

# Bilateral Retrobulbar Optic Neuropathy in the Setting of Interferon Alpha-2a Therapy

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## Key Words

Interferon alpha · Optic neuropathy · Retrobulbar · Adverse drug reaction · Anti-drug antibody

## Abstract

The development of biopharmaceutical agents, including the interferons (IFN), offers new treatment options for a wide range of medical conditions. Such advancements, however, have not come without risk to patients. Optic neuropathy in the setting of IFN therapy has been previously documented and is usually attributed to anterior ischaemic optic neuropathy; however, the pathophysiology remains poorly understood. Retrobulbar optic neuropathy associated with IFN treatment has not been described in the medical literature to date. We report the case of a 38-year-old Caucasian female with refractory acute myeloid leukaemia who developed painless bilateral blurred vision within 2 weeks of commencing a course of IFN alpha-2a. Extensive clinical workup demonstrated bilateral retrobulbar optic neuropathy. We report the clinical evaluation of this first documented case and discuss the possible aetiologies of her presentation.

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## Introduction

Interferons (IFN) are naturally occurring glycoprotein cytokines clinically used as biologic response modifiers [1]. IFN alpha-2a is a synthetic form of IFN alpha, which is produced by recombinant technology and has been approved by the US FDA to treat chronic myelogenous leukaemia, hairy cell leukaemia and AIDS-related Kaposi's sarcoma. Despite being generally well tolerated, ocular adverse reactions have been documented. Our case shows a

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variant of optic neuropathy not previously reported in the literature and we discuss possible aetiologies.

### Case History

A 38-year-old Caucasian female with an 18-month history of acute myelogenous leukaemia (AML; NPM1 negative, FLT3 negative, CEPB $\alpha$  positive) was referred for ophthalmological assessment with painless bilateral blurred vision, which had slowly worsened over 3 weeks. Her clinical course of AML had been refractory to treatment (table 1), prompting a course of non-pegylated IFN alpha-2a (3 million units subcutaneously 3 times per week for 4 weeks). Visual deterioration occurred within 2 weeks of commencing IFN alpha-2a therapy. The patient presented 1 week after the 4-week course had been completed. Her additional medications were fluconazole 200 mg orally daily, aciclovir 200 mg orally TDS and sulfamethoxazole/trimethoprim 160/800 mg BD 2 days per week. She had no history of hepatitis C, hypertension or diabetes, no family history of eye disorders, ate a healthy diet and denied smoking or the consumption of alcohol.

On examination, visual acuity was 20/30 in the right eye and 20/40 in the left eye. She read the Ishihara control plate only, with both eyes open. Examination of the anterior segments, optic discs, maculae and peripheral retinae was unremarkable (fig. 1a, b) with no disc oedema or haemorrhage, disc-at-risk appearance or retinal nerve fibre layer loss. Intraocular pressure was within normal limits in both eyes. No relative afferent pupillary defect was observed. Cover and motility testing were normal with no pain on eye movement. Blood pressure was 99/68 mm Hg with systolic readings between 98 and 110 mm Hg over the previous month.

Optical coherence tomography (Spectralis, Heidelberg Engineering, Heidelberg, Germany) showed normal macular structure and peripapillary retinal nerve fibre layers in both eyes (fig. 1c–f). Automated perimetry (Humphrey Visual Field 30-2; Carl Zeiss Meditech Inc., Oberkochen, Germany) demonstrated bilateral central scotomata (fig. 1g, h). Full-field and multifocal electroretinography (RETI-port/scan; Roland Consult, Brandenburg, Germany) were within normal limits (fig. 2) [2, 3]. Pattern-reversal visual-evoked potential testing (RETI-port/scan; Roland Consult) showed no reproducible responses above baseline in either eye (fig. 2) [4]. MRI (GE Signa LX MRI, 1.5 T; Fairfield, Conn., USA) did not detect any optic nerve, intraorbital or intracranial pathology (fig. 3). Serum biochemistry and liver function tests were within normal limits. Haematological parameters, demonstrating profound neutropenia and thrombocytopenia, and recent normal viral serological testing are summarised in table 2. Urine microscopy and culture were negative for infection. Lumbar puncture was not performed.

Unfortunately, the patient was unable to attend for follow-up due to deterioration in her clinical condition. Postmortem examination was not performed.

### Discussion

IFN alpha-2a is a glycoprotein produced biosynthetically with anti-tumour, antiviral and immunomodulatory activity [1]. Medical conditions that may be managed with IFN alpha include chronic hepatitis C, renal cell carcinoma, low-grade non-Hodgkin's lymphoma, chronic myelogenous leukaemia, cutaneous T-cell lymphoma and AIDS-related Kaposi's sarcoma [5].

