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Case report

Nonarteritic anterior ischemic optic neuropathy associated with interferon and ribavirin in a patient with hepatitis C

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ABSTRACT

Purpose: To report a case of a temporal artery biopsy negative anterior ischemic optic neuropathy associated with a recently completed course of pegylated interferon 2 α with ribavirin for chronic hepatitis C.

Observations: Despite the early presentation with symptoms and prompt treatment with systemic intravenous steroids the patient experienced deterioration of their optic neuropathy over the following few days. Although nonarteritic anterior ischemic optic neuropathy is a common disorder with known risk factors, the timing of onset of symptoms in our patient was suggestive of a possible etiology related to treatment with ribavirin and interferon 2 α, as found in the previously reported cases.

Conclusions and importance: There have been a few reported cases of the association between the use of interferon/ribavirin for treatment of chronic hepatitis with nonarteritic anterior ischemic optic neuropathy. In these cases stopping the drug caused some improvement of symptoms or halting the progression of optic neuropathy. Having reviewed the literature on previous cases, we postulate that there may be a dose related reaction to explain the delay and deterioration of vision in some cases despite stopping the drugs. We also advise that any person who is started on this treatment for chronic hepatitis are appropriately counselled as to the potential optic nerve side effect of the drug, based on the evidence reported in the literature.

1. Introduction

There are well recognised risk factors for nonarteritic anterior ischemic optic neuropathy (NAION), which include cardiovascular comorbidities such as diabetes and hypertension, as well as hypermetropia or a small crowded optic disc. There have been previous case reports suggesting that antiviral therapy, such as those used in the treatment of chronic hepatitis C, can cause a form of NAION.[1,2] At the onset of visual symptoms, the patients in these cases were either on established interferon antiviral treatment or had recently completed therapy. We report a case of probable pegylated interferon α and ribavirin associated NAION, its clinical course on steroid therapy and review the evidence for interferon associated NAION in hepatitis C patients.

The hepatitis C virus (HCV) was first identified in 1989, and has been reported to infect 160 to 170 million people worldwide.[3] Approximately 15–45% of infected patients clear the virus spontaneously without any treatment.[4] The remaining 55–85% develop chronic liver disease.[4] In 2010 approximately 500,000 people died worldwide from hepatitis C-related liver diseases.[5] Three years later, that number increased to 700,000.[6] The detection and treatment of hepatitis C cases are made difficult by two factors: a mostly silent acute phase and delayed symptoms in the chronic phase. It has been reported that up to 85% of infected patients are asymptomatic in the acute phase, and in those where the infection becomes chronic, symptoms can take several years to appear.[7]

In the United States, the treatment of chronic hepatitis C is a rapidly evolving area since the introduction of protease inhibitors in 2011 and the current guidelines were updated recently by the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA).[8] There is expected to be further changes with newer drugs with different mechanisms of action in the coming future. The initial antiviral treatment of choice is based on the patient's genotype of HCV infection (of which there are six types) and the extent of liver cirrhosis. Antiviral therapies are associated with a number of

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adverse side effects in several organs, many of which are attributed to interferon therapy.[3] Ophthalmic side effects of pegylated interferon α include macular edema,[11] retinal hemorrhage, and combined choroidal and retinal perfusion deficits.[12] Among those ophthalmic side effects, NAION has been reported in several patients.

Ischemic optic neuropathy is characterized by reduced vision, which is caused by damage to the optic nerve due to insufficient blood supply. It constitutes a serious cause of visual impairment, possibly leading to blindness, primarily in the middle-aged and elderly population.[13] Ischemic optic neuropathy can affect the anterior or posterior portion of the optic nerve, which receive their blood supply from different vessels. The arteritic form is caused by Giant Cell Arteritis (GCA), while the nonarteritic form is a multifactorial disease with a number of predisposing and precipitating risk factors.[13] NAION has an incidence of about 8000 cases each year in the United States.[14]

2. Case report

A 62-year-old Caucasian woman presented with a week history of reducing central vision in her right eye which had significantly worsened in the two days prior to assessment. She also complained of retro-orbital pain and an intermittent right temporal headache extending into her neck. She denied other symptoms of GCA, including jaw claudication, but admitted to noticing some non-intentional weight loss.

