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Original Article

Hepatitis C virus as possible etiologic factor in idiopathic nephrotic syndrome among Egyptian patients

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Abstract: Hepatitis C virus (HCV) infection is associated with a variety of extrahepatic disorders, including cryoglobulinaemia and glomerulonephritis. Hepatitis C virus (HCV) glomerulopathy may be present as a primary glomerular disease.

Our study included 50 adult Egyptian patients who were diagnosed as idiopathic nephrotic syndrome (NS). We described the clinical, pathological and immunological features of these patients. There was a high prevalence (50%) of HCV infection among these patients. The studied risk factors included history of; blood transfusion (16%) operation (24%) or antibilharzial drugs (76%). Hepatomegaly was observed in 24% of cases.

Membranoproliferative glomerulonephritis (MPGN) was the commonest pathological type associated with HCV (48%). Other patterns included focal segmental glomerulosclerosis (FSGS) in 32%, membranous in 8% and minimal change glomerulonephritis in 12%. Cryoglobulins were detected in 5.6% of 18 patients with HCV and idiopathic NS.

Pateints having HCV infection and membranoproliferative glomerulonephritis had hypocomplementemia and antinuclear antibodies were detected in 41.6%.

Realising that HCV infection may be linked to different glomerulopathies, thus routine screening for HCV should be considered in serologic work-up of patients with glomerulopathy. Nevertheless, seroepidemiological studies including larger number of patients with glomerulopathy are therefore necessary to specify its relation with HCV infection.

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Introduction

Hepatitis C virus (HCV) is an RNA virus, identified in 1989 [1] causing both acute and chronic liver disease [2]. Chronic hepatitis C virus infection is associated with several extrahepatic syndromes, including mixed cryoglobulinaemia, polyarteritis nodosa, sicca like syndrome [3-6] and immunologically mediated renal diseases [7]. Several studies have been reported linking HCV and the occurrence of chronic glomerular diseases especially membranoproliferative glomerulonephritis (MPGN) [8-10]. Studies in the USA, Italy and Japan suggest that HCV may be an important cause of cryoglobulinaemic and idiopathic MPGN [10]. It is likely that HCV is also an important cause of glomerulonephritis in other areas of the world, but this had been unrecognized. This is due to the fact that these patients often lack clinical evidence of liver disease, and present clinically as a primary renal syndrome [8,9] with minimally elevated transaminases and a remote history of exposure to HCV.

We have no available data in Egypt regarding this link. Thus the objective of this study was to detect the prevalence of HCV among Egyptian patients who were previously diagnosed as idiopathic nephrotic syndrome (NS) and to study if it has a possible etiologic role in such patients.

Materials and methods

This study included fifty patients (attending the outpatient clinic of Urology and Nephrology center of Mansoura University) they were diagnosed as idiopathic nephrotic syndrome, 32 males and 18 females, their age ranged from 16 to 50 years. HCV infection was diagnosed in all patients by testing for the presence of HCV antibodies using (ORTHO-

HCV, Ortho Diagnostic system) and HCV-RNA (polymerase chain reaction).
According to this result patients were divided into two groups:
Group I (50%) was positive and group II (50%) was negative for HCV antigens and antibodies. All patients were investigated for liver function tests, serum creatinine, urinary protein/24h., serum complement, abdominal ultrasonography and renal biopsy.
Those twenty five patients with HCV infection were investigated for antinuclear antibodies and cryoglobulins and then categorised according to the pathological findings of renal biopsy into 2 groups, one with membranoproliferative glomerulonephritis and the other with other pathological types.

Results

The clinicopathological and laboratory features of the studied patients are shown in tables (1-8).

Analysis of the results

Table 1. shows that males constituted 68% of patients with HCV infection compared to 60% of patients without. Females constituted 32% and 40% respectively with a statistically insignificant difference (P>0.05).
Table 2. shows that the mean age of patients in HCV group was 35.96 ± 8.36 years while it was 29.60 ± 7.31 years in group II with a statistically insignificant difference (P> 0.05).
Table 3. shows that history of blood transfusion was present in 16% of group I while it was 12% in group II with statistical insignificant difference (P>0.05). History of operation was present in 24% of group I patients while it was 12% in group II with statistical insignificant difference (P>0.05). History of antibilharzial drugs was present in 76% of HCV positive group while it was 48% among HCV negative group with statistical significant difference (P< 0.05).
Hepatomegaly was present in 24% of the patients in HCV positive group while it was found in only 4% in the patients of HCV negative group with statistical significant difference (P<0.05).
Table 4. shows that the serum bilirubin was 0.66 ± 0.46 mg/dl in group II cases while it was 0.53 ± 0.20 mg/dl among HCV negative group with statistical insignificant difference (P> 0.05).
The mean level of SGPT was 35.76 ± 29.53 IU/L in group I while it was 19.8 + 13.5 IU/L in group II with statistical significant difference (P< 0.05).
The mean level of SGOT was 43.32 ± 29.89 IU/L and 22.48 ± 6.01 IU/L in group I & II respectivly with statistical significant difference (P< 0.05).
The mean level of serum albumin was 2.48 ± 0.59 g/dl and 2.32 ± 0.67 g/dl in group I & II respectivly with statistical insignificant difference (P> 0.05).
The mean value of cholesterol levels were 378.8 ±85.8 mg/dl and 350.0 ± 67.8 mg/dl in group I & II respectivly with statistical insignificant difference (P>0.05).

