Romanian Journal of Ophthalmology, Volume 60, Issue 3, July-September 2016. pp:188-194

CASE REPORT

Combined etiology for bilateral and simultaneous optic neuropathy in a patient with ciancobalamin deficit and hepatitis C treated with peg-interferon and ribavirin

Pantalon Anca Delia, Danielescu Ciprian, Chiseliță Dorin
"Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iaşi, Romania; Department of Ophthalmology, "Sf. Spiridon" University Hospital, Iaşi, Romania

Correspondence to: Anca Delia Pantalon, MD, PhD, FEBO
Department of Ophthalmology, "Sf. Spiridon" University Hospital, Iaşi
1 Independenţei Square, code: 700115, Iaşi, Romania
Mobile phone: +40 740 686 865, E-mail: anca_pantalon@yahoo.com

Accepted: July 18, 2016

Abstract

We report the case of a 53-year-old female patient who developed bilateral sudden visual acuity loss after 15 weeks from the initiation of Peg-Interferon and Ribavirin treatment for hepatitis C. Debut was simultaneous and asymmetric, reported in the morning, at awakening. No pain or other symptom was reported by the patient.

Results. At presentation, visual acuity was 0.2 in RE and 3/ 50 in LE. Pupillary reflexes were sluggish and severe dyschromatopsia was documented in both eyes (Ishihara plates). Fundus examination revealed bilateral pale optic disc edema, more prominent in LE, with splinter hemorrhages in the RNFL around the optic disk. Visual field exam demonstrated severe defects in 3 quadrants of the RE, whereas in the LE, it was impossible to perform the investigation due to VA<0.1. Neurologic evaluation was normal; other possible causes of systemic vasculitis were excluded by negative lab tests. Acute inflammatory markers (fibrinogen and ESR) and mild pancytopenia were the only documented laboratory changes in this patient. Anamnesis cleared the traditional risk factors for conventional AION (hypertension, diabetes, ischemic heart disease, and hypercholesterolemia). Cranial and orbital CT scan and MRI findings were normal. Patient was withdrawn from the Interferon and Ribavirin treatment and was administered methyl prednisolone pulse therapy (1g/ day) for 3 days, continued with oral Prednisone (60 mg/ day) tapered slowly for over 12 weeks. VA increased to 0.8 during treatment in the RE, but visual recovery in the LE was not as spectacular (0.16) as in the fellow eye. Modified latencies and amplitudes in evoked visual potentials examination during 4 months time emphasized bilateral optic atrophy. Optic nerve sufferance was amplified by a low level of vitamin B12, detected by chance at the last eye visit. Due to the general condition, dietary supplementation was not possible.

Conclusion. A case of a patient with bilateral and simultaneous NAION caused by IFN and Ribavirin treatment for hepatitis C, who was also vitamin B12 deficient, was analyzed. Therefore, a combined etiology for optic atrophy was explained.

Keywords: bilateral simultaneous AION, hepatitis C, Peg-Interferon, vitamin B12 deficit

Introduction

Interferon (IFN) alpha2a is widely used to treat chronic hepatitis C, either alone or in combination with Ribavirin. Pegylated forms enhance patient adherence and compliance to treatment by reducing the frequency of

administration due to an extension of IFN half-life from 4 to 22-60 hours [**1**]. Various systemic side effects of IFN include fever, influenza-like symptoms, thrombocytopenia, neutropenia, depression, and thyroid disorders [**2**]. Adverse effects are usually are rare (<1%), mild and reversible at ocular level: optic neuropathy, subconjunctival hemorrhage, trichomegaly, and cystoid macular edema [**3**]. Retinopathy has been more described in patients with diabetes, hypertension, dyslipidemia, and coagulopathy. Severe complications include raised intraocular pressure [**4**], neovascular glaucoma [**5**], retinal detachment [**6**] and intraocular hemorrhage [**7**]. Non-arteritic anterior ischemic optic neuropathy (NAION) is rarely reported as a complication of Peg-Interferon treatment. Ribavirin has no documented intraocular toxicity, few conjunctivitis cases being reported [**8**]. Only a small percentage of patients with vitamin B12 deficit develop visual system dysfunction, generally associated with a genetic predisposition for this type of optic neuropathy [**9**].