Her past medical history included osteoarthritis, gout, type 2 diabetes mellitus and hypertension. Her past ophthalmic history included narrow iridocorneal angles for which she had bilateral laser iridotomies in 2007.

In August of 2014 she was seen by her medical doctor with complaints of restless legs. Despite therapy, symptoms did not improve and routine blood tests found repeatable deranged liver function tests. Viral serology screen revealed her to be Hepatitis C positive (genotype II) despite being low risk for transmission. She was treated with Ribavirin 400 mg twice a day and pegylated interferon α 2A injections once weekly. She completed her last course in August of 2015, one week prior to presenting to the eye unit.

She was mildly hypermetropic in both eyes with a spherical equivalent of +3.50 in either eye. Visual acuity was $20/30^{+3}$ on the right eye and 20/20 on the left. Palpating the temporal arteries on both sides demonstrated a good pulse with no irregular thickening or tenderness. She had a right-sided relative afferent pupillary defect (RAPD) with reduced color vision (13/17) using Ishihara plates. A superior visual field defect was also noted on confrontation testing of the right eye. The left eye pupil examination, color vision and confrontation fields were within normal limits. Slit lamp examination of both eyes revealed normal appearance of the cornea, conjunctiva and lens and no cells were seen in the anterior chamber or in the vitreous. Fundus examination of the right eye revealed diffuse optic disc swelling (Fig. 1). The left eye assessment was within normal limits. (Fig. 2). Optical Coherence Tomography (OCT) demonstrated a relative increase of the peripapillary optic nerve fibre layer thickness in the right eye (Fig. 3). Initial blood tests showed a C-reactive protein (CRP) of 14 (normal<5), erythrocyte sedimentation rate (ESR) of 147 (normal <20) and platelet count of 193 (normal 150–450).

Our working diagnosis was a right-sided arteritic anterior ischemic optic neuropathy (AAION) and she was commenced on high dose intravenous steroid therapy of Methylprednisolone 1 g daily for 3 days. This was converted to oral Prednisolone 60 mg daily for 7 days followed by a taper over the subsequent weeks. A right temporal artery biopsy was performed within 48 hours which was reported as showing no evidence of inflammatory vascular changes. She was also seen by the rheumatology team who arranged an echocardiogram and an ultrasound carotid Doppler scan to rule out an embolic causes of her vision loss. These were found to be within normal limits. Magnetic resonance imaging of the head and orbits showed mild cerebral ischemic changes and no other abnormalities.

In the next few days the vision remained slightly reduced and there was no clinical change. The right optic disc remained swollen in appearance.

Despite her treatment, she unfortunately developed further deterioration of her vision and at her last outpatient visit four weeks post presentation, her visual acuity was reduced to 20/200 in the right eye.

3. Discussion

Corticosteroids are the mainstay of treatment of AAION due to GCA. Although they are not considered the standard of care in the treatment of NAION, there are some studies that show some potential benefit.[15] Clinical improvement in these studies was restricted to the first 6 months after optic neuropathy onset, suggesting that any loss still present after 6 months may be permanent. The clinical validity of these findings are still quite controversial as the study design was not randomized, blinded or placebo controlled.

There have been several case studies reporting the occurrence of NAION in hepatitis C patients treated with interferon and/or ribavirin. It was reported that a hepatitis C patient treated with interferon and ribavirin presented with bilateral, simultaneous NAION.[16] The authors also observed bilateral paresthesia in both hands and feet, reinforcing the hypothesis of a systemic toxicity. Both interferon and ribavirin were discontinued. While one eye improved following treatment cessation, the other eye worsened. The damage was still present 4 weeks after treatment cessation.[16]

A recent review found 23 previously reported cases of NAION that occurred during anti-hepatitis C therapy. This suggested that NAION could be a rare association of interferon/ribavirin therapy, considering that a number of cases might not have been reported.[16] Among these 23 cases, 12 patients were treated with interferon and ribavirin, and 11 patients with interferon alone.[16]

