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Incidence and risk factors of retinopathy in Egyptian patients with chronic hepatitis C virus treated with pegylated interferon plus ribavirin

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SUMMARY

Background: Data are scarce on ocular complications in Egyptian patients with chronic hepatitis C treated with pegylated interferon and ribavirin therapy. The aim of this study was to investigate the development of retinal lesions induced by interferon therapy for chronic hepatitis C.
Methods: We prospectively analyzed 84 patients with chronic hepatitis C (total 168 eyes), who underwent combination pegylated interferon and ribavirin therapy for 48 weeks. Visual acuity, color vision, and visual field were measured, and a fundus assessment was made at baseline, at 12, 24, and 48 weeks post the commencement of treatment, and at follow-up, 1 month after treatment. Past medical and ocular histories, visual symptoms, and the results of a full ophthalmologic assessment were recorded for each patient.
Results: Twenty-two patients (26%) developed retinopathy. Retinal hemorrhage was observed in eight patients. Four patients complained of visual disturbance. Retinopathy disappeared in 16 patients (73%) despite the continuation of combination therapy. However, retinopathy persisted in six patients with retinal hemorrhage and three of them stopped treatment. A comparison of the clinical backgrounds between the patients with and without retinopathy showed no significant differences with regard to gender, HCV RNA level, white blood cell count, platelet count, hemoglobin level, or fibrosis score. However patients with retinopathy were of older age, had a higher prevalence of hypertension and diabetes mellitus, and more often did not respond to therapy. Multiple logistic regression analysis revealed that hypertension and diabetes were factors predicting retinopathy.
Conclusion: Retinopathy associated with interferon α-2a and ribavirin combination therapy tends to develop in patients of older age with hypertension and diabetes.

1. Introduction

The primary aim of antiviral therapy in patients with chronic hepatitis C is a sustained virological response (SVR), defined as undetectable serum hepatitis C virus (HCV) RNA by a sensitive molecular assay at 24 weeks after the end of treatment. Combination therapy with pegylated interferon (peginterferon) and ribavirin is currently recognized as the standard treatment of chronic hepatitis C, resulting in an SVR rate of 40–50% in patients infected with HCV genotypes 1 and 4, and around 80% in those infected with HCV genotypes 2 and 3.[1–3]

Various adverse effects have been reported due to the use of interferon. An influenza-like syndrome, characterized by fever, chills, myalgias, arthralgias, and headache, is the most common adverse effect. Toxicities of the central nervous, hematopoietic, gastrointestinal, urinary, cardiovascular, musculoskeletal, and endocrine systems have also been described. However, ocular toxicity was not reported before the use of interferon for chronic hepatitis.[4] The association of HCV infection and retinopathy has been described in the literature. The reported ophthalmic manifestations of HCV infection are keratoconjunctivitis sicca, ischemic retinopathy, macular edema, and ischemic neuropathy.[5–7]

Following the introduction of interferon for the treatment of hepatitis, retinal complications have been reported with a higher prevalence in patients with diabetes. Typical ocular lesions include cotton-wool spots and retinal hemorrhages at the posterior fundus, particularly around the optic disc. Cotton-wool spots and retinal hemorrhages may occur alone or together. Retinal hemorrhages appear as superficial linear and patchy forms, or as white-centered bleeding. The retinopathy may develop unilaterally or bilaterally. Blocking of background fluorescence by retinal hemorrhages and non-perfused areas at the cotton-wool spots can be seen by fluorescein angiography.[8]

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Subsequently, several papers have shown that a substantial proportion of patients undergoing interferon monotherapy develop retinopathy.[9–11] However, the prevalence of retinopathy is variable, which is presumably attributed to the difference in the treatment regimen and/or background of patients.

In interferon–ribavirin combination therapy, diabetes, hypertension, and response to treatment[12,13] have been considered possible risk factors. However, the results are not conclusive because of the small number of patients examined, as they have been from case reports and case series.[14–18] The aim of this study was to investigate the development of retinal lesions induced by interferon therapy for chronic hepatitis C and to retrospectively analyze the risk factors.