Case

We present the case of a 54-year-old female with complaints of sudden bilateral painless drop of vision, reported after awakening in the morning. Patient was diagnosed 3 years before with hepatitis C and started the treatment with IFN alfa2a (180 µg/ week, Pegasys®, Hoffman-LaRoche, Swizerland) and Ribavirin (1000 mg/ day, Copegus®, Hoffman-LaRoche, Swizerland), 15 weeks before the symptoms occurred. She had none of the traditional systemic risk factors for conventional NAION (diabetes, hypertension, ischemic heart disease, or hypercholesterolemia), denied jaw claudication, neck pain, trauma, headache, or periorbital pain. On examination, the visual acuity in the RE was 0.2 and 3/ 50 in the LE. Intraocular pressure was 12 mmHg in both eyes, normal anterior segment examination (slit lamp), full ductions and versions. Ishihara color plates test revealed severe non-systematized dyschromatopsia in both eyes; pupillary responses were sluggish bilaterally, diameter 3 mm. Fundus examination showed bilateral optic disc edema, more prominent in the LE with splinter hemorrhages around the optic disc area (**Fig. 1**); mild macular edema was present in the LE. Visual field testing (Humphrey Field Analyzer II, Carl Zeiss Meditech) showed severe defects in 3 quadrants of the RE (**Fig. 2**), whereas in the LE, the test could not be performed due to VA<0.1. OCT examination (Cirrus OCT, Carl Zeiss Meditech ®) confirmed the clinical aspect previously described (**Fig. 3 a,b**).

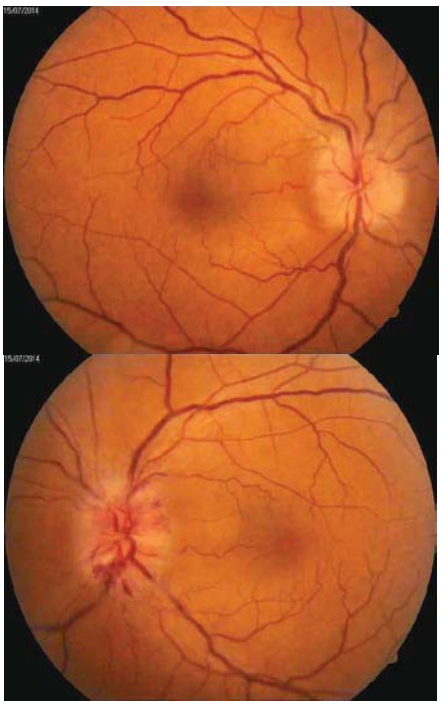

Fig. 1 Bilateral NAION – Optic disc edema. Visible splinter peridiscal hemorrhages and mild macular edema (LE)

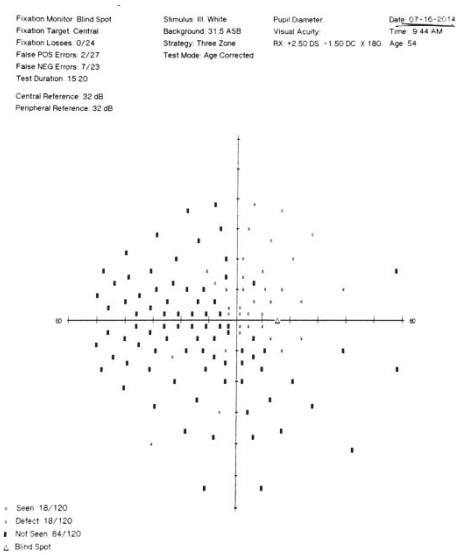

Fig. 2 Visual field examination RE (at presentation) – Full Field 120*, 3 zones – severe vision loss, absolute defects in 3 quadrants; LE could not be performed due to VA<0.1

