Short communication

Interferon-alpha toxicity and reversible bilateral optical neuropathy: A timely withdrawal of the drug

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A B S T R A C T

Clinical case: A patient with chronic, painless, bilateral loss of vision, after significant intake of interferon-α (IFNα) and ribavirina due to liver transplant. Ocular fundus is normal. A suspected retrobulbar optic neuropathy is confirmed by a prolongation of the latency of the patient's visual evoked potential. There being no prior record of risk factors and with the patient's systemic analysis giving normal results, the clinical improvement and the electro-physiological tests conducted after the drug was withdrawn point to interferon as negatively affecting the bilateral optic nerve.

Discussion: Interferon-α is used in the treatment of viral and neoplastic illnesses. Currently the drug is formulated as pegylated interferon alpha (IFNα-p) in order to reduce toxicity and increase tolerance. The most common secondary effects are flu symptoms, asthenia and weight loss. Affected ocular tissue is rare and optic neuropathy is also an infrequent complication: retinopathy at the beginning of treatment is, however, more frequent. The most widely accepted hypothesis as to the cause of toxicity is the presence of circulating immune complexes. It is, therefore, essential for ophthalmologists to be aware of the toxicity of this drug in order to be able to withdraw it in good time, thus preventing potentially irreversible sight loss.

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Toxicidad por interferón alfa y neuropatía óptica bilateral reversible: una retirada a tiempo

R E S U M E N

Caso clínico: Paciente que acude por pérdida crónica de visión bilateral indolora en el que destaca el uso de Interferón alfa (IFNα) y ribavirina para un trasplante hepático. Con un fondo de ojo normal, la sospecha de neuropatía óptica retrobulbar viene confirmada por la...
Hepatitis crónica por VHC
Latencia prolongada
Potenciales evocados visuales

prolongación de la latencia de los potenciales evocados visuales. Sin antecedentes de riesgo y con un estudio sistémico normal, la mejoría clínica y de las pruebas electrofisiológicas tras retirar el fármaco señalan al IFNα como causa de la afectación del nervio óptico bilateral. Discusión: El IFNα es un tratamiento usado en enfermedades virales y neoplásicas. Actualmente es formulado como Interferon alfa pegilado (IFNα-p) para reducir toxicidad y mejorar su tolerancia. Sus efectos secundarios más comunes son synrome gripal, astenia y pérdida de peso. La afectación ocular es rara y la neuropatía óptica es una complicación infrecuente siendo más frecuente la retinopatía en el inicio del tratamiento. La hipotéisis más aceptada como causa de la toxicidad es la existencia de complejos inmunes circulantes. Así pues se de vital importancia para el oftalmólogo conocer la toxicidad de este fármaco para saber retirar a tiempo el mismo, evitando una posible pérdida visual irreversible.

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Introduction

At present, pegylated interferon alpha (IFNα-p) (pegylated interferon alpha 2b, Pegintron®, Shering-Plough) is used in chronic treatments for viral and neoplastic diseases due to its antiproliferative role. A case of optic neuritis is presented, reversible by means of IFNα-p.

Clinical case

Patient, 44, who visited due to painless vision loss with onset a few months earlier. History includes liver transplant and 14 months earlier started treatment with subcutaneous pegylated interferon alpha (IFNα-p), 100 μg/week and oral ribavirin (RBV) at a dose of 800 mg/day, for controlling hepatitis C virus

Fig. 1 – Optical papilla at vision loss onset.

Fig. 2 – 30-2 SITA-FAST campimetry: first field after visual loss, observing scotoma in central 5°. RE: PHG: general sensitivity reduction, DM: −4.00 dB; LE: PHG: beyond normal limits, DM: −4.66 dB (17-7-08).
Fig. 3 – Evolution of visual evoked potentials (VEP): stimulation with pattern-reversal and EEG record in Oz, by means of subcutaneous electrodes; (a) conduction defect. Bilateral P100 wave latency delay with acceptable amplitude preservation (12-7-08). Normal latency values: 84–114 ms and amplitudes at 3–21 μV; (b) after withdrawing the drug, slight improvement was observed in conduction through optic nerves, with discrete latency recovery: (5-9-08); (c) P100 latency normal after right and left monocular stimulation. Conduction recovery through visual pathway of both optic nerves (May 2009); (d) latest VEP, improved latency and amplitude (November 2011).