2. Materials and methods

This study was undertaken at the virology and ophthalmology clinics of Minia University Hospital, Minia, Egypt from January 2009 to January 2011. Patients with histologically confirmed chronic hepatitis C by liver biopsy and who fulfilled the criteria for treatment were enrolled in this study. Liver biopsy results and the METAVIR score were recorded for every patient. All patients were treated weekly with 180 mg subcutaneous peginterferon α-2a and oral ribavirin at a total daily dose of 1000–1400 mg according to body weight.

Serum HCV RNA was detected by qualitative reverse-transcription polymerase chain reaction (RT-PCR; Amplicor HCV, Roche Diagnostics). The serum HCV load was determined by quantitative RT-PCR (Amplicor HCV Monitor Test, version 2.0, Roche Diagnostics). HCV RNA genotyping was performed using a second-generation line probe assay (LiPA; Innogenetics, Brussels, Belgium).

The end-of-treatment response (ETR) was assessed by qualitative PCR assay. ETR was defined as an undetectable serum HCV RNA level at the end of treatment. A non-responder was defined by the presence of viremia (less than 2 log reduction) at 12 weeks, or 24 weeks, or at the end of therapy.

3. Ophthalmologic examination

All patients were examined by an expert ophthalmologist at our hospital. The ophthalmologist was not blinded to patient baseline clinical data (e.g., diabetes, hypertension). The optic fundi were examined before therapy was started, at 12, 24, and 48 weeks after the start of treatment, and at 4 weeks after the end of treatment. Patients with a pretreatment abnormal fundus examination were excluded from the study. The ophthalmologic examination included: visual acuity assessment using Landolt C rings optotype, fundus examination using an indirect ophthalmoscope, and pupillary reaction examination (for direct and indirect light reflex, and swinging flash light test). When retinal abnormalities were detected, colored fundus photographs were obtained and fluorescence angiography carried out for documentation and comparison. Data recorded included visual complaints, visual acuity, pupillary reactions, and retinal findings.

The study was approved by the ethics committee of our centers and was carried out in accordance with the Declaration of Helsinki and the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients provided written informed consent before enrollment.

4. Statistical analysis

Data entry and analysis were all done with an IBM compatible computer using SPSS software version 13 (SPSS, Chicago, IL, USA). Results were expressed as mean ± standard deviation (SD), median (interquartile range), or number (%). Comparisons between the mean and median values were done using the unpaired *t*-test and Mann–Whitney test. Comparisons between categorical data (*n* (%)) were done using the Chi-square test. Logistic regression analysis was performed to determine the risk factors. A *p*-value of ≤ 0.05 was considered significant; <0.01 was considered highly significant.

5. Results

Of 560 patients with chronic hepatitis C attending our clinic, 240 were treated with peginterferon–ribavirin therapy. One hundred and sixteen consecutive patients fulfilled the criteria for our study, but only 84 patients agreed to participate. Sixty-one of these patients were males and 23 were females; their median age was 43.4 years (range 24–55 years). All patients had HCV genotype 4.

At the end of peginterferon–ribavirin combination therapy, 59 (70%) patients had an ETR and 25 (30%) patients were non-responders. Twenty-two out of 84 patients (26%) developed retinopathy at various time-points. The retinopathy findings were predominantly cotton-wool spots, followed by retinal hemorrhage (Figure 1). On fluorescence angiography, all patients with cotton-wool spots showed areas of capillary non-perfusion, signifying retinal ischemia, and areas of blocked fluorescence in the case of retinal hemorrhage.

Other ocular manifestations included anterior ischemic optic neuropathy (AION) in two cases, optic neuritis in one patient, abnormal color vision in six patients, diminished visual acuity in four patients, and abnormal pupillary reaction in three patients (Figure 1).

We compared the characteristics of patients who developed retinopathy and those who did not. There were no statistically significant differences between the two groups with regard to gender, HCV RNA level, white blood cell count, platelet count, hemoglobin level, or fibrosis score before treatment (Table 1). The patients with retinopathy were significantly older. Hypertension, diabetes, and non-response to therapy were more prevalent in patients who developed retinopathy. Retinal hemorrhages were not more common in those with METAVIR scores of 3–4 or with underlying coagulopathies.

Logistic regression analysis of factors affecting retinopathy was also carried out. Hypertension and diabetes were found to be factors predicting retinopathy (Table 2).