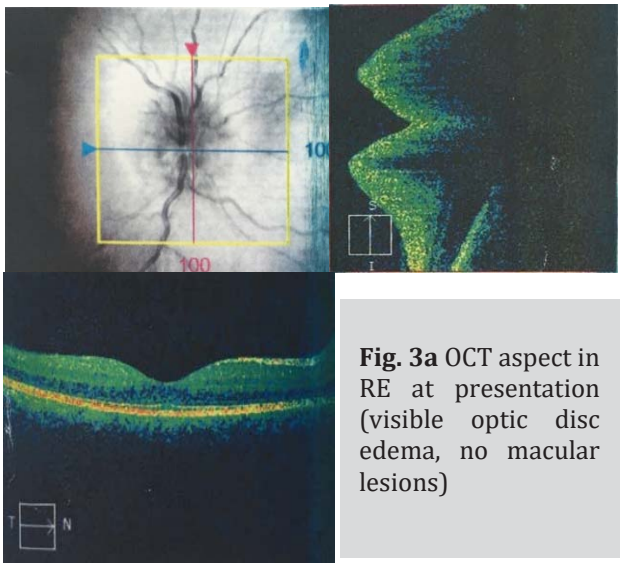

Fig. 3a OCT aspect in RE at presentation (visible optic disc edema, no macular lesions)

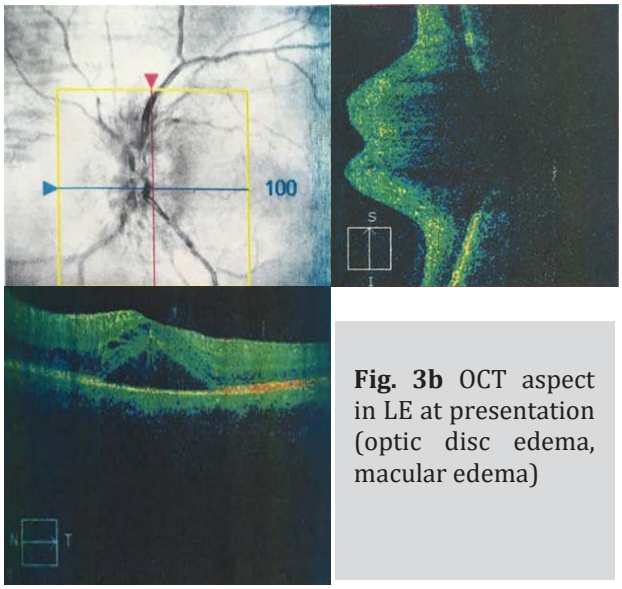

Fig. 3b OCT aspect in LE at presentation (optic disc edema, macular edema)

Contrast CT scan MRI of the brain and orbits showed no optic nerve or intracranial abnormalities. Lumbar puncture demonstrated a normal opening pressure, with a normal protein and glucose level, no white blood cells and scarce erythrocytes. The hemogram showed a hemoglobin level of 12 mg/ dl and mild pancytopenia (white cell count 3170 cells/ µl, platelet count 95.000 cells/ µl, lymphocytes 930 cells/ µl, monocytes 1870 cells/ µl). Also a slight increase in the mean erythrocyte volume was measured and was found to be of 99.7 fL. The comprehensive metabolic panel showed no abnormalities. Antinuclear antibodies, angiotensin converting enzyme, rapid plasma reagin, neuromyelitis optica (NMO) IgG, cANCA, pANCA and cryoglobulins were all negative. Thyroid function tests were normal. Active phase reactants exhibited mildly increased titers (ESR = 22mm/ hr and fibrinogen 421 mg/ dl).

Both Peg-Interferon alpha2a and Ribavirin were discontinued. The patient received iv hydration fluids and pulse therapy with methyl-prednisolone (1g/ day) – 3 days, then 60 mg/ day of oral Prednisone tapered slowly over the next 12 weeks. Slowly the visual acuity increased in the RE to 0.8scnc, whereas in the LE the improvement was not as spectacular as in the fellow eye (VALE = 0.16scnc). Humphrey perimetry demonstrated an improvement in the RE, whilst in the LE it was the first recorded result showing an altitudinal defect (**Fig. 4**). Visual evoked potentials showed initially increased latencies and decreased amplitudes in the RE, whereas in the LE, the result could not be recorded due to the severely affected optic nerve. At 3 months the morphology of the waves improved, yet there were still increased latencies and decreased amplitudes in the RE. Recordings in the LE were possible only in one channel (A2), from the temporal fibers, indicating severe optic atrophy (**Fig. 5, 6**; **Table 1, 2**). Further on, at 6 months, the visual acuity obtained a stable plateau, yet the neurologist suggested a dosage of vitamin B12. The result showed a decrease in its level (vitamin B12 serum level = 166 pg/ ml, range 240-799 pg/ ml), thus adding a compound of nutritional deficit to the optic nerve dysfunction. Unfortunately, the patient could not be supplemented due to the general condition that prohibited any substitutive therapy. At the last visit, at 24 months, the general and ophthalmological statuses were constant and similar to the ones at the previous visits (**Fig.** 7).