Visual loss secondary to IFN treatment has been well documented. A review performed in 2011 identified 471 cases, the vast majority of which were retinal in origin [6]. However, in a recent review identifying 36 cases [7], anterior ischaemic optic neuropathy (AION) has also been linked with varied indications for IFN alpha treatment, unilateral or bilateral involvement, magnitude of visual loss and extent of recovery. Identified risk factors for IFN-associated optic neuropathy include hepatitis C and thrombocytosis. In 2010, Berg et al. [8] discussed a number of possible theories in support of an ischaemic mechanism for IFN-induced optic neuropathy, including capillary disruption due to infiltration by aggregated granulocytes secondary to elevated plasma complement levels, lymphocyte infiltration from immune complex deposition and adherence of activated leukocytes to the vascular endothelium.

Our patient developed bilateral optic neuropathy localised to the retrobulbar optic nerves 2 weeks after commencing IFN treatment for AML. Retinal-associated visual loss and AION were ruled out by normal examination and investigation 3 weeks after symptom onset. She did not show recognisable risk factors for IFN-associated AION, nor typical vascular risk factors. Other forms of optic neuropathy, including the demyelinating, toxic, inflammatory, infiltrating and inherited forms, have been excluded, and clinical investigation findings were not typical of paraneoplastic or leukaemic optic neuropathy. Visual loss could not definitively be attributed to IFN alpha-2a treatment; however, an absence of risk factors for other causes of optic neuropathy raised strong suspicion.

The mechanism of visual loss in our patient is unknown. Given that IFN-associated visual loss is thought to be ischaemic in origin, it is possible that she had bilateral posterior ischaemic optic neuropathy. However, none of the common causative factors such as perioperative hypotension and blood loss, giant cell arteritis and risk factors for atherosclerotic vascular disease were present [9]. Non-ischaemic causal mechanisms were also plausible. An infiltrative retrobulbar optic neuropathy in the setting of refractory AML is a differential diagnosis; however, the simultaneous development of bilateral disease observed in this case is more consistent with a toxic effect than an infiltrative process. The absence of cerebrospinal fluid analysis adds difficulty to the assessment of an infiltrate, but the appearance on MRI films is not suggestive of an infiltrative process. Anti-drug antibody formation to IFN alpha has been observed in the treatment of hairy cell leukaemia, renal cell carcinoma and chronic hepatitis C with a variable time of onset from weeks to months after commencing treatment [10]. Anti-drug antibodies are more commonly seen in patients treated with non-pegylated IFN [10], as was our patient. It is conceivable that anti-drug antibodies result in a non-ischaemic retrobulbar optic neuropathy secondary to immune complex deposition; a commercially available test for anti-IFN alpha-2a antibodies is not currently available to test this hypothesis.

This is the first well-documented case report of bilateral retrobulbar optic neuropathy in the setting of IFN alpha-2a. Further case reports are required to determine the incidence of this form of optic neuropathy and the causal mechanisms. The development of commercially available testing of anti-drug antibody levels for IFN alpha may provide further circumstantial evidence for an antibody-mediated disease process. Patients treated with IFN who experience visual loss need prompt ophthalmic assessment to consider ceasing the therapy, as visual loss can be bilateral and irreversible.

#### Disclosure Statement

The authors have no conflicts of interest to disclose.