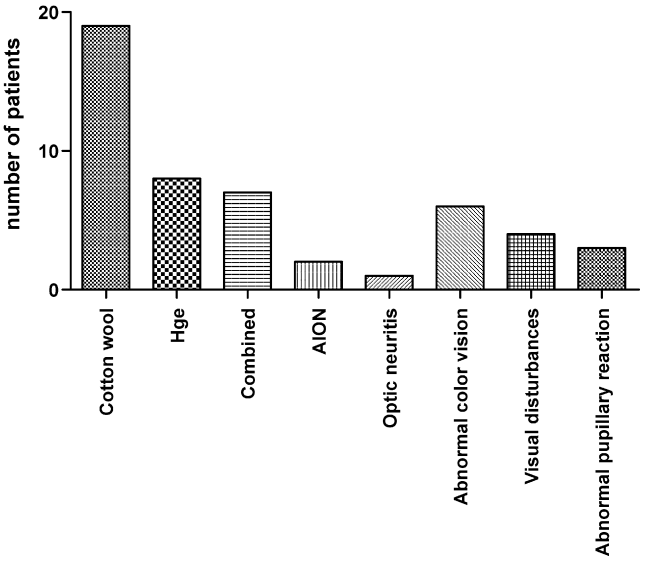

Figure 1. Ophthalmologic manifestations in chronic hepatitis C patients treated with peginterferon–ribavirin therapy (Combined: cotton-wool spots and hemorrhage; Hge, retinal hemorrhage; AION, anterior ischemic optic neuropathy). Data are presented as the number of patients.

Table 1
Characteristics of patients with and without retinopathy during peginterferon–ribavirin combination therapy

	Retinopathy ($n=22$)	No retinopathy ($n=62$)	p-Value
Age (years), mean ± SD	48.8 ± 6.2	41.7 ± 8.2	<0.05
Sex female, n (%)	7 (32%)	16 (26%)	0.59
ALT level, median (IQR)	34 (5–120)	52 (12–95)	0.1196
HCV RNA (copies/ml), median (IQR)	35 490 (11 760–300 000)	34 640 (5500–300 000)	0.123
Fibrosis METAVIR score, n (%)			
F1–F2	15 (68%)	42 (68%)	1.00
F3–F4	7 (32%)	20 (32%)	
Hemoglobin (mg/dl), mean ± SD	11.7 ± 1.3	11.3 ± 1.6	0.15
Neutrophil count (cells × 10^9/l), median (IQR)	2.55 (1.10–5.70)	2.30 (1.30–19.00)	0.82
Platelet count (cells × 10^9/l), median (IQR)	110.50 (67.00–180.00)	115.00 (60.00–1100.00)	0.76
Diabetes mellitus, n (%)	13 (59%)	3 (5%)	<0.0001
Hypertension, n (%)	9 (41%)	3 (5%)	0.0002
Response to treatment, n (%)			
Responder	9 (59%)	50 (81%)	0.0002
Non-responder	13 (41%)	12 (19%)	

SD, standard deviation; ALT, alanine aminotransferase; IQR, interquartile range; HCV, hepatitis C virus.

Table 2
Logistic regression analysis of factors associated with retinopathy

Variable	OR	95% CI	p-Value
Age	1.65	0.84–3.23	0.14
Sex	0.47	0.006–34.9	0.73
Hemoglobin	192.89	0.0–1.1	0.89
White blood cell count	0.14	0.0–57.5	0.52
ALT	0.459	0.3–1.5	0.14
Platelets	208.4	0.1–1.9	0.16
Viral load	0.214	0.12–1.4	0.1
Liver fibrosis	0.26	0.008–8.7	0.45
Diabetes mellitus	0.002	0.0–1.4	0.05
Hypertension	3.6	4–6.6	0.001
Response to therapy	0.2	0.03–2.1	0.09

OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase.

Follow-up of patients with retinopathy showed that 16 patients improved on ophthalmologic treatment. Six patients continued to have retinopathy while on ophthalmologic treatment, and three of these patients discontinued interferon therapy at their request (Table 3).

Table 4 shows the clinical course of the 22 patients with retinopathy during peginterferon–ribavirin therapy. The retinopathy findings were predominantly cotton-wool spots, followed by retinal hemorrhage.

