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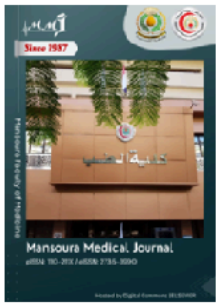

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Sahar El-Tarshouby

Mansoura Ophthalmic Center, Faculty of medicine

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By

Sahar El-Tarshouby, MD*

From

Mansoura Ophthalmic Center, Faculty of medicine

ABSTRACT

Egypt has the highest prevalence of hepatitis C in the world. Retinopathy is a well recognized side effect of interferon therapy. The aim of this study was to document the incidence of retinopathy in patients treated with pegylated interferon and ribavirin for hepatitis C and to assess the need to screen for retinal complications.

Patients and Methods :

Patients started on treatment were included in this study. The past medical and ocular history, visual symptoms and results of full ophthalmological assessment performed 2 and 4 months after starting treatment were noted. Any patient with retinal changes was followed up at 2 month intervals for 6 months. Flourescein angiography and OCT were done to document and follow up of any abnormality when appropriate.

Results :

Of 25 patients 6 had evidence of retinopathy including cotton wool spots and haemorrhages. Two of these showed fine mottling of the retinal pigment epithelium in the foveal region of both eyes. Flourescein angiography showed retinal pigment epithelium(RPE) atrophy in both patients with foveal thinning on OCT.

Four cases showed resolution of the retinopathy while the patients completed their course of treatment.

Conclusion :

Serial dilated fundus examinations for patients on interferon therapy with ribavirin is justified.

The world health organization has declared hepatitis C a global heath problem, with approximately 3% of the world's population infected with the hepatitis C virus (HCV). There are more than 170 million HCV chronic carriers at risk of developing liver cirrhosis and/or hepatocellular carcinoma[1] .

Egypt has the highest prevalence of hepatitis C virus in the world, ranging from 6 to 28% with an average of approximately 13.8% in the general population. These estimates lead roughly to 9 million persons who had acquired HCV infection.[2]

An ischemic retinopathy is commonly seen in patients infected with HCV. This may be the result of therapy with interferon or a manifestation of a systemic vasculitis induced by the infection itself[3].

Alpha interferon (Alpha-IFN) is widely used in the treatment of viral hepatitis, either alone or combined with other antiviral therapies such as ribavirin. Ophthalmologic side effects were first reported in 1990 by Ibeke et al[4] in the form of retinopathy. IFN-induced retinopathy was thereafter described as an association of cotton-wool spots, retinal hemorrhage and microaneurysms[5].

Recently, a long acting form of interferon alfa has been developed known as pegylated interferon. This drug has slower absorption, a reduced volume of distribution and lower elimination rates as well as more sustained virological response[5].

The local treatment protocol in our area is pegylated interferon in combination with ribavirin.

The aim of this study was to document the incidence of retinopathy in patients treated with pegylated interferon and ribavirin for hepatitis C and to assess the need to screen for retinal complications.

PATIENTS AND METHODS

This study included patients with serologically proven chronic hepatitis C. Patients started on combination treatment with pegylated interferon and ribavirin were referred for ophthalmic examination. Patients with a dense cataract, glaucoma, retinopa-

thies or any other ocular abnormality were excluded from this study. Also patients with poorly controlled diabetes and hypertension, autoimmune diseases and patients with cardiovascular diseases were excluded from this study. Ocular and past medical histories were taken. Full ocular examination was performed for each patient including best corrected visual acuity assessment, slit lamp examination, applanation tonometry and dilated fundus examination.

Fundus photography and fluorescin angiography were done using Topcon TRC fundus camera with IMAGEnet 2000(Topcon) to document and access any abnormal findings when appropriate.

Some retinopathy patients underwent OCT scan of the macula using OCT unit (Zeiss-Hymphery). OCT was performed after appearance of retinopathy and every 2 months for follow up of macular thickness.

Patients were examined pretreatment and every 2 months after starting their treatment till the end of therapy. Patients with new visual symptoms were examined sooner.

Treatment Protocol :

All patients were treated with weekly intramuscular injection of Peginterferon alfa-2a (Pegasys-Roche) 180μgm for 24 weeks, in combination with oral ribavirin which was administered twice daily. The total daily dose of ribavirin was 600mg for patients whose weight was less than 60 Kg and 800 mg for those whose weight more than 60 Kg.