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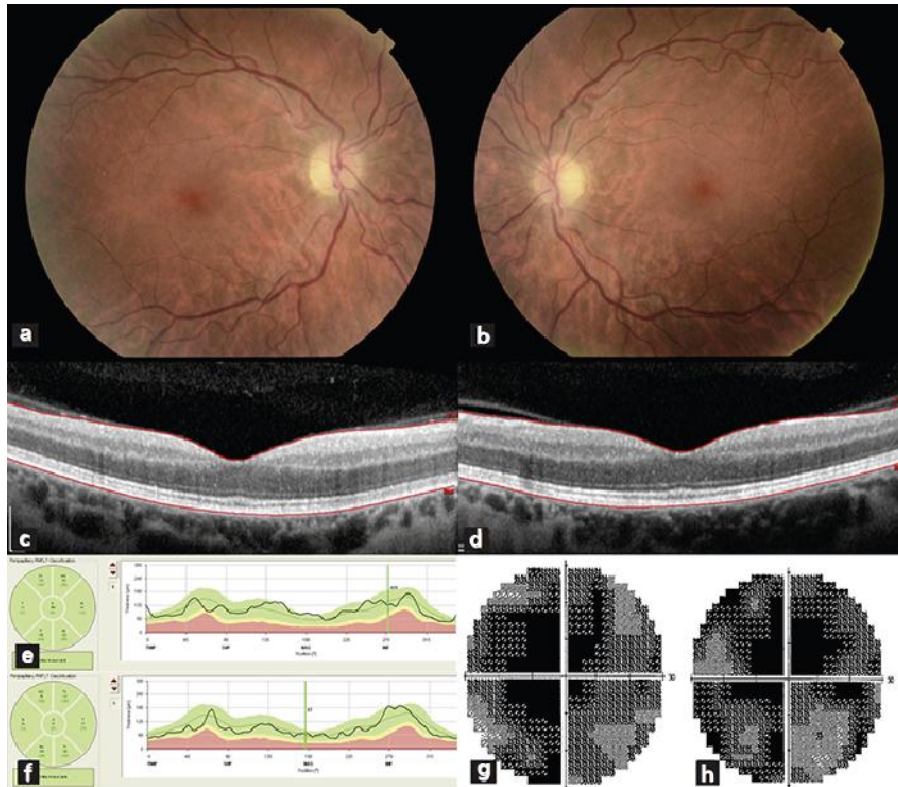
**Table 1.** Timeline of the patient's treatment for AML

Time prior to initial ophthalmological assessment	Event
18 months	Diagnosed with AML 7+3 induction chemotherapy regimen (cytarabine IV for 7 days and anthracycline IV for 3 days) Consolidation regimen of high-dose ARA-C
12 months	Relapse of AML Enrolled in the VALOR study (a multi-national, double-blinded, randomised controlled trial of patients with a first-relapse of AML) Patients in this trial are randomised to receive an intermediate dose ARA-C with either vosaroxin or a placebo Consolidation regimen of FLAG
5 months	Double-cord allogeneic stem cell transplantation
5 weeks	Commenced IFN alpha-2a at a dose of 3 million units subcutaneously 3 times per week for 4 weeks
3 weeks	Patient began to experience bilateral painless blurred vision, which progressively worsened

ARA-C = arabinofuranosyl cytidine. FLAG = fludarabine, high-dose cytarabine and granulocyte colony-stimulating factor.

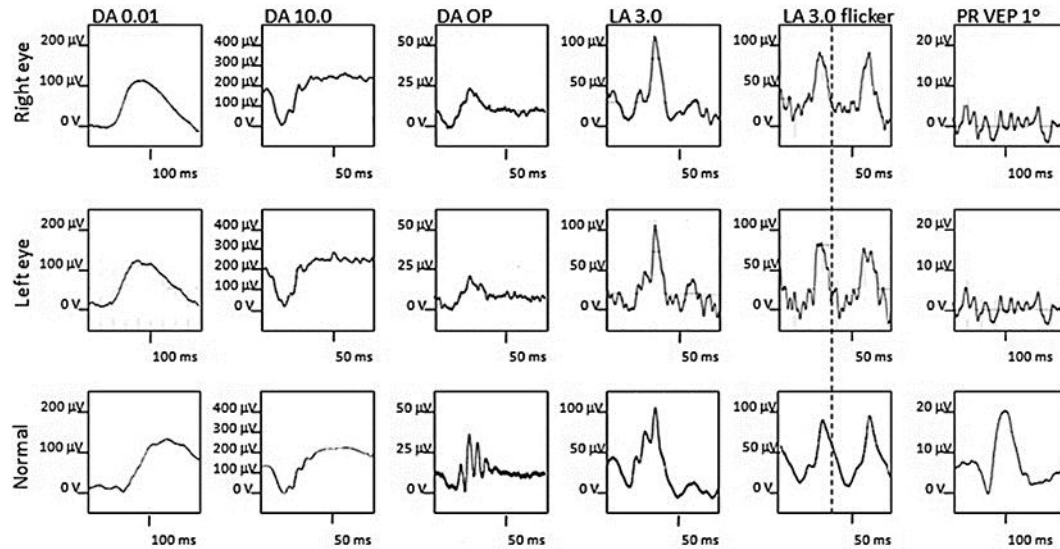
**Table 2.** Haematological parameters and biochemistry of a 38-year-old Caucasian female patient who developed reduced vision in both eyes 2 weeks after treatment of AML with IFN