Regarding color vision abnormalities, six patients were recorded to have abnormal color vision using pseudoisochromatic plates (Ishihara plates, n = 12): two patients with mild impairment (10/12; 11/12), two patients with moderate impairment (7/12; 8/12), and the last two patients had anterior ischemic optic neuropathy with severe impairment (2/12; 3/12).

The abnormal pupillary reactions included a partial afferent pupillary defect in which there is a paradoxical pupillary reaction, as the abnormal pupil shows initial dilatation instead of constriction on exposure to pen torch light by swinging reflex, and this abnormal reaction signifies optic nerve abnormality, as in the case of anterior ischemic optic neuropathy detected in two cases in this study (Figure 2).

6. Discussion

It has been hypothesized that interferon-α therapy may cause deposition of immune complexes in the retinal vasculature. Leukocyte infiltration with subsequent retinal ischemia could then lead to capillary non-perfusion and thus cotton-wool spot formation.[19] Cotton-wool spots are not generally the cause of visual compromise, but they are a significant finding because they can be indicative of an underlying vascular disease, such as diabetes mellitus or hypertension. Retinal hemorrhages do not usually cause significant visual disturbance, but occasionally acuity may be affected because of a macular hemorrhage. There is evidence that interferon inhibits the proliferation and migration of vascular endothelial cells in vitro, and it has demonstrated the ability to inhibit experimental intraocular neovascularization.[20–22]

The frequency of retinopathy associated with peginterferon–ribavirin combination therapy in the present study was 26%. The frequencies reported in other studies range from 16% to 64%.[12,13,22] It appears that there may be geographic differences in the incidence of interferon-associated retinopathy. The frequencies noted in recent reports from the UK have been as low as 0% (in a prospective study[23]) and 3.8% (in a retrospective study[24]). In the first study 42 men and 10 women were followed. No patients reported any subjective visual symptoms and no patient developed optic disc changes or permanent fundus changes over the follow-up period. In the second study, of 183 patients, 29 (16%) had diabetes and 85 (46%) had hypertension. Seven (3.8%) had retinal changes on follow-up, and treatment was discontinued in three (1.6%). Of the seven with ocular changes, two had hypertension and one had both hypertension and diabetes. In Southeast Asia, the frequencies of retinopathy have been reported as 34.4%[25] and 100%.[26] In the first study 11 of 32 patients (34.4%) developed retinopathy. Cotton-wool spots were found in six patients, retinal hemorrhages in four, and branch retinal vein occlusion in one (one eye). Hypertension was found to be the most significant risk factor for developing retinopathy. In the second study, all of the patients (six patients) developed a soft retinal exudate and five developed retinal blot hemorrhage.

Table 3
Follow-up of patients with retinopathy, from onset until the follow-up after treatment

	Baseline[a]	At 12 weeks	At 24 weeks	At 48 weeks	At follow-up
Number of patients with retinopathy	0	8	7	7	-
Improved[b]	0	7	4	5	16
Continued[c]	0	1	3	2	6

[a] Baseline: before beginning interferon.
[b] Improved with treatment and follow-up by an ophthalmologist.
[c] Continued: persistent retinopathy after the end of treatment.

Table 4
Clinical course of each patient with retinopathy during peginterferon–ribavirin therapy