When considering all 23 patients, visual loss occurred between 1 and 40 weeks after therapy onset, the average being 15.4 ± 12.6 weeks (mean ± standard deviation). The data for visual loss onset was missing in four of the reported cases. Visual loss was unilateral or bilateral and of the 12 patients that received combination therapy with interferon and ribavirin, 6 experienced bilateral visual loss. In the 11 patients that received interferon only, 5 experienced bilateral visual loss. Different forms of interferon were used for treatment including interferon alfa 2a (4 cases), interferon alfa 2b (7 cases), natural interferon alfa (1 case), and in 13 of the cases the type of interferon therapy was not specified.[16] This suggests that the occurrence of NAION is not necessarily associated with a specific form of interferon.

In 17 cases out of 23, follow-up information was collected over an average of 8 month period. Twenty five eyes of these 17 patients showed improvement following cessation of interferon therapy, while one patient with unilateral NAION showed improvement in symptoms without the discontinuation of therapy.

A recent case was reported on irreversible NAION as a complication of interferon therapy for chronic hepatitis C. Loss of vision occurred suddenly and bilaterally 5 months after treatment onset with interferon and ribavirin.[17] After ophthalmic evaluation, antiviral therapy was discontinued. The loss of vision remained unchanged 1 year after treatment discontinuation. Furthermore,

Fig. 1. Retinal fundus photograph of the right eye showing an indistinct swollen appearance of the optic disc margins (A) and a normal macular appearance (B).

Fig. 2. Retinal fundus photograph of the left eye showing a grossly normal appearance of the optic disc with distinct margins (A) and a normal appearance of the macular (B).

Fig. 3. Optical Coherence Tomography derived optic disc retinal thickness profiles for the right eye (A) and the left eye (B). Note the global increased thickness on the right eye, which can be consistent with optic disc swelling.

another case of bilateral NAION shortly after treatment onset with interferon for CHC was reported.[18] Loss of vision occurred suddenly in the left eye 2 months after treatment onset. Loss of vision extended in the right eye, but after treatment discontinuation, vision returned to normal.[18] Most recently in 2014, a case of severe retinopathy and NAION after interferon and ribavirin treatment for chronic hepatitis C was reported.[19] Loss of vision occurred suddenly and bilaterally 11 weeks after treatment onset. Antiviral therapy was discontinued and 5 years later, the patient recovered good visual function.

4. Conclusion

Although considered controversial, a study advocated administering large doses of corticosteroids immediately after diagnosing NAION to potentially improve visual outcome.[15] However, no other study has been able to replicate his findings.

In our case report, the patient's vision continued to deteriorate despite early treatment with high dose corticosteroids. Based on our case as well as other case reports, the onset of visual symptoms of interferon associated NAION appears to occur at any time during or after therapy with interferon. In those cases where vision did not improved, we noted that the treatment was either complete or near

complete. This was the case in our patient who had recently finished her course and experienced deterioration of her visual acuity despite our best treatment efforts. This may imply a dose-related prognosis with interferon alfa.

We do acknowledge that although our patient did have other risk factors for developing NAION, such as hypermetropia, age, diabetes mellitus and hypertension, the timeline of the development of her eye symptoms in relation to her therapy with antivirals would be more in keeping with the other reported cases of interferon alfa and ribavirin related NAION.

Studies have shown that HCV can cause mixed cryoglobulinemia resulting in small to medium vessel vasculitis.[20] Therefore, we should remember to never rule out this possibility. Furthermore, we cannot rule out the possibility that HCV is causing the NAION via other intermediate factors.[21]

Even though NAION is an uncommon complication of interferon treatment, the damage to visual function can be severe and permanent.[16] These cases highlight the need to counsel patients about the relatively rare but potentially sight threatening ophthalmic association of interferon/ribavirin therapy prior to commencement of antiviral treatment. It also increases the awareness of clinicians to consider the association between this antiviral therapy and NAION with similar clinical scenarios.

Patient consent

Written consent to publish this report was obtained from the patient.

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Conflict of interest

There is no conflict of interests. Authors have nothing to disclose.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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