Test	Value	Reference range
Haemoglobin	117 g/l	115–150
White cell count	$1.4 \times 10^9/l$	4.0–11.0
Platelets	$10 \times 10^9/l$	140–400
Neutrophils	$0.1 \times 10^9/l$	2.0–8.0
Lymphocytes	$1.3 \times 10^9/l$	1.2–4.0
Monocytes	$0.1 \times 10^9/l$	0.0–0.5
Eosinophils	$0.0 \times 10^9/l$	0.0–0.1
Basophils	$0.0 \times 10^9/l$	0.0–0.5
Total protein	71 g/l	65–85
Lactate dehydrogenase	411 IU/l	210–420
Urate	0.18 mmol/l	0.15–0.40
Serum folate	27.3 nmol/l	>12.2
Serum B12	185 pmol/l	150–600
Syphilis serology	Negative	
HIV serology	Negative	
Hepatitis A IgG antibody	Detected	
Hepatitis B surface antigen	Not detected	
Hepatitis B core total antigen	Not detected	
Hepatitis C antibody	Not detected	
Toxoplasma IgG antibody	Equivocal	
Varicella zoster virus IgG antibody	Detected	
Cytomegalovirus IgG antibody	Not detected	
Herpes simplex virus IgG antibody	Detected	
Epstein-Barr virus viral capsid antigen	Detected	
Epstein-Barr virus viral PCR	Not detected	

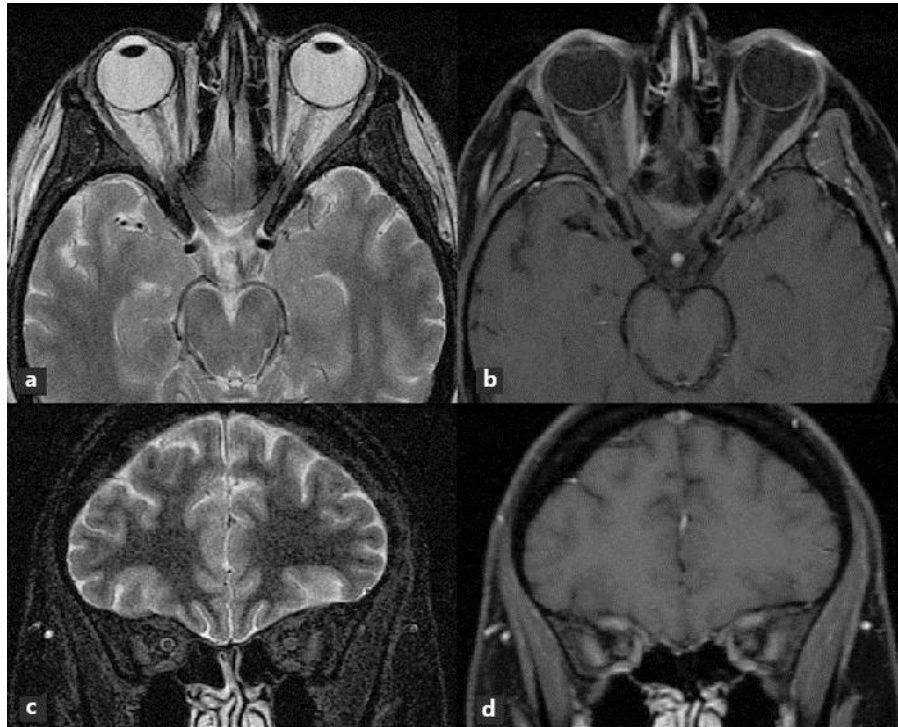


**Fig. 1.** Fundus photographs demonstrating normal retina and optic discs (**a** right eye; **b** left eye), normal horizontal optical coherence tomographic macular scans including the foveal centres (**c** right eye; **d** left eye) and retinal nerve fibre layer scanning (**e** right eye; **f** left eye) and visual field testing showing bilateral central scotomata (**g** left eye, fixation losses 2/15; **h** right eye, fixation losses 5/21).





**Fig. 2.** ISCEV standard electroretinogram and visual-evoked potential for the right and the left eye of our 38-year-old female patient who developed reduced vision in both eyes 2 weeks after treatment of AML with IFN, demonstrating normal-field electroretinogram and non-detectable pattern-reversal visual-evoked potential. DA = dark adapted; LA = light adapted; OP = oscillatory potentials; PR VEP = pattern-reversal visual-evoked potential.



**Fig. 3.** MRI of the brain and orbits, comprising axial T2 (a), post-contrast fat-suppressed T1 slices (b) as well as coronal T2 (c) and post-contrast fat-suppressed T1 views (d). No cause for the patient's decreased vision was identified from this investigation.