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The effect of cytokine polymorphism on the outcome of hepatitis C viral infection in children

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ABSTRACT
Background: *Cytokines are important mediators of inflammation throughout viral diseases, such as hepatitis C virus (HCV).Cytokine genetic polymorphisms could also modify the autoimmune reaction to this infectious disease.*
Purpose: *The goal of this study was to look into the rate of genetic markers linked to IL-10, TGF-β, IL-6, TNF-α and IFN-γ polymorphisms and their relationship to the consequences of HCV infection.*
PatientsandMethods: *This study was carried out on a group of 40 chronic HCV pediatric patients, at the Alexandria University Pediatric Hospital (Shatby), Egypt. individuals were divided into two groups based on the response to lFN (Responders and non-responders) and clinically followed-up for 3 months.*
Results: *There was statistically significant difference between responding and non- responding groups after treatment with IFN, also between responding patients before and after treatment. (P<0.05).*
The combination of IL10-1082 GA and IL 6-174 GC and other genotypes were statistically significant higher among non- responding group (P<0.05). Also, the highest positive predictive value was present in combination genotypes (IL-1082GA/IL6-174GC) among non-responding groups.
Conclusion: *The findings of this study suggest that the gene polymorphisms of IL-10, TGF-β, IL-6, TNF-α and IFN-γwere linked to liability to the occurrence of chronic HCV infectious disease among children.*
Keywords: *cytokines; gene polymorphism; hepatitis C infection; children.*

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I. INTRODUCTION

HCV was first identified in 1989 (1)as the major causative agent of parenteral transmitted and community acquired non A, non B hepatitis. (2) According to the World Health Organization (WHO), 170 million of population globally are diseased by the hepatitis C viral infection (HCV). However, the level of HCV infection fluctuates globally. In the year 2000, for example, Egypt had the greatest rate of reported infectious diseases, which were widely contributed to the utilization of contaminated parenteral anti-schistosomal medications. As a result, the average predominance of HCV antibodies in Egyptians is 22%. (3)

Chronicity is the predominant unique characteristic of HCV, affecting at least 85% of acute HCV cases. (4)Chronic viral hepatitis (C) is a chief problem of hepatocellular carcinoma (HCC) in many parts of the world. The neoplasm is more common in patients who have had the disease for a long time (average 29 years), and the significant proportion have cirrhosis. (5)

Cytokines play an essential role in viral infection protection, whether indirectly (by assessing the dominant pattern of host immune response) or directly (by inhibiting viral replication) (Figure 1). Even so, cytokines can damage the liver regarding the inflammatory reaction to a viral agent. Estimated 80 to 90% of potently people with the disease establish chronic infection after the acute infection; approximately half of them have increased transaminases, indicating continuing liver inflammation. (6)

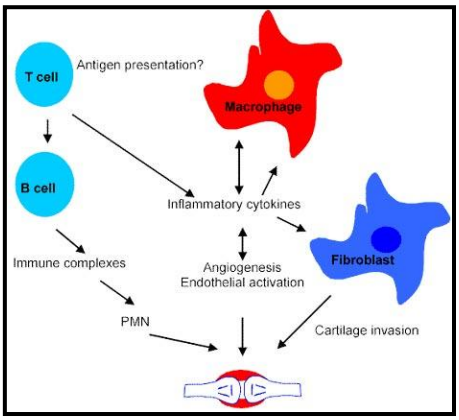


Figure (1): Cytokines and immune response

Chronic Hepatitis c infection is characterised by an abundance of cytokines. In the lack of a complete virology restoration, the ongoing inflammation causes liver damage. (7) In actuality, the quantity of inflammation correlates with the expression of these cytokines. In addition, current cellular immunity is likely to aid in the development of liver fibrosis.

