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CHRONIC HEPATITIS C;

THYROID DYSFUNCTION IN CHRONIC HEPATITIS C PATIENTS TREATED WITH PEG INTERFERON AND RIBAVIRIN

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ABSTRACT… Background: Pegylated interferon (PEG-IFN) plus ribavirin combination was the main treatment for chronic hepatitis C (CHC) patients in Pakistan till 2016. An important side effect of this combination was thyroid dysfunction (TD). **Objectives:** To evaluate thyroid function abnormalities in Chronic Hepatitis C patients treated with PEG-IFN and ribavirin. **Study Design:** Descriptive study. **Setting:** Outpatient Department of Gastroenterology and Hepatology, Nishtar Hospital Multan. **Period:** January to September 2016. **Methods:** Using non-probability consecutive sampling. There were 337 CHC patients enrolled in the study who fulfilled the inclusion criteria. Patients were given PEG-IFN plus ribavirin combination therapy and at 12 weeks their serum Thyroid Stimulating Hormone (TSH) levels were measured to identify any TD. Data was entered and analyzed by computer program SPSS-17. **Results:** Of these 337 cases, 211 (62.6%) were male patients while 126 (37.4%) were female patients. Mean age of our cases was noted to be 30.92 ± 5.84 years. Mean disease duration was 16.19 ± 6.42 months. In our study 98 patients (29.1%) had genotype 2 while 239 (70.9%) had genotype 3. TD was seen in 28 (8.3%) patients, 70% of whom were females. Equal number of cases of Hypothyroidism and hyperthyroidism were seen (14 each). Hypothyroidism was significantly associated with relatively older age group patients and genotype 3 (p value <0.05). A statistically significant association ($p<0.05$) was found between hyperthyroidism and genotype 3, female gender and younger patients. **Conclusion:** PEG-IFN plus ribavirin combination therapy induces TD among patients with CHC with equal incidence of hypothyroidism and hyperthyroidism.

Key words: Pegylated Interferon (PEG-IFN), Ribavirin, Chronic Hepatitis C (CHC), Thyroid Dysfunction (TD).

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INTRODUCTION

Chronic Hepatitis C is a major global health problem. WHO states that there are 71 million people with chronic hepatitis C infection (CHC).[1] Both acute and chronic hepatitis can occur as a result of hepatitis C virus (HCV). The incidence of acute HCV infection has sharply decreased in the United States during the past decade. However, its prevalence remains high. This is because HCV persists in 75% of patients who are acutely infected. The virus persists in the liver in about 85% of those infected.[2]

The treatment of CHC has rapidly evolved in the recent years. However till last year PEG-IFN based regimes were the cornerstone of treatment in Pakistan. The combination of interferon and ribavirin achieved cure rates up to 50–80%.[3] However, treatment was often hampered by intolerable physical and psychiatric side effects. IFNa has several adverse effects, ranging from influenza like symptoms to severe hematologic abnormalities and pulmonary complications.[4]

The side effects of IFN therapy on thyroid gland are also well established. Manifestations of thyroid disease induced by PEG-IFN plus ribavirin combination therapy vary widely in frequency in many studies and have been reported to be in the range of 3.9–27.2%.[5-7] Females and Asians are at higher risk, and hypothyroidism is more common than hyperthyroidism.[7] There were limited studies from South Punjab of these sort. So this study was done to evaluate the TD in CHC patients treated

with PEG-IFN plus ribavirin combination therapy.

METHODS

This descriptive case series was conducted at outpatient department of Gastroenterology and Hepatology, Nishtar Hospital Multan from January to July 2016. The study design was descriptive case series and the sampling technique was non-probability consecutive sampling. There were 337 patients enrolled in the study. The inclusion criteria included all treatment naïve hepatitis C patients having disease duration greater than 6 months, ages between 20 to 40 years, both males and females and having Genotype 2/3. All those having co-infection with hepatitis B, liver cirrhosis, pregnancy and history of using amiodarone and lithium were excluded from the study. Informed consent was taken from all the patients. Patients fulfilling the inclusion criteria were given pegylated IFN alpha-2a 1.5ug/kg/week subcutaneously and ribavirin orally in two divided doses daily (1,000 mg for ≤ 75 kg, 1,200 mg for > 75 kg).

Demographic data was collected of each patient using a pre-designed Performa. At 12 weeks of therapy blood tests for TSH was performed. Data was recorded for Hypothyroidism (TSH ≥ 4 mIU/L) and Hyperthyroidism (TSH <0.2 mIU/L). Data was analyzed with statistical analysis program (SPSS version17). Effect modifiers like age, gender, genotype and duration of hepatitis C were controlled by stratification. Post stratification chi square test was applied p ≤0.05 was considered statistically significant.

RESULTS

Our study included a total of 337 cases meeting inclusion criteria, of which 211 (62.6%) were males and 126 (37.4%) were females (Table-I). Mean age of our cases was noted to be 30.92 ± 5.84 years. Males had a mean age of 32 ± 5.93 years while females mean age was 29.11 ± 5.23 years (p < 0.001). More than half of our study was in the age range of 30 – 40 years.

Mean disease duration was 16.19 ± 6.42 months (range 7 to 42 months). Most of our cases (70.6%) had disease duration ranging from 6 – 24 months. Genotyping of hepatitis C virus revealed that 98 (29.1%) had genotype 2 while 239 (70.9%) had genotype 3.