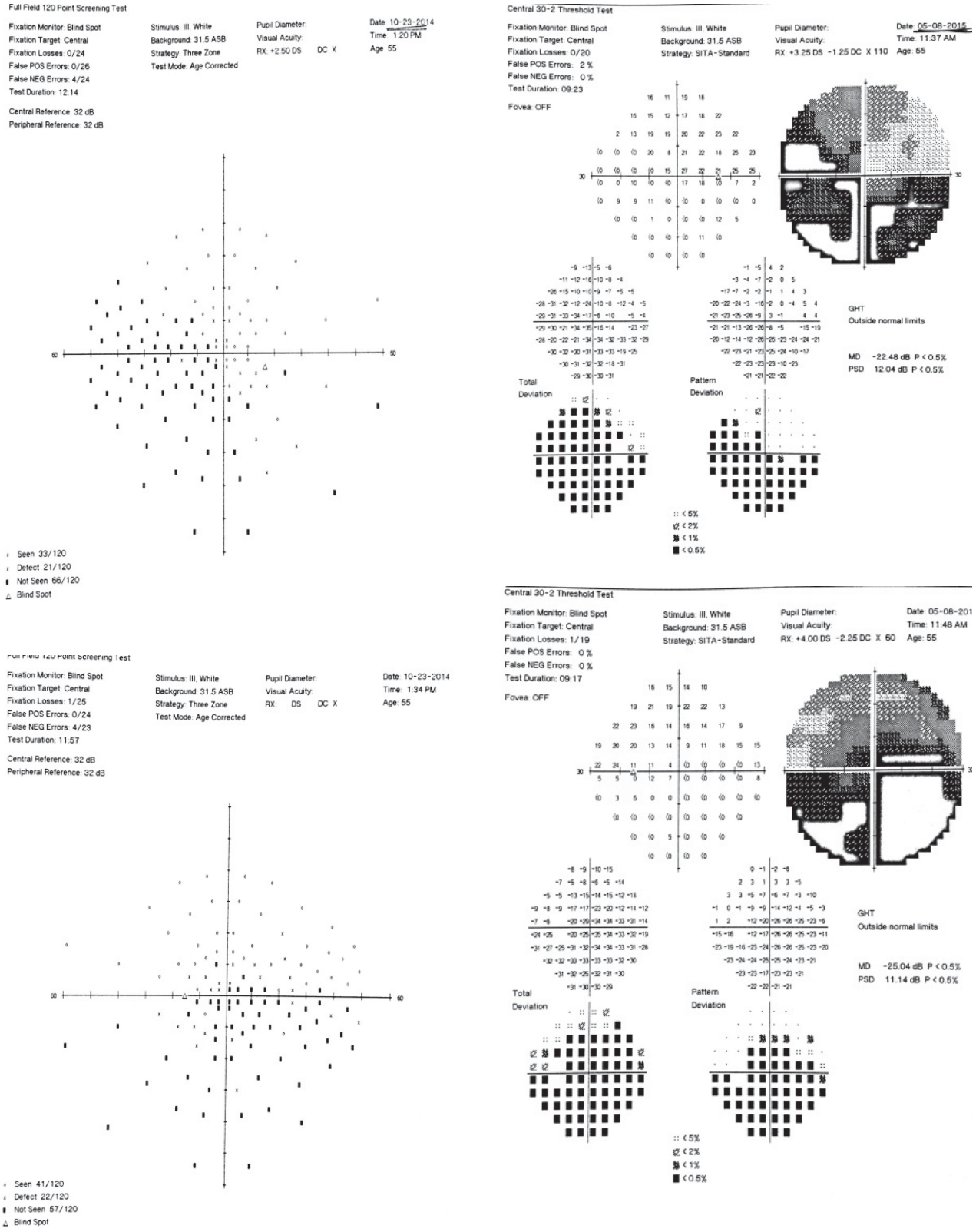

Fig. 4 Visual field changes at 3 months after presentation – Full field 120*, 3 zones (RE – slight improvement of visual field defects compared to baseline; LE – altitudinal defect).
30-2 Threshold test. General reduction of retinal sensitivity (RE MD = -22.48 dB; LE MD = -25.04 dB) and significant visual loss in both hemifields (RE PSD = 12.04 dB; LE PSD = 11.4 dB)

