilateral	6 months	20/400 OD; 20/80 OS	<20/400 OD; 20/80 OS
57, Male (32)	CHC	IFN alpha-2b and ribavirin	Unilateral	6 months	20/60	20/20
40, Female (36)	CHC	Natural IFN alpha	Unilateral	2 months	20/30	20/20

CHC, chronic hepatitis C; IFN, interferon; NAION, nonarteritic anterior ischemic optic neuropathy; OD, right eye; OS, left eye; OU, both eyes; pegIFN, pegylated interferon; RCC, renal cell carcinoma.

TABLE 2

World Health Organization causality assessment of suspected adverse drug reactions

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction about which more data is essential for a proper assessment or the additional data are under examination

Unassessible/Unclassifiable: A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.