There are two possible patterns of cytokine production. (8)Type 1 reactions are distinguished by the producing of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF- α) and interleukin-2 (IL-2) that preserve antigen-specific cell - mediated immunity. (8) Type 2 reactions are distinguished by the presence of, IL-5, IL-10 and IL-4 that enhance humorous immune reactions. An asymmetry in cytokines as helper T-cell (Th) type 1 or type 2 is thought to be involved in chronicity of HCV pathogenesis. The serious hepatic damage shown in chronic HCV disease is linked to an increase in intrahepatic cytokines (Th1-like), with intrahepatic IL-2 and IFN-γ mRNA appearance increasing while IL-10 (Th2-like cytokine) expression decreasing. (9)

Cytokines construction like TNF-α that produces TGF-ß, can activate Kupffer cells. The majority of T cells infiltrating the liver in chronic stage are Th1 cells. In some studies of cytokines in hepatic tissue have revealed that intrahepatic T1-like cytokines mRNA including IL-6, IL-1ß, IFN-γ, IL-2, IL-8 and TNF-α and are up regulated in chronic Hepatitis c. (10) The degree of histologic injury is related to the stage of countenance of T1 like cytokines like IFN-γ and IL2. (11)

Sequencing of the human genome revealed single differences at specific positions, these normal variations are called single nucleotide polymorphisms (SNPs). (12)

Cytokine polymorphism is important in immune response regulation.In viral Hepatitis (HCV), improper cytokine levels appear to be contributing to viral persistence and therapy response.Cytokine genetics are polymorphic at particular areas, and alterations in regulatory/coding zones have been demonstrated to impact all cytokine expression and exudation. (9)

The purpose of our trail was to assess the occurrence of associated with TNF-α, IFN-ϒ, IL-10, TGF-β, and IL-6 genotypes polymorphisms and their link to the of HCV infection illness outcome.

II. MATERIALSAND METHODS

This study was carried out on a group of 40 chronic HCV pediatric patients, at the Alexandria University Pediatric Hospital (Shatby), Egypt and clinically followed-up for 3 months.

A written informed consent to participate to the study was obtained from patient's parents in accordance with the declaration of Helniski and following the directions of the faculty ethical committee.

Based on the treatment outcome, patients were subdivided into responders and non-responders. The responders were identified by a minimum of a 2 log decrease in the viral load as estimated by quantitative PCR after 3 months of treatment with IFN. The panel of cytokine SNPs was correlated with the response to treatment, and the level of serum Alanine amino transferase (ALT) as an indicator of liver injury. Diplo types of the different SNPs were also correlated with the treatment outcome accordingly.

Inclusion criteria

Chronic PCR RNA positive HCV pediatric patients for more than 6 months, aged from 5-15 years old and candidate for IFN therapy.

Exclusion criteria

Patients received previous IFN therapy within the previous 6 months. Patients had concomitant HBV, other chronic liver disease or decompensated liver disease (cirrhosis).

Data collection

Patients were subjected to taking the history by questionnaire (from the patient or his guardian), complete clinical examination and laboratory investigations including:

Serum anti-HCV antibody was tested by ELISA (13) (Adaltis Italia S.P.A.), baseline and end of treatment viral load was performed by Quantitative PCR (14) (Cobas , Roche),serum ALT (15)(Dimension, Siemens) and complete Blood Picture.(16) (Automated cell counter, Sysmex).
Genotyping of cytokine was accomplished by PCR qualitatively using tray of cytokine genotyping (conago park, U.S.A, CA) (17) for five cytokines including; Interleukin-6 (IL-6), Interferon-γ (IFN- γ), Interleukin-10 (IL-10), tumor necrosis factor-α (TNF- α) and transforming Growth Factor-β (TGF- β).
Assessment of (HCV antibodies) was performed using the enzyme linked immunosorbant assay kit for HCV antibodies (supplied by Adaltis Italia S.P.A.). (Table 1)

Table (1): interpretation of enzyme immune assay

Sample/Cut off ratio S/Co	Interpretation
<0.9	Negative
0.9-1.1	Equivocal
>1.1	Positive

Principle (13): Hepatitis C virus antibodies test kit is a fourth generation enzyme immunoassay. Microplates are coated with HCV-specific peptides derived from "core" and "NS" (Non-structural) regions encoding for conservative and immune dominant antigenic determinants (Core peptide, recombinant NS3, NS4, NS5 peptides).
Extraction of genomic DNA Principle (18):The QIAamp *DNA Mini Kit* designed to isolate genomic DNA (from whole blood or buffy coat). (Figure 2)