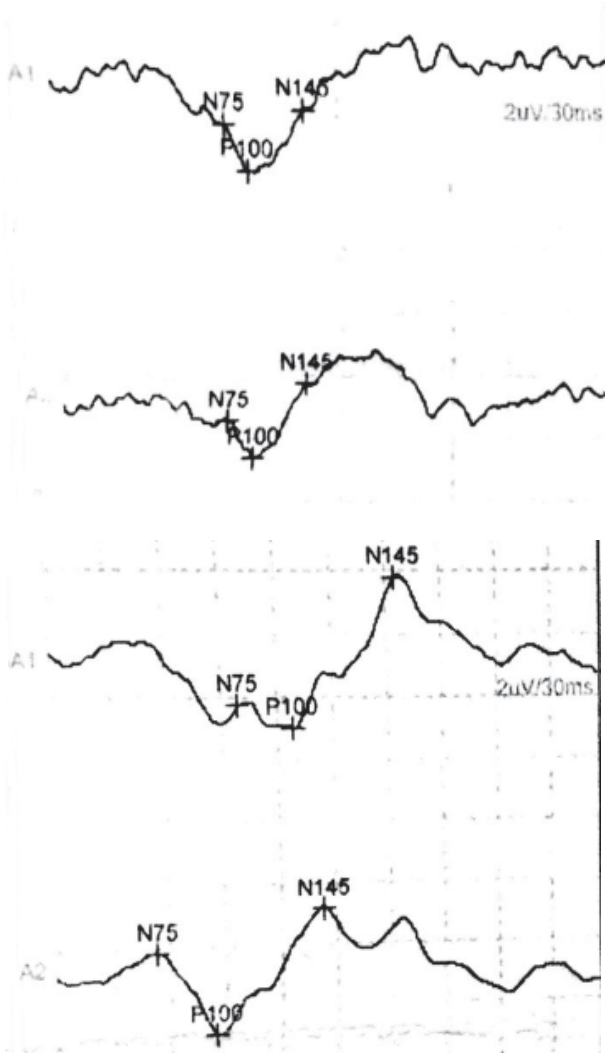

Fig. 5 RE – increased latencies and decreased amplitudes in visual evoked potentials (VEP) examination at presentation and 4 months follow up

Table 1. VEP parameters - RE at presentation and 4 months follow up

RE PEV recordings (at presentation)	**N75**	**P100**	**N145**
A1	90.9	102.9	133.2
A2	88.8	102.9	131.1
RE PEV recordings (4 months follow up)			
A1	100.2	129.6	186.9
A2	54.3	85.8	144.6

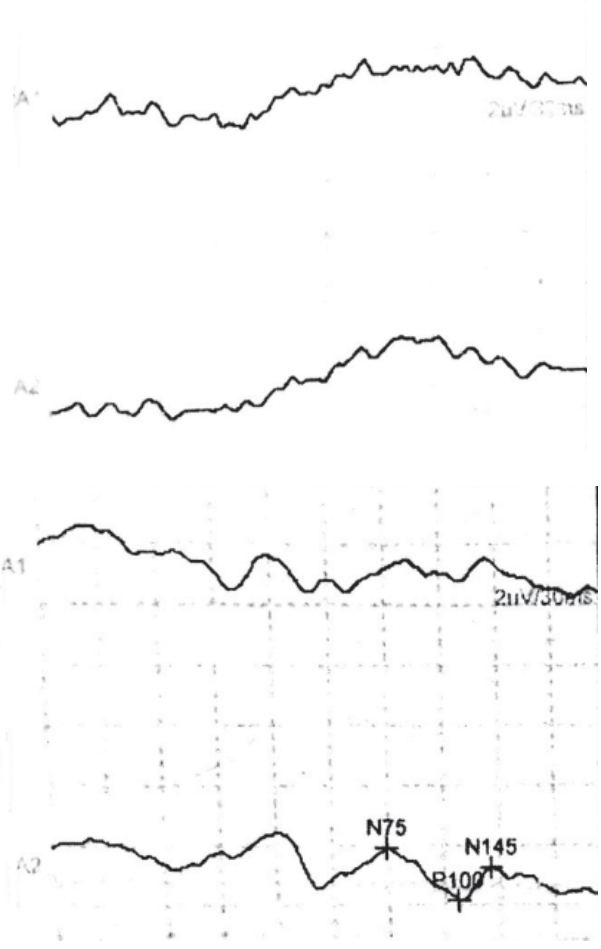

Fig. 6 LE - non-recordable parameters in VEP exam at presentation. Recordable data only in channel A2 (fibers from the temporal side) showing severe optic atrophy at 4 months follow up