The mean value of 24 hours urinary protein was 3.77± 2.26 gm in group I while it was 3.68 ± 3.11 gm in group II with statistical insignificant difference (P>0.05).

The mean level of serum creatinine was 0.92 ± 0.22 mg/dl and 0.88 ± 0.28 md/dl in group I & II respectivly with statistical insignificant difference (P>0.05).

The pathological findings of the renal biopsy as shown in table 5 include, focal segmental glomerulosclerosis in 32%, membranoproliferative in 48%, membranous in 8% and minimal change in 12% among patients in group I while it was focal segmental glomerulosclerosis in 60%, membrano-proliferative glomerulonephritis in 8%, membranous glomerulonephritis in 4%, minimal change glomerulonephritis in 12% and mesangial proliferation in 16% of group II cases. A statistical significant difference between both groups was present in FSGS, MPGN and mesangial proliferation (P<0.05).

Table 6. shows that the mean value of complement three (C_3) was 92.59±40.47 mg/dl among HCV positive patients with MPGN group while it was 141.49±33.96 mg/dl among the same group with other pathological types with statistical significant difference (P<0.05).

The mean value of complement four (C_4) was 22.72±14.81 mg/dl in HCV positive patients with MPGN while it was 45.51±14.20 mg/dl among patients in the same group with other pathological types with statistical significant difference (P<0.05).

Table 7. shows that the antinuclear antibodies were strongly positive in 8.3% but weak positive in 33.3% of HCV positive patients with MPGN compared to 23.1% and 7.7% respectively among patients in the positive group with other pathological types with a statistical significant difference (P>0.05).

Table 8. shows that croyoglobulins were detected in 9.1% among 11 patients with HCV associated MPGN compared to 0% among 7 patients with HCV and with other pathological types but this comparison is not statistically valid as one group contains only one subject.

Table 1. Sex distribution of the studied patients according to HCV infection

HCV / Sex	HCV (positive) No	%	HCV (negative) No	%	Total No	%
Males	17	68.0	15	60.0	32	64.0
Females	8	32.0	10	40.0	18	36.0
Total	25	100.0	25	100.0	50	100.0

* (P>0.05)= non-significant.

Table 2. Means ± S.D. of age among the studied patients according to HCV infection

HCV / Age (years)	HCV positive (n.=25)	HCV negative (n.=25)	T	P
Mean	35.96	29.60	2.864	> 0.05*
S.D.	±8.36	± 7.31		
Range	19.0-50.0	16.0-50.0		

* = insignificant.

Table 3. Risk factors for HCV infection in studied patients

Character	HCV positive (n.=25) No	%	HCV negative (n.=25) No	%	Total (n.=50) No	%	Z	P
History of :								
Bl. transfusion	4	16.0	3	12.0	7	14.0	0.408	>0.05*
Operation	6	24.0	3	12.0	9	18.0	1.104	>0.05*
Anti-B drugs	19	76.0	12	48.0	31	62.0	2.040	<0.05**
Hepatomegaly	6	24.0	1	4.0	7	14.0	2.038	<0.05**

* Non-significant ** Significant

Table 4. Liver function tests and parameters of nephrotic syndrome among our patients according to HCV infection

HCV / Lab. tests	HCV positive x + S.D.	HCV negative x + S.D.	t	P
.S. bilirubin	0.66 ± 0.46	0.53 ± 0.20	1.259	>0.05*
. SGPT	35.76 ± 26.53	19.8 ± 13.5	2.457	<0.05**
. SGOT	43.32 ± 29.89	22.48 ± 6.01	3.417	<0.05**
.S. Albumin	2.48 ± 0.59	2.32 ± 0.67	0.924	>0.05*
.S. cholesterol	378.8 ± 85.8	350.0 ± 67.8	1.311	>0.05*
.S. creatinine	0.92 ± 0.22	0.88 ± 0.28	0.553	>0.05*
.U. protein/24h	3.77 ± 2.26	3.68 ± 3.11	0.109	>0.05*

* Non-significant ** Significant

Table 5. Renal histopathology in both HCV positive and negative groups

HCV / Pathology	*HCV positive*		*HCV negative*		*Total*		Z	P
	No	%	No	%	No	%		
FSGS	8	32.0	15	60.0	23	46.0	1.986	>0.05**
MPGN	12	48.0	2	8.0	14	28.0	3.150	>0.05**
Membraous	2	8.0	1	4.0	3	6.0	0.595	<0.05**
Minimal change	3	12.0	3	12.0	6	12.0	-	-
Mesangial prolif	0.00	0.00	4	16.0	4	8.0	2.085	<0.05**
Total	25	100.0	25	100.0	50	100.0		

* Non-significant ** Significant

Table 6. Complement levels among HCV positive group accoding to the results of renal histopathology

Biopsy / Complement	*MPGN*	*Others*	*T*	*P*
	X ± S.D.	X ± S.D.		
C3	92.59 ± 40.47	141.49 ± 33.96	3.282	<0.05**
C4	22.72 ± 14.81	45.51 ± 14.20	3.927	<0.05**

* Significant.