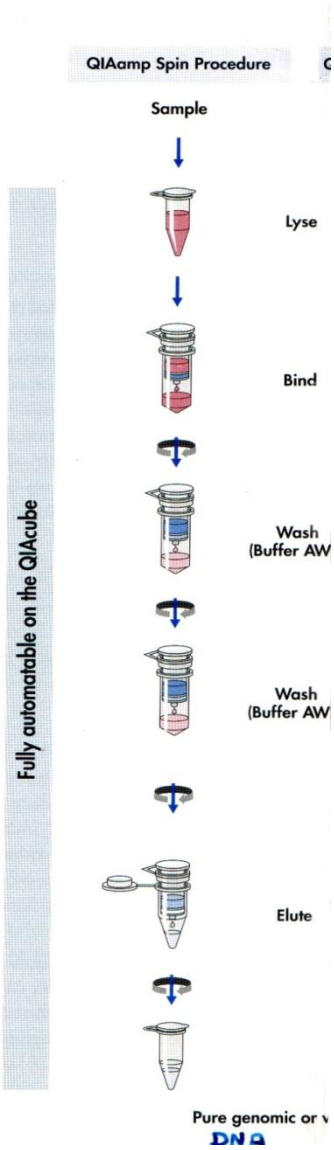
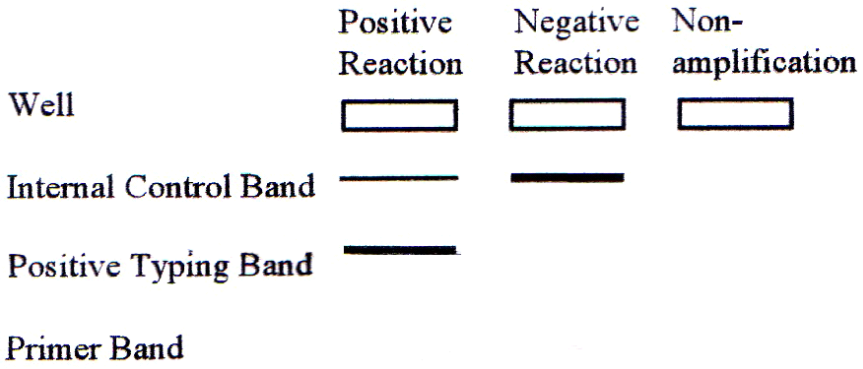


Figure (2): The QIAamp procedure

Cytokine polymorphism was assessed by PCR amplification using sequence specific primers (PCR-SSP). (19)

Principle: The PCR-SSP technique is based on the concept that fully linked oligonucleotide primers are more efficient than misaligned oligonucleotide primers in boosting a target gene through Taq polymerase (recombinant enzyme). Couples of primer are intended to have good fits with a small alleles group. Exactly matched primer pairs lead through target DNA sequence amplification (+ve outcome) under strictly controlled PCR conditions, whereas misaligned primer pairs do not lead to significant in amplification (-ve outcome).

Following the PCR amplification, were divided by agarose gel electrophoresis divided and envisioned using the amplified DNA fractions, ethidium bromide staining and ultraviolet light exposure. The involvement or lack of a particular amplified DNA segment was used to interpret PCR-SSP findings. Because amplification during the Pcr amplification can be hampered by a variety of factors (poor DNA quality, pipetting mistakes and so on), an inner management primer couples was added to each Pcr amplification.



The following gel run is an example of a responder HCV patient

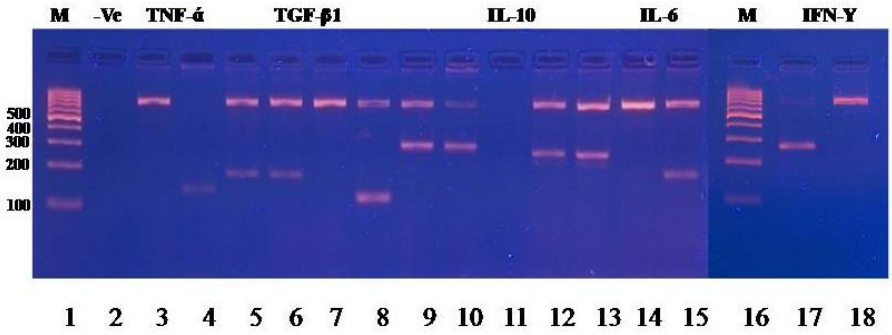


Figure (3): Gel interpretation.