Table 2. VEP parameters - LE at presentation and 4 months follow up

LE PEV recordings (at presentation)	**N75**	**P100**	**N145**
A1	non-recordable		
A2	non-recordable		
LE PEV recordings (4 months follow up)			
A1	non recordable		
A2	180.9	219.0	237.3

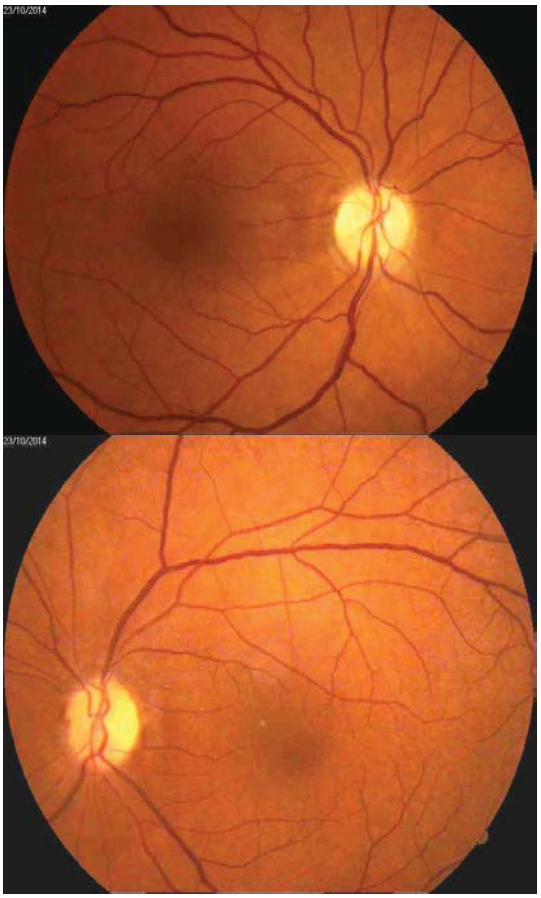

Fig. 7 Fundus appearance – optic atrophy (pale discs) in both eyes at the last follow up visit

Discussion

Vision loss secondary to IFN treatment has well been documented. A review from 2011 identified 471 cases, but the majority developed retinal complications [**10,11**]. Frauenfelder recently identified 36 cases of NAION that have been linked to IFN treatment, with unilateral or bilateral involvement and different visual loss extents [**12**]. Berg reported 23 cases of NAION in the setting of interferon alpha therapy, of which 11 patients experienced bilateral NAION. All reported cases lost vision between 1-40 weeks after treatment initiation, 13 cases received combined treatment Interferon alpha and Ribavirin [**13**].

Yet, bilateral and simultaneous NAION is rare and typically suggests systemic toxicity. Our case reported such a situation in a patient treated with IFN and Ribavirin for hepatitis C, in whom a B12 deficit co-existed, although detected by chance. Although many cases recover spontaneously, only by cessation of Interferon treatment, in our case, the recovery was asymmetric and proportional to the initial VA decay, despite supportive treatment and medication withdrawal. Diabetes mellitus, hypertension, anemia, thrombocytopenia, and high triglyceride levels are risk factors for interferon-associated complications [**14**]. In our case, the patient had none of the afore-mentioned risk factors, except for thrombocytopenia. Vitamin B12 deficit triggers visual system dysfunction only in a small number of patients, generally in those with a genetic predisposition to this type of optic neuropathy [**9**]. Although in our case, the most probable cause of the NAION was related to the Interferon administration, the co-existence of this nutritional deficit added a supplementary risk factor for optic neuropathy. Co-administration of Ribavirin does not contribute to ocular complications [**15**].

