CLINICAL CASE

Anterior ischemic optic neuropathy complicating interferon alpha and ribavirin therapy in patients with chronic hepatitis C

Neuropathie optique ischémique antérieure compliquant le traitement par interféron alpha et ribavirine chez des malades atteints d’hépatite chronique C

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Summary  Ophthalmological complications with interferon therapy are rare, usually mild and reversible, and do not require the withdrawal of antiviral treatment. Anterior ischemic optic neuropathy is an uncommon complication of interferon treatment. From January 1998 to December 2007, three patients developed anterior ischemic optic neuropathy during antiviral treatment, with a favourable course after interferon was discontinued. Periodic Ophthalmological examinations, including visual acuity and fundus examinations should be performed before starting and during treatment, particularly in patients with vascular risk factors. Antiviral therapy should be stopped immediately if severe ophthalmologic complications occur.

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Résumé Les complications ophtalmologiques du traitement par interféron sont rares, habituellement minimes et réversibles, ne nécessitant pas l’arrêt du traitement antiviral. La neuropathie optique ischémique antérieure est une complication rare du traitement par interféron. De janvier 1998 à décembre 2007, trois cas de neuropathie optique liés à l’interféron ont été observés dans notre service, avec une évolution oculaire favorable après interruption de l’interféron. Des examens ophtalmologiques périodiques incluant une évaluation de l’acuité visuelle et un fond d’œil devraient être réalisés avant de débuter un traitement par interféron et pendant le traitement, particulièrement chez les malades ayant des facteurs de risque

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Ophthamological complications related to interferon therapy are rare, usually mild and reversible, and don’t require treatment withdrawal [1]. The most typical adverse ocular event with interferon is retinopathy, characterized by cotton wool spots and retinal hemorrhages especially around the optic nerve. Visual loss is usually absent or limited and reversible after discontinuation of therapy [2–4]. Anterior ischemic optic neuropathy is an uncommon complication of interferon treatment which can dramatically impair visual function [2]. Ten cases of anterior ischemic optic neuropathy in patients with chronic hepatitis C who received interferon-based therapy have been reported in the literature [5]. We prospectively recorded and analyzed three cases of patients who developed anterior ischemic optic neuropathy during antiviral treatment in our cohort of 809 patients with chronic hepatitis C treated by standard or pegylated interferon-ribavirin. Clinical and angiographic findings were monitored. Interferon was discontinued in all cases but the antiviral treatment was begun again in one case after a favourable course of the visual complications.

**Case report 1**
A 68-year-old woman presented with painless blurred vision in the left eye. Medical history included well-controlled hypertension and chronic hepatitis C, probably as a result of a blood transfusion during a childhood appendectomy. Hepatitis C virus (HCV) genotype was 1b, HCV-RNA level was 6.5 log_{10} IU/mL and liver biopsy showed an A2F3 score according to the Metavir classification. The patient had not responded to standard interferon for 12 months and relapsed after combined interferon ribavirin 1000 mg/day. In February 2004, pegylated interferon-α2a was started at a dose of 180 μg/week combined with ribavirin. Eight weeks later, the patient complained of a sudden bilateral decrease in visual acuity which the ophthalmologic examination confirmed (2/10 in the right and left eye). Fundus examination revealed bilateral disc oedema. Fluorescein angiography confirmed the bilateral anterior ischemic optic neuropathy. There was no response to the visual evoked potentials in either eye. Inflammatory, infectious, tumoral and vascular diseases were excluded. HCV-RNA was positive in the 12th week and antiviral treatment was discontinued. The outcome was favourable three months later with total regression of optic disc oedema and improvement of visual acuity to 8/10 in the left and right eyes.

**Case report 2**
A 61-year-old woman with well-controlled hypertension was diagnosed with chronic hepatitis C in June 1998. HCV genotype was 1b, HCV-RNA level was 5.6 log_{10} IU/mL, and liver biopsy showed A2F2 score according to the Metavir classification. The patient had not responded to standard interferon for 12 months and relapsed after combined interferon ribavirin 1000 mg/day. In February 2004, pegylated interferon-α2a was started at a dose of 180 μg/week combined with ribavirin. Eight weeks later, the patient complained of a sudden bilateral decrease in visual acuity which the ophthalmologic examination confirmed (2/10 in the right and left eye). Fundus examination revealed bilateral disc oedema. Fluorescein angiography confirmed the bilateral anterior ischemic optic neuropathy. There was no response to the visual evoked potentials in either eye. Inflammatory, infectious, tumoral and vascular diseases were excluded. HCV-RNA was positive in the 12th week and antiviral treatment was discontinued. The outcome was favourable three months later with total regression of optic disc oedema and improvement of visual acuity to 8/10 in the left and right eyes.