Statistical studies

The collected data were coded, tabulated and statistically analyzed utilizing the Predictive Analytics Software *(PASW Statistics 18).* Numbers and percentages were used to describe qualitative data. The Chi-square test was used to examine the relationship between categorical variables. Since more than 20% of the cells had a predicted numbers of less than 5, chi-square correction was performed utilising Firsher's Exact test or Monte Carlo correction.

The median, minimum, and maximum values, as well as the mean and standard deviation, were used to describe quantitative data. Different variables agreement with the consequence was utilized and was articulated in following criteria; accuracy, negative predictive value, positive predictive value, specificity and sensitivity.

III. RESULTS

The study included a group 3 of 40 chronic HCV pediatric patients, receiving IFN-based therapy at the Alexandria University Pediatric Hospital (Shatby), Egypt and clinically followed-up for 3 months.

Their ages ranged from 5-15 years with a mean age of 9.83±2.57, the patients were 35 males (87.5%) and 5 females (12.5%).

A history of blood transfusion was positive in 22 patients (55%), haemodialysis was positive in 1 patient (2.5%), previous surgery was positive in 10 patients (25%) and positive family history for HCV in 5 patients (12.5%).

HCV antibody was positive in all patients (100%) **(S/Co>1.1)** and HCV viral load was positive in all cases at the start of treatment and was positive in 7 patients (17.5%) and negative in 33 patients (82.5%) after 3 months.

Table (2): Table shows distribution of the studied cases according to demographic data and clinical investigations.

	No	%
Sex		
Male	35	87.5
Female	5	12.5
Age (years)		
Range	5.0 – 15.0	
Mean ± SD	9.83 ± 2.57	
Hb (g/dl)		
Range	7.80 – 14.5	
Mean ± SD	11.91 ± 1.21	
WBC($X10^9$/L)		
Range	2.10 – 11.70	
Mean ± SD	6.57 ± 2.11	
PLT($X10^9$/L)		
Range	86.0 – 657.0	
Mean ± SD	294.75 ± 98.0	
ALT(U/L)		
Range	25.0 – 311.0	
Mean ± SD	69.87 ± 47.85	
AST(U/L)		
Range	19.0 – 261.0	
Mean ± SD	49.43 ± 37.03	
HCV antibody		
-ve	0	0
+ve	40	100
HCV viral load after 3 month (IU/ML)		
-ve	33	82.5
+ve	7	17.5

Table (3): Comparison between non responder cases and responder cases according to ALT.

	Response to IFN				FEp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
ALT					
High ALT	1	14.3	26	78.8	0.003*
Normal ALT	6	85.7	7	21.2	

FEp: p value for Fisher Exact test

*: Statistically significant at $p \leq 0.05$

High ALT was statistically significant detected among responding groups (78.8%).

Table (4): Table shows odds ratio of ALT.

	Non responder	Responder+	OR	95% CI (lower – upper)
ALT				
High ALT	1	26	22.286*	(2.290 – 216.918)
Normal ALT®	6	7		

ALT was higher by 22 fold in responding groups than non-responding

Table (5): Table shows the distribution of the studied cases according to Response to lFN

	No	%
Response to lFN		
Non responder	7	17.5
Responder	33	82.5

In our study the majority of the cases were responders (82.5%) and non-responders were only 17.5%.

Table (6): Comparison between non-responding and responding patients according to PCR

PCR (Iu/ml)	Response to IFN		p_1
	Non responder (n = 7)	Responder (n = 33)	
At start of treatment ($x10^3$)			
Range	22.02 – 1500.0	1.01 – 3250.0	
Mean ± SD	335.40 ± 526.18	343.58 ± 647.76	0.695
Median	210.0	129.09	
After 3 months ($x10^3$)			
Range	0.21 – 330.0	< 0.10	
Mean ± SD	74.17 ± 116.77		<0.001*
Median	27.0		
p_2	0.180	<0.001*	

p_1: p value for Mann Whitney test
p_2: p value for Wilcoxon signed ranks test
There was statistically significant difference between responding and non- responding groups after treatment with IFN-γ also between responding patients before and after treatment. (P<0.05).