Interferon induced ischemic optic neuropathy is believed to have a multifactorial pathophysiology depending on several factors [**8**]. Suspected mechanisms for ischemia are interferon induced lymphocyte and vascular adhesion molecule activation, increased immune complex circulation and accumulation of these in the small vessels in the retina or around the optic disk. Moreover, Interferon elicits increases in some interleukins and MHC2 proteins and its immunomodulation feature [**8,12**]. Another mechanism seems to induce ischemia by triggering systemic hypotension and fluctuations in blood pressure [**8**], enhancing the optic nerve damage. Inflammatory changes seem to involve only myelin and respected axons, thus enabling reversibility of symptoms after withdrawing the medication, whereas pure ischemic axonal damage results in irreversible vision loss. Our case seemed to promote both ischemia and inflammation mechanisms in the same patient considering the bilaterality and the asymmetric visual recovery at the end of the follow up period. Although our treatment included hydration, prevention of hypotension, discontinuation of interferon therapy and systemic corticosteroids could not provide a full visual recovery.

In conclusion, the treatment with Interferon alpha may induce bilateral, simultaneous NAION through various mechanisms, which might influence the degree of optic nerve damage. When other risk factors are added (e.g. nutritional), it is difficult to estimate the prognosis and the visual recovery is less predictable and poorer.

References

1. Bailon P, Palleroni A, Schaffer CA, Spence CL, Fung WJ, Porter JE, Ehrlich GK, Pan W, Xu ZX, Modi MW, Farid A, Berthold W, Graves M. Rational design of a potent, long-lasting form of interferon: a 40 kDa branched polyethylene glycol-conjugated interferon alpha-2a for the treatment of hepatitis C. Bioconjug Chem. 2001 Mar-Apr; 12(2):195-202.
2. Baron S, Tyring SK, Fleischmann WR Jr. The interferons. Mechanisms of action and clinical applications. JAMA. 1991 Sep 11; 266(10):1375-83.
3. Schulman JA, Liang C, King J. Posterior segment complications in patients with hepatitis C treated with interferon and ribavirin. Ophthalmology. 2003 Feb; 110(2):437-42.
4. Kuga K, Hasumura S, Nagamori S, Toda G, Kitahara K. Intraocular hemorrhage developing during interferon therapy. Intern Med. 1996; 35:15–18.
5. Ayaki M. Development of neovascular glaucoma in the course of interferon alpha therapy for hepatitis type C. Br J Ophthalmol. 1994; 78:238.
6. Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, Nishioji K, Katagishi T, Nakagawa Y, Tada H, Sawa Y, Mizuno M, Kagawa K, Kashima K. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol. 1996; 25:283–291.
7. Yamada H, Mizobuchi K, Isogai Y. Acute onset of ocular complications with interferon. Lancet. 1994; 343:914.
8. Knyzer MD, Lifshitz T, Mira M, Kratz A, Zlotnik A. Anterior ischemic optic neuropathy in a patient with hepatitis C treated with interferon-alpha and ribavirin. Isr Med Assoc J. 2011 Apr; 13(4):251-3.
9. Wilhelm H, Grodd W, Schiefer U, Zrenner E. Uncommon chiasmal lesions; demyelinating disease, vasculitis and cobalamin deficiency. Ger J Ophthalmol. 1993 Aug; 2(4-5):234-40.
10. Fuzzard D, Mack H, Symons RC. Bilateral retrobulbar optic neuropathy in the setting of Interferon alpha 2a therapy. Case Rep Ophthalmol. 2014; 5:270-276.
11. Fragoso YD, Paggiaro MSS, Mastromauro R, Wilson HM. Literature systematic review on the ophthalmological side effects of interferons. Arq. Bras Oftalmol. 2011; 74:306-310.
12. Frauenfelder FW, Frauenfelder FT. Interferon alpha associated anterior ischemic optic neuropathy. Ophthalmology. 2011; 118:408-411.
13. Berg K, Nelson B, Harrison A, McLoon L, Lee M. Pegylated Interferon alpha associated optic neuropathy. J Neuroophthalmol. 2010 June; 30(2)117-122.
14. Sifton DW. Physicians' Desk Reference. 55. 2001, Montvale, NJ: Medical Economics.
15. Guyer DR, Tiedeman J, Yannuzzi LA, Slakter JS, Parke D, Kelley J, Tang RA, Marmor M, Abrams G, Miller JW. Interferon-associated retinopathy. Arch Ophthalmol. 1993; 111:350–356.