Table 7. Antinuclear antibodies in both groups

Biopsy / ANA	*MPGN (n=12)*		*Others (n=13)*		*Total (n.=25)*		Z	P
	No	%	No	%	No	%		
Weak	4	33.3	3	23.1	7	28.0	0.57	>0.05*
Strong	1	8.3	1	7.7	2	8.0	0.59	>0.05*
Total	5	41.6	4	30.8	9	36.0	0.42	<0.05*

* Non-significant

Table 8. Cryoglobulins in both groups

Biopsy / Cryoglobulins	*MPGN (n=11)*		*Others (n=7)*		*Total (n.=18)*	
	No	%	No	%	No	%
Cryoglobulins	1	9.1	0	0.0	1	5.56

Discussion

Hepatitis C virus (HCV) is an RNA virus, identified in 1989 [1]. It causes both acute and chronic liver disease and is a major cause of both transfusion associated and sporadic non-A non-B hepatitis. Persistent infection occurs in approximately 50% of patients, it is often clinically silent and may result in chronic active hepatitis, cirrhosis and possibly hepatocellular carcinoma [2]. Chronic hepatitis C virus infection, when presist for over ten years and especially in prescence of chronic active hepatitis or cirrhosis, is associated with several extrahepatic syndromes, including mixed cryoglobulinaemia, polyarteritis nodosa and sicca like syndrome [3-6]. HCV infection may be associated with immunologically mediated renal diseases [7]. Several studies reported the link between HCV and

chronic glomerular diseases especially membrano-proliferative glomerulonephritis [8-10]. However we have no available data in Egypt regarding this link.

In this study, we reported an association of HCV infection with idiopathic NS in 50% of the studied patients. Similarly, many reports confirmed this association [7,9,11]. The high percentage of anti-HCV seropositivity suggests that this virus may play an important role in the pathogenesis of this immune-mediated glomerulonephritis. One the other hand, other reports did not find such association [12,14]. This difference may be related to the endemicity of HCV in Egypt as its prevalence ranged from 10-20% among the general population [15]. Other factors considered may include specific genotype associated with particular complication as glomerulonephritis and the duration of infection [16]. Exposure to risk factors was present in 40% of HCV positive patients including blood transfusion (16%) or operations (24%) (table 3). Other reports showed different results (16,9). This may be related to different prevalence and endemicity of HCV among different population [17], different genotypes [18] and different habits [19]. The majority (76%) of our HCV positive patients received one or more courses of antibilharzial drugs (table 3). This may be related to the endemicity of schistosomiasis in Egypt [19]. The relationship between HCV and glomerulopathy in the presence or absence of schistosomiasis should be speciefied as different relations were reported [16,20].

It is of interest that the presence of hepatomegally among the patients with HCV (24%) was significantly higher than those without HCV (4%) (table 3). The mean values of SGPT and SGOT among patients with HCV were significantly higher than those without HCV (table 4) this is in a greement with other reports [7,9]. However, the lower values of transaminase may be related to the effect of the administrated corticosteroid [21], different genotypes and the absence of HBV infection [19].

In this study, membranoproliferative glomerulo-nephritis was the commonest (48%) pathological pattern among patients with HCV (table5) and this is similar to many reports [9,11,16].

Our patients with HCV and membranoproliferative glomerulonephritis showed lower level of complement 3 and complement 4 than those with HCV and other pathological types (table 6). MPGN is known to be associated with hypocomplementemia and is sometimes called hypocomplementemic glomerulonephritis [22]. The presence of antinuclear antibodies (ANA) was detected in 36% among patients with HCV (table 7) which could be related to the association between chronic HCV infection and development of autoantibodies [23].

Cryoglobulins were detected in one out of eighteen patients, with HCV and idiopathic NS (table 8). Different reports showed different results [9,16,24]. This difference may be related to several factors including; the duration and severity of chronic liver disease [25], different geographical areas [24], the administrated immunosuppressive drugs [26,27] and previous HBV infection [7,28]. Follow up of cryoglobulins is recommended as it may develope later [9].

We may conclude that there was a high prevalence of HCV infection among patients with idiopathic NS. Those with MPGN, hepatomegally, elevated transaminases and history of antibilharzial drugs are at increased risk. MPGN was the commonest pathological type associated with HCV.

Accepting that HCV infection may be linked to several glomerulopathies, routine screening of these patients for HCV should be considered in their serologic work-up. Nevertheless, seroepidemiological studies including larger number of patients with glomeulopathy are necessary to specify its relation with HCV infection.

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