Table (7): The following table shows Comparison between non responding and responding patients according to TNF-α polymorphism

	Response to IFN				MCp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
TNF-α					
GG	5	71.4	24	72.7	
GA	2	28.6	8	24.2	1.000
AA	0	0.0	1	3.0	

MCp: p value for Monte Carlo test
The G/G and AA genotypes were higher among the responders (72.7% and 3% respectively), while G/A genotype was higher among non-responders (28.6%), however not significant (P>0.05).

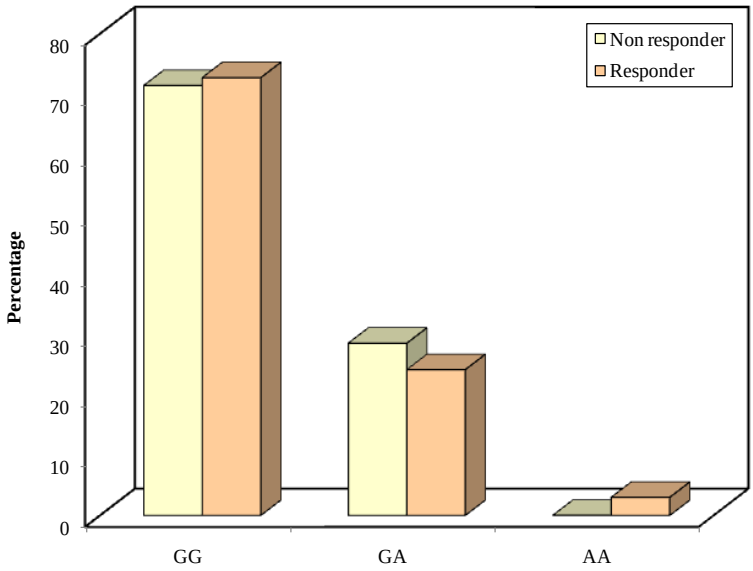


Figure (4): Comparison between non-responding and responding patients according to TNF-α polymorphism.

Table (8): Comparison between non-responding and responding patients according to TGF-β codon 10 polymorphism.

	Response to IFN				MCp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
TGF-β codon 10					
TT	4	57.1	12	36.4	
TC	1	14.3	13	39.4	0.438
CC	2	28.6	8	24.2	

MCp: p value for Monte Carlo test

The T/T and C/C genotypes were higher among non-responders (57.1% and 28.6% respectively), while T/C genotype was more prevalent in responders (39.4%) but not significant (P>0.05).

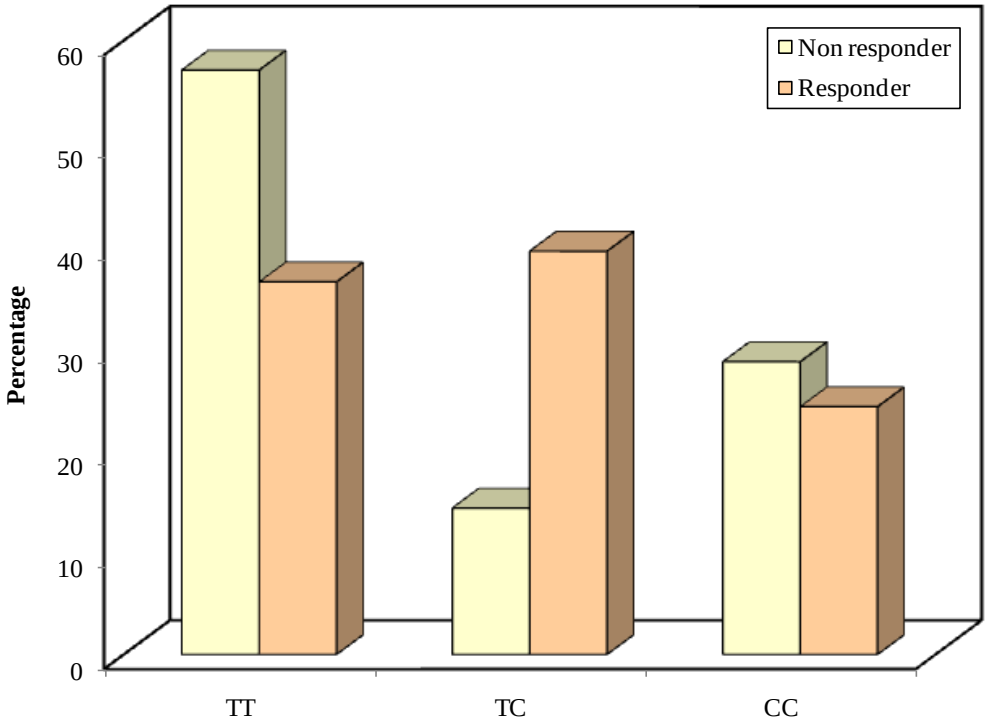


Figure (5): Comparison between non-responding and respondingpatients according to TGF-β codon 10 polymorphism.