RESULTS

Between January 2006 and January 2007, 30 patients were examined, All were about to start treatment with pegylated interferon alfa and ribavirin according to the local protocol. Three patients were excluded because treatment was withdrawn within the first weeks of therapy and 2 patients were excluded because of noncompliance with the ophthalmologic surveillance. Finally 25 patients were included in the present study. They were 13 men and 12 females with age ranging from 32 to 63 years (42±10ys).

Ophthalmologic examinations be-

fore treatment :

No abnormalities were found on slit lamp biomicroscopy and fundoscopic examinations.

Ophthalmologic examinations during treatment :

During treatment signs of retinopathy were found on fundoscopic examinations in 6 patients (24%) consisting of Cotton wool spots and/or haemorrhages. The retinopathy occurred by 8-12 weeks after initiation of therapy.

This was bilateral in 5 patients and unilateral in one. No microaneurysms occurred.

Diabetes mellitus was present in 5 of 25 patients examined, all of them had INF retinopathy. Systemic hypertension was present in 4 patient but only one had retinopathy.

Four patients (16%) of the 6 had transient retinopathy in the form of few scattered cotton wool spots and or haemorrhage in the posterior pole. They continued treatment in the presence of retinopathy and the retinopathy disappeared in all 4 cases in 4-8 weeks period. Non of these patients had macular oedema, disc changes or visual acuity disturbances.

The other 2 cases had diminution of visual acuity, they showed cotton wool spots with fine mottling of retinal pigment epithelium in the foveal region of both eyes. Fig.(1&2). Flouresscein angiography and OCT were done for the 2 cases. Stoppage of interferon therapy for both cases, showed no improvement of visual acuity(less than 6/24) and absorption of the cotton wool spots with permanent RPE atrophic changes in the foveal region.

Fig.(1) showed fundus photography after two months of start of INF. Floureseine angiography showed blocked fluorescence corresponding to the cotton wool spot seen in fundus of the right eye. The left eye showed starting RPE atrophic changes in the fovea.

Fig.(2) Showed Fundus photography of the same patient two months later. Both showed fine mottling of the retinal pigment epithelium in the foveal region. Early phase angiography

shows early hyperfluorescence in the temporal part of the foveal avascular zone.

The hyperfluorescene in both eyes "more obvious in the left eye" remains the same site, size and shape all over the angiogram but fades in intensity in the late phase of the angiogram indicating window defect caused by atrophy of the retinal pigment epithelium with intact choriocapillaris layer.

OCT was done for the two patients demonstrated marked thinning of the macular (foveal thickness less than 70 ◦in the four eyes) that was not improved after stoppage of INF. Fig.(3)