**Case report 3**
A 71-year-old man had had chronic hepatitis C since 1999. HCV genotype was 1a, HCV-RNA level was 5.5 × 10^6 eq.v/mL and the histological score of a liver biopsy was A2F4 according to the METAVIR classification. Standard interferon-α2a (3 million units × 3/week) and ribavirin was started in March 2000. Seven months after starting treatment, the patient presented with sudden decreased vision in the right eye. HCV-RNA had been undetectable since week 12 of therapy. Visual acuity was 6/10 with correction in the left eye, 2/10 in the right eye. Fundus examination showed disc oedema in the right eye. Fluorescein angiography confirmed optic neuropathy with peripapillary hemorrhage. There was no response to visual evoked potentials in the right eye. Antiviral treatment was discontinued and the patient received methyl prednisolone 1 g for three days. A control ophthalmologic examination one month later showed that visual acuity had improved to: 5/10 in the right eye and 7/10 in the left eye with correction while optic disc oedema had resolved. The antiviral treatment was started again with the ophthalmologist’s approval. HCV-RNA was undetectable at the end of treatment, one year and two years after discontinuation, suggesting a sustained virological response. Ophthalmological examinations in 2003, 2004, 2005, 2006 and 2007 showed a visual acuity of 6/10 in the right eye and 8/10 in the left eye.
Anterior ischemic optic neuropathy in patients with chronic hepatitis C

Discussion

Anterior ischemic optic neuropathy is an uncommon complication of interferon treatment. Sixteen cases of anterior ischemic optic neuropathy have been reported in the literature [5]. In 10 cases, anterior ischemic optic neuropathy occurred during treatment of chronic hepatitis C [2,6—13] and in one case during antiviral treatment for acute hepatitis C [14]. Two other cases occurred during interferon treatment of cancer [15], one case during treatment of primary thrombocytopenia [6], one case during treatment of malignant melanoma [16] and one case during treatment of amyotrophic lateral sclerosis [17]. Anterior ischemic optic neuropathy may dramatically impair visual function [2]. Predisposing factors have not been clearly identified, except for classic vascular risk factors [2].

Patients with diabetes, arterial hypertension, dyslipidemia and hypercoagulable conditions are more apt to develop these changes [1]. We report three cases of anterior ischemic optic neuropathy out of 809 patients (0.37%) with chronic hepatitis C receiving antiviral treatment. Anterior ischemic optic neuropathy occurred within three weeks to seven months after beginning interferon treatment and ribavirin for chronic hepatitis C. Two patients had typical risk factors for anterior ischemic optic neuropathy. Purvin has suggested involvement of the posterior ciliary arterius rather than the retinal vessels as a possible cause of anterior ischemic optic neuropathy [15]. Lohmann et al. hypothesized that interferon could produce auto-antibodies and thus cause deposition of immune complexes in the small retinal or optic cytokines causing an inflammatory reaction of the blood vessels that could then lead to ischemia [16,18]. For two cases, anterior ischemic optic neuropathy occurred during pegylated interferon and ribavirin treatment and one case occurred during standard interferon and ribavirin treatment. These case reports are unusual because anterior ischemic optic neuropathy did not occur during the first treatment with standard interferon in two patients, and after reintroduction of the antiviral treatment in one patient. The treatment was discontinued in the three case reports like the cases reported in the literature, except for one report that antiviral treatment was not discontinued due to a favourable visual outcome [11]. The resolution of anterior ischemic optic neuropathy after discontinuation of interferon in our patients suggests a causal reaction. This favourable course is uncommon in anterior ischemic optic neuropathy with vascular causes, suggesting another mechanism. One patient received methyl prednisolone, a steroid drug prescribed by the Ophthalmologist resulting in a favourable course of the visual complications. Interferon was then begun again resulting in a sustained viremic response. In the literature, two patients [5,14] received steroids after interferon treatment was discontinued, but there was no improvement in visual function. The course was favourable in our patients within one month to three months. In the literature, the course of anterior ischemic optic neuropathy occurring during interferon treatment for chronic hepatitis C was favourable in four cases [10—13], and was not resolved in three cases [2,6,8].

Anterior ischemic optic neuropathy is uncommon, unpredictable and the frequency is unknown with interferon therapy. It should be emphasized that it can occur at any time after interferon therapy is begun. We recommend periodic Ophthalmological examinations, including visual acuity and fundus examinations before starting treatment, and during treatment particularly in patients with vascular risk factors. Therapy should be stopped immediately if severe ophthalmologic complications occur.

References