Short communication

Pegylated interferon and ribavirin associated retinopathy in patients with hepatitis C

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Abstract
Case report: We describe two patients with chronic hepatitis C, treated with pegylated interferon and ribavirin, who developed multiple cotton-wool spots in the retina of both eyes. The ocular findings were identified as pegylated interferon associated retinopathy, and in one case spontaneously resolved and in the other after the treatment was withdrawn.

Discussion: Interferon is an immunomodulating cytokine used as a first line treatment of hepatitis C. Numerous adverse effects have been reported, but ocular ones are less known. We believe that periodic ophthalmological examinations during this treatment are required in order to detect these complications, which can be serious.

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Retinopatía asociada a interferón pegilado y ribavirina en pacientes con hepatitis C

Resumen
Caso clínico: Se describen dos pacientes portadores de hepatitis C y tratados con interferón pegilado y ribavirina que desarrollaron múltiples exudados algodonosos en la retina de ambos ojos. El cuadro oftalmológico fue etiquetado de retinopatía asociada a interferón pegilado y en un caso cedió espontáneamente y en otro tras su retirada.

Discusión: El interferón es una citocina inmunomoduladora utilizada como primera línea de tratamiento de la hepatitis C. Numerosos efectos adversos han sido descritos, pero los oculares son menos conocidos. Consideramos necesario el seguimiento oftalmológico sistemático durante el tratamiento con interferón por la posibilidad de detectar dichas complicaciones, algunas graves.

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Introduction

Interferon (IFN) is an immuno-modulating cytokine having antiviral activity as well as antiangiogenic and antiproliferative properties. In addition, IFN alpha derivatives (peginterferon α-2a and α-2b) conjugated with polyethylene glycol (pegylated) increase their persistence in blood, thus requiring lower doses. Peginterferons constitute the treatment of choice for chronic hepatitis C combined with ribavirin (a synthetic nucleotide analogous to guanidin, with antiretroviral properties and immuno-regulating activity). The adverse effects derived from their use comprise ocular complications, mainly in the retina.

Clinical case

Case 1

A sixty-five year old female diagnosed of chronic hepatitis due to virus C genotype 1 with a viral charge of 4,300,000 copies/ml and arterial hypertension (HT). Treatment was established with pegylated IFNα-2b (180 μg/week) together with ribavirin (800 mg/day). Considering the HT history of the patient, an ophthalmological exploration was requested and carried out 15 days after beginning the treatment. Visual acuity (VA) was of 10/10 with correction in both eyes and in the ocular fundus (OF). The papilla and maculae were normal. Arterial sclerosis and venous tortuosity with pathological arterial-venous crossings.

After 3 months and while being free of symptoms the patient was reassessed. She exhibited the same VA but the OF revealed multiple cotton-like exudates in arches and posterior pole, respecting the macular area, as well as some microhemorrhages and microaneurysms. The condition was labeled as IFN retinopathy (Fig. 1) and it was decided to continue the treatment due to the absence of repercussion in the VA, the high viral charge and the possibility of a close follow-up.

The virological response was late in week 24 and for this reason the treatment was extended 72 weeks with good response. During the treatment neutropenia appeared, reaching a maximum of 600/mm³ and anemia with a maximum level of 8.5 g/dl de hemoglobin, although the IFN dose was not modified.

In subsequent controls, the patient always maintained the same VA, the exudates gradually reabsorbed with only one micro-hemorrhage remaining in the superior temporal vascular arch of the right eye (Figs. 2 and 3).

Case 2

A male, 37, former parenterally administered drug addict, diagnosed with chronic hepatitis due to virus C genotype 4 with low viral charge (75,754 UI/ml). Treatment was established with pegylated IFNα-2b (100 μg/week) and ribavirin (1 g/day).
Two months after beginning the treatment the patient visited the practice referring blurred vision and spots in the visual field dating back about 10 days. The ophthalmological exploration revealed a VA of 0.8 with correction in both eyes and multiple cotton-like exudates in the posterior pole. The diagnostic was retinopathy due to IFN and the treatment was suspended. In successive controls the condition gradually improved and 3 months later the patient exhibited a VA of 10/10 in both eyes and the OF only revealed one cotton-like exudate in reabsorption below the left fovea.

Discussion

The use of IFN involves several adverse effects, the most common being a pseudo-feverish condition although ophthalmological alterations can also appear and, due to the involvement of the central nervous system, hematopoetic, gastrointestinal, urinary, cardiovascular, muscle-skeleton and endocrine alterations may also emerge.

The most typical ocular complication is ischemic retinopathy with cotton-like exudates, retinal hemorrhages in the posterior pole and above all around the optic disc, as well as microaneurysms. These conditions could be accompanied by hyperemia and macular edema. In addition, the literature describes sub-conjunctival hemorrhage, choroidal neovascularization, vessel spasms, neovascular glaucoma, retinal vascular occlusions, ischemic optic neuropathy and Vogt-Koyanagi-Harada like.¹

Retinopathy, secondary to the use of IFN, is known since 1990, with a prevalence which varies according to each series between 18% and 86%,² although with pegylated IFN prevalence seems to be lower, of 16–19%.³ There is a relationship between the dosage and duration of the treatment. It rarely appears before between 8 and 12 weeks after beginning the therapy. It is normally asymptomatic and is associated to good VA. It could disappear spontaneously in the course of the treatment or rapidly if IFN is suspended, in the majority of cases without visual sequelae.² Suspending the treatment is advisable with reduced VA and the appearance of intense retinal ischemia.¹ Typically, the pathogeny has been attributed to the deposit of immunocomplexes in retinal vessels and also to the fact that IFN increases the adherence of leukocytes to the vascular endothelium.²⁴ Recently, Nagooka et al.⁵ assessed the retinal vascular function, finding endothelial dysfunction in these patients. In addition, both the hepatitis C virus and IFN induce the formation of a large variety of thrombogenic Ac.⁴

In addition to causing tearing and conjunctivitis, ribavirin could contribute to retinopathy due to its synergic action in combination with IFN.⁴ Diabetes, HT and anemia have been described as risk factors³ for the development and progression of retinopathy and for this reason these patients must be followed up very closely.

Even though some publications question the need of routine ophthalmological assessments² for asymptomatic patients in treatment with IFN, the literature describes cases of ocular complications with severe visual loss.¹ VA and OF assessments should be made before beginning treatment and at 3-month intervals. If retinopathy is determined, monthly or quarterly checkups should be made up to full resolution.

Conflict of interests

None of the authors have declared any conflict of interests.

References