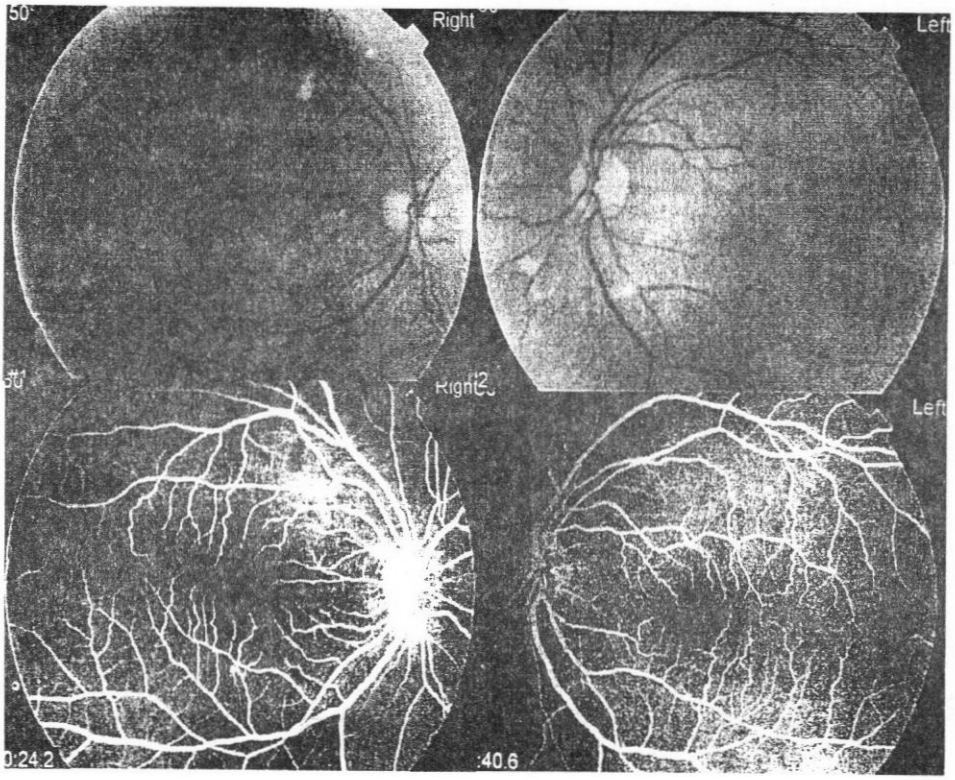

Fig. (1) showing both eyes of a fifty-four old female on interferon therapy. Both eyes show cotton-wool spots (the right eye in the upper temporal quadrant and the left eye shows multiple cotton wool spots all around the optic disc most marked inferiorly).

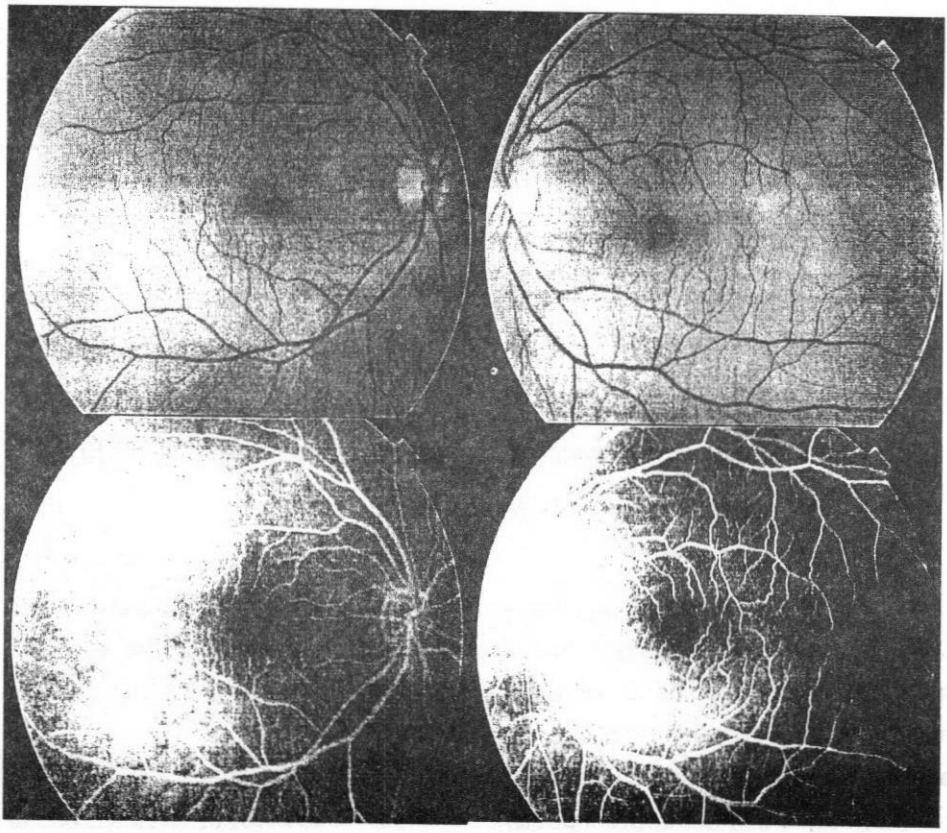

Fig. (2) The same patient who developed mottling of the retinal pigment epithelium in foveal region with flourescein angiography four months after start of therapy

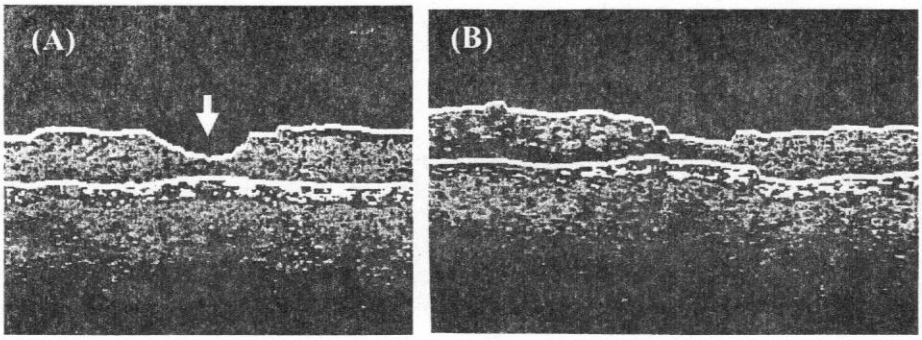

Fig. (3): OCT follow up of the patient in fig. (1)