TD was seen in 28 (8.3%) patients, out of which 21 were females and only 7 were males. Females were much more likely to develop TD as compared to males (Odds Ratio 5.8, p value 0.0001) Hypothyroidism was noted in 14 (4.2%) patients while hyperthyroidism in 14 (4.2%). The type of thyroid dysfunction was stratified according to age and gender of patients, disease duration and genotyping. (Table-II,III). Hypothyroidism was significantly associated with relatively older age group patients and genotype 3 (p value <0.05). Hyperthyroidism was significantly associated with female gender, relatively younger age group, early disease duration and genotype 3 (p value <0.05).

Characteristic	n (%)
Age(years)	
Mean ± SD	30.92 ± 5.84
Range	21 to 40
Gender	
Male	211 (62.6%)
Female	126 (37.4%)
Age Groups	
20-30 years	140 (41.5%)
30-40 years	197 (58.5%)
Disease Duration (months)	
6-24 months	238 (70.6%)
>24 months	99 (29.4%)
Genotypes	
Genotype 2	98 (29.1%)
Genotype 3	239 (70.9%)
Thyroid Dysfunction (TD)	28 (8.3%)
Hypothyroidism	14 (4.2%)
Hyperthyroidism	14 (4.2%)

Table-I. Baseline demographic and clinical characteristic of patients (n=337)

DISCUSSION

Hepatitis C is distributed worldwide, and chronic infections affect up to 80% of the subjects. Consequently, interferon- (IFN) therapy has frequently been used. IFN is one of a group of cytokines with antiviral, anti-proliferative, and immunomodulatory properties. IFN based regimens have several side effects, provoking dose reduction in up to 40% of cases and treatment withdrawal in up to 14% of cases.

Variables		Hypothyroidism		p Value
		Yes (%)	No (%)	
Gender	Male	7 (3.2)	210 (96.8)	0.40
	Female	7 (5.6)	119 (94.4)	
Age Groups (years)	20-30	1 (0.7)	139 (99.3)	0.01
	30-40	13 (6.4)	190 (93.6)	
Disease Duration (months)	6-24	8 (3.4)	230 (96.6)	0.37
	>24	6(5.7)	99 (94.3)	
Genotypes	Genotype 2	0 (0)	98 (100)	0.01
	Genotype 3	14 (5.7)	231 (94.3)	

Table-II. Stratification of hypothyroidism with regards to different variables.

Variables		Hyperthyroidism		P Value
		Yes (%)	No (%)	
Gender	Male	0 (0)	211 (100)	0.000
	Female	14 (11.1)	112 (88.9)	
Age Groups (years)	20-30	14 (10.0)	126 (90.0)	0.000
	30-40	0 (0)	197 (100)	
Disease Duration (months)	6-24	14 (5.9)	224 (94.1)	0.013
	>24	0 (0)	99 (100)	
Genotypes	Genotype 2	0 (0)	98 (100)	0.013
	Genotype 3	14 (5.9)	225 (94.1)	

Table-III. Stratification of hyperthyroidism with regards to different variables.

Thyroid dysfunction are also well established. Symptoms of fatigue, increased sleepiness and depression can common in hypothyroidism and can also occur as a result of interferon therapy. For this reason Hypothyroidism can escape clinical diagnosis.

Of the 337 patients in our study group, 62.6% were males. This is similar to most studies that have reported male preponderance from 54 to 84%[8-13], while one study showed more females CHC patients.[14] Mean age of our patients was 30.92 ± 5.84 years, which was less as compared to most studies with means between 36-39 years.[8,9,12,14] More than 70% of our study had genotype 3 which is similar to what Qazi et al [10] reported (71.4%).

The frequency of TD was 8.3% in our study. Various studies estimate the incidence of TD from 3% to 18.5%.[9,12,13,15,16,17] Equal frequency of hypothyroidism and hyperthyroidism (4.2%) was noted in our study. A local study reported the frequency of hypothyroidism in 0.93%, hyperthyroidism in 1.86% and biphasic thyroiditis in 0% of patients.[18] Nadeem et al reported hypothyroidism in 2.8%, hyperthyroidism in 3.7% and biphasic thyroiditis in 0.9% of patients.[8] Hameed et al[12] reported hypothyroidism in 14.5% and hyperthyroidism in 4%. Vezali et al[13] reported hypothyroidism in 18% and hyperthyroidism in 2.3%. Yen et al reported hypothyroidism in 6.4% and hyperthyroidism in 5.1%. Bini et al[16] reported hypothyroidism in 8% and hyperthyroidism in 2.7%. Foldes et al[17]showed hypothyroidism in 8.7%.

TD was more common in female (16.7%) versus males (3.3%) in our study. Out of the 28 patients who developed TD, there were 7 (25%) males and 21 (75%) females. Vezali et al[13], Yan et al and Hameed et al[12] reported 69.2%, 69.1% and 70.3% patients to be females out of total patients who developed TD, respectively. Nadeem et al also reported TD to be more common in females.[8] The results of all of these are comparable to our study.

CONCLUSION

Thyroid function abnormalities are common after PEG-IFN plus ribavirin combination. There was equal incidence of hypothyroidism and hyperthyroidism. Clinicians must screen all patients being treated with this therapy for early

diagnosis and proper management of thyroid problems.

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Too many people are trying to find the right person instead of being the right person.

– Unknown –

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Waseem Sarwar Malghani	Study concept, design, data collection, interpretation of resutls.	
2	Farooq Mohyud Din Chaudhary	Data collection, drafting.	
3	Muhammad Ali Wadhak	Drafting, data collection.	
4	Asma Tameez Ud Din	Drafting.	
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