Patient	Age, years	Sex	Underlying disease		Response to therapy	Ocular manifestations after treatment (time of discovery)	Course
			Hypertension	Diabetes mellitus			
1	42	M	+	+	NR	Cotton-wool spots and diminished visual acuity (24 weeks)	Persistence of ocular findings
2	55	M	–	+	R	Cotton-wool spots (48 weeks)	Recovery of ocular manifestations
3	32	F	–	–	NR	Cotton-wool spots and retinal hemorrhage; abnormal pupillary reaction (12 weeks)	Recovery of ocular manifestations
4	54	M	+	+	R	Cotton-wool spots (12 weeks)	Recovery of ocular manifestations
5	49	F	–	+	NR	Optic neuritis and retinal hemorrhage (12 weeks)	Severe visual impairment
6	42	M	+	+	NR	Cotton-wool spots (24 weeks)	Recovery of ocular manifestations
7	46	M	+	+	NR	Cotton-wool spots (24 weeks)	Recovery of ocular manifestations
8	51	M	–	+	R	Cotton-wool spots and abnormal color vision (48 weeks)	Recovery of ocular manifestations
9	53	M	–	+	NR	Cotton-wool spots (12 weeks)	Recovery of ocular manifestations
10	51	M	–	–	R	Cotton-wool spots and diminished visual acuity (24 weeks)	Recovery of ocular manifestations
11	51	M	+	+	R	Cotton-wool spot and abnormal color vision (24 weeks)	Recovery of ocular manifestations
12	54	M	+	+	NR	Cotton-wool spot and retinal hemorrhage (12 weeks)	Recovery of ocular manifestations
13	55	M	–	–	NR	Cotton-wool spots and diminished visual acuity (48 weeks)	Recovery of ocular manifestations
14	55	F	+	–	R	Cotton-wool spots and abnormal pupillary reaction (48 weeks)	Recovery of ocular manifestations
15	47	F	–	+	NR	Retinal hemorrhage and AION (12 weeks)	Recovery of ocular manifestations
16	52	M	+	–	R	Cotton-wool spots (12 weeks)	Recovery of ocular manifestations
17	47	F	–	+	R	Cotton-wool spots (12 weeks)	Recovery of ocular manifestations
18	47	M	–	–	NR	Retinal hemorrhage and abnormal pupillary reaction (48 weeks)	Minimal visual impairment
19	49	M	–	–	R	Cotton-wool spots and abnormal color vision (24 weeks)	Minimal visual impairment
20	38	F	–	–	NR	Retinal hemorrhage and diminished visual acuity (48 weeks)	Mild impairment of the visual acuity
21	46	F	–	+	NR	Cotton-wool spots and retinal hemorrhage (48 weeks)	Recovery of ocular manifestations
22	39	M	+	–	NR	Retinal hemorrhage and AION (24 weeks)	Significant visual loss

M, male; F, female; NR, non-responder; R, responder; AION, anterior ischemic optic neuropathy.

Figure 2. (A) Colored fundus photo showing areas of cotton-wool spots and blot dot hemorrhage at the posterior pole. (B) Fluorescence angiography showing areas of blocked fluorescence by hemorrhages (gray arrow), and areas of capillary drop-out signifying retinal ischemia (white arrows).

In this study, hypertension, diabetes, and older age were found to be significant risk factors for peginterferon–ribavirin-induced retinopathy. The common mechanism is the vascular effect. Chronic hypertension predisposes patients to interferon-induced retinopathy through thickening of the walls of the arteries and small arterioles.[27] The fact that hypertensive retinopathy induces the formation of flame-shaped hemorrhages and white cotton-wool spots, which are also seen in interferon-induced retinopathy, implies that systemic hypertension and interferon-induced retinopathy may be related to each other. Although diabetes mellitus has been shown to be associated with retinopathy in some studies,[10,11] other studies have reported no association between diabetes and interferon–ribavirin-induced retinopathy.[13,28] In those studies the number of patients with diabetes mellitus was very low.

Non-response to interferon therapy was more prevalent in patients who developed retinopathy. We have no explanation for this, but the presence of a co-morbidity such as diabetes mellitus in patients with retinopathies could be a risk factor for non-response. This issue should be clarified in further studies.

Most of the patients in this study were asymptomatic, so there was no need to discontinue interferon–ribavirin therapy except in three patients. This is in accordance with other studies that have stated that in spite of the presence of retinopathy, the full course of treatment should be completed.[8,12,18]

The fact that retinopathy occurred more frequently in patients with hypertension, diabetes mellitus, and of older age suggests that these patients should be carefully monitored. With periodic

examination of the optic fundi, major retinal complications may be prevented or at least detected earlier. Therefore, patients who undergo interferon–ribavirin combination therapy, particularly those with hypertension, diabetes, or of older age should undergo periodic examination of the optic fundi.

To conclude, the incidence of retinopathy associated with combination pegylated interferon plus ribavirin therapy in our locality tends to be higher than that reported in the USA and Europe and lower than that reported in Asia. Hypertension, diabetes, and older age put the patient at higher risk of retinopathy induced by antiviral therapy. We recommend careful ophthalmologic monitoring in these patients.

Conflict of interest: No conflict of interest to declare.

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