(HCV). The patient exhibited congenital coagulation factor VII deficit and received transfusions in 1985, 1987 and 1996, the possible cause of HCV infection. After liver condition worsened, the patient underwent liver transplant in 2005. After 18 months, biopsy revealed signs of chronic hepatitis with slight fibrosis (F1), and treatment was established with IFNα-p and RBV. The patient exhibited early response without normalization of the viral charge up to the seventh month, thus the treatment was extended one year. At present the patient exhibits good liver function, remains rejection-free and with undetectable viral charge.

Ophthalmological exploration revealed visual acuity (VA) in both eyes (BE) of 0.15, with a normal anterior pole, tonometry and ocular fundus (Fig. 1). Supplementary studies revealed general sensitivity deficit and scotoma in the central 5' of the visual field in BE (Fig. 2) (Sita-Standard strategy, Central Study 24-2, Humphrey Campimeter Carl Zeiss Meditec AG, 07740 Jena, Germany). Visual evoked potential (VEP) exhibited bilateral delay in P100 wave latency with acceptable amplitude preservation (Fig. 3a). In collaboration with the liver transplant unit and due to presumed neuropathy caused by αIFNα-p and normal results in other systemic risk factors (normal general analytics, normal sedimentation rates, normal folic acid, baseline hypocoagulability, normal syphilis serological prior data, absence of data suggesting toxic-metabolic neuropathy due to nicotine–alcohol), it was decided to immediately suspend said medication.

Subsequently, patient vision progressively improved, reaching within 3 months VA in BE: 0.7 as well as VEP (Fig. 3b). After one-year follow-up, CCVA was observed to be stable with normal ocular fundus (Fig. 4), as well as VEP (June 2009–2012) (Fig. 3c and d) and campimetries (Fig. 5a and b).

Discussion

Interferon-α is a glycoprotein segregated in the presence of viral infections which displays antiproliferative, antiangiogenic1–3 and immunomodulating properties. It is the treatment of choice in chronic hepatitis due to hepatitis C and B virus (HCV-HBV).1 Ophthalmological complications are rare and include trychomegalia,2 hemorrhage and retinal arterial occlusions, cotton-like exudates, anterior ischemic optic neuropathy (AION)1–5 and Vogt–Koyanagi–Harada like conditions.5 At the beginning of treatment, asymptomatic retinal expressions are frequent but these are reversible when medication is suspended.1,5

AION is infrequent, and can occur between 3 weeks and 6 months after beginning the treatment. It could leave irreversible sequelae even after withdrawing the drug.1,5 The etiopathogenic mechanism could be the deposit of immunocomplexes in the optic nerve microcirculation2,3 or immune-inflammatory response, as well as the direct effect
of interferon due to inhibition of endothelial cell proliferation and migration and/or diminished optic nerve perfusion due to its hypotensive properties. Therefore, arterial pressure control as well as drug suspension is part of the treatment. The use of aspirin, corticoid bolus and hemodilution are inefficient and unpredictable.

While the literature describes AION with peripapillary signs and unilateral involvement, this case is bilateral retrobulbar optic neuritis. Considering delayed latency with preserved amplitude, it may well be a case of precocious inflammatory neuritis. The authors hypothesize that the pro-inflammatory effect involved only myelin and respected axons, thus enabling the reversal of symptoms after withdrawing the medication. However, published ischemic etiology cases with pure axonal involvement are irreversible. This could be due to the use of non-pegylated IFNα and to the dosage. This is mentioned only in one publication describing a case similar to this one. Or in the association of ribavirin, used only in 2 cases. Finally, the case described has the longest follow-up period with 14 months of evolution.

To conclude, although neuritis due to VHC have been described, all data suggest that the observed bilateral neuropathy was a consequence of IFNα-β treatment due to the controlled viral charge and complete improvement and recovery after withdrawing the drug.

Fig. 4 – Ocular fundus within normal limits (January 2012).
Conflict of interests
No conflict of interests has been declared by the authors.

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