(A) OCT line scan through the fovea showing central foveal thickness measuring 60 μ (Arrow) after 2 months of start of INF therapy. BCVA is 6/60

(B) 4 months after stoppage of IFN no change of the central foveal thickness (55μ). BCVA is still 6/60

DISCUSSION

Ocular side effects are well known complications of interferon and ribavirin therapy for hepatitis C with the most common of these being ischaemic retinopathy characterized by haemorrhages and cotton wool spots. However, various atypical interferon-associated ocular complications have been reported including oculomotor nerve paralysis, optic disc edema, subconjunctival, preretinal and vitreous hemorrhage and retinal vein occlusion. Severe visual losses due to atypical ocular complications have been reported[6], but they were not reported in this study.

The ocular side effects of ribavirin included a mild watery eye and conjunctivitis[7] which were not seen in this study.

The incidence of serious ocular pathology associated with treatment with anti-HCV therapy may be very high and is likely associated with peg-IFN alpha[8].

Previous case series have commented on the time of onset of retinopathy in relation to the start of treatment. Most reported onset of the

retinopathy in the first 8-12weeks following the start of treatment[6], the same was in this study.

Pathogenesis of IFN-associated retinopathy is unknown although some investigators have suggested deposition of immune complexes in the retinal vasculature and leucocyte infiltration that cause retinal ischaemia with resultant capillary non perfusion and nerve layer infarctions as reported in studies using flouresein angiography, that showed poorly perfused retinal areas in patients with IFN retinopathy[9].

Reported risk factors for interferon retinopathy include hypertension diabetes mellitus, high interferon doses and pegylated interferon[10]. In this study all diabetic patients showed interferon transient retinopathy. Kawano et al found 80% of hypertensive patients treated with interferon developed retinopathy[11], but in this study only one hypertensive patient showed INF retinopathy. This study did not demonstrate this association in hypertensive patients as the number of hypertensive patients in this series was too small to derive any conclusions.

In this study the incidence of interferon related retinopathy is 24%. The reported incidence in the literature varies from 18-86%[7]. This variability could be related to several factors including the type and dose of interferon, associated systemic conditions frequency of eye examination and the presence of underlying retinal vascular disease.

Jain et al(2001)[7] suggested that atypical retinal lesions with interferon may represent incidence rather than a true association with interferon use, but this study did not agree with them as there was no previous retinopathy and the appearance of foveal mottling of both eyes in two patients shortly after initiation of systemic interferon, it is likely that interferon is the major determinant in the development of these changes.

Tokai et al suggested that interferon-associated retinopathy progressed and the visual acuity decreased even after termination of interferon therapy [12].

Savant and Gillow (2002) reported that INf-induced retinopathy is not al-

ways self limiting and Benign and they recommended ophthalmic examination of patients pretreatment to look for pre-existing retinopathy and subsequent examinations while on treatment. If severe ocular toxicity occurs, INF therapy should be discontinued[13]. But the study of Cuthberston et al[14] for screening for IFN retinopathy revealed that routine screening is not justified as that retinopathy is temporary and asymptomatic, but jain et al[7] recommended ophthalmic follow up of patients only who are symptomatic.

Schulman et al[15] experienced a rate of 69% retinal ischeamic changes that require ocular monitoring and they emphasized that the symptomatic permanent visual loss experienced by patients along with the need to discontinue therapy indicate the need for careful regular monitoring of patients receiving interferon for hepatitis C.

Conclusion :

Retinopathy during IFN therapy is generally transient resolving spontaneously, stoppage of treatment is seldom required. However the long term consequences of this retinopathy are unknown. Patients with retinopathy should be closely observed, as this retinopathy is associated mostly with retinal capillary non perfusion which can lead to permanent visual disability, patients should be followed by serial dilated fundus examination, so screening is justified.

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