Table (9): Comparison between non-responding and responding patients according to IL 10 polymorphism.

	Response to IFN				MCp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
IL 10 -1082					
GG	1	14.3	15	45.5	FEp = 0.210
GA	5	71.4	4	12.1	FEp = 0.003*
AA	1	14.3	14	42.4	FEp = 0.224
IL 10 -819					
CC	3	42.9	15	45.5	
CT	4	57.1	15	45.5	1.000
TT	0	0.0	3	9.1	
IL 10 -592					
CC	4	57.1	18	54.5	
CA	3	42.9	12	36.4	1.000
AA	0	0.0	3	9.1	

MCp: p value for Monte Carlo test

FEp: p value for Fisher Exact test
*: Statistically significant at $p \leq 0.05$
There are three SNPs for IL-10 promoter region (-1082,-592 and -819). For the IL-10 -1082, there was significant increasing of G/A genotype among non-responders (71.4%). ($P<0.05$). As regards to IL-10 -819, The T/T genotype, was more prevalent among responders (9.1%) with no cases detected among non-responders hence not significant.
As regards to IL 10 -592 polymorphism , The A/A genotype was more prevalent among the responders (9.1%) and not detected among non- responders hence insignificant.

Table (10): The odd's ratio among IL 10-1082 polymorphism

	Non responder	**Responder**	**OR**	**95% CI (lower – upper)**
IL 10-1082				
GG+AA®	2	29	18.125*	(2.59 – 126.72)
GA	5	4		

This table show that IL 10-1082 G/A polymorphism is statistically significant higher (18.125 fold) among the non-responders.

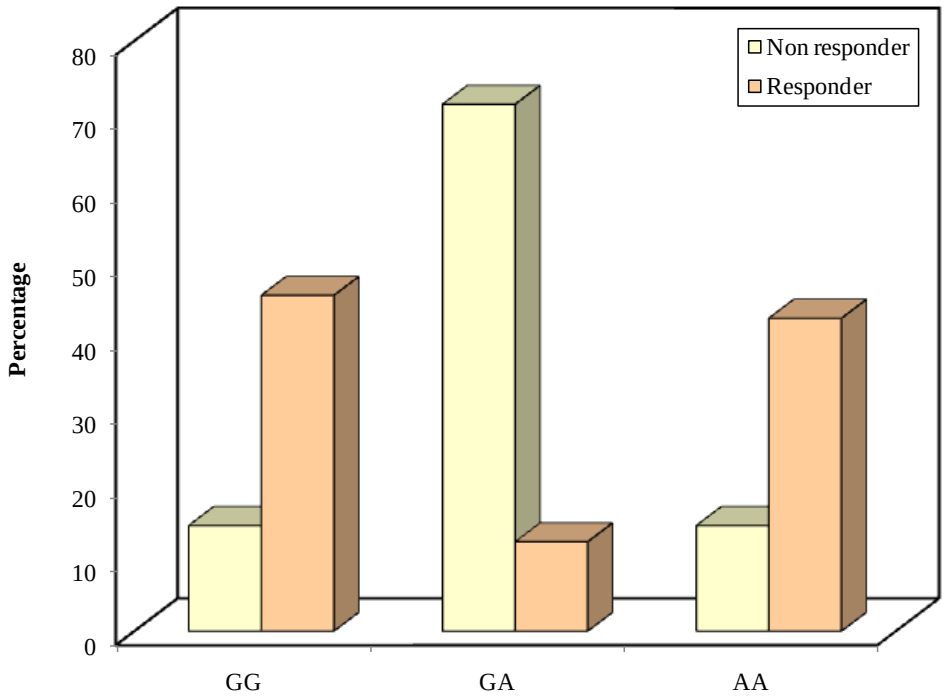


Figure (6): Comparison between non-responding and responding patients according to IL10 -1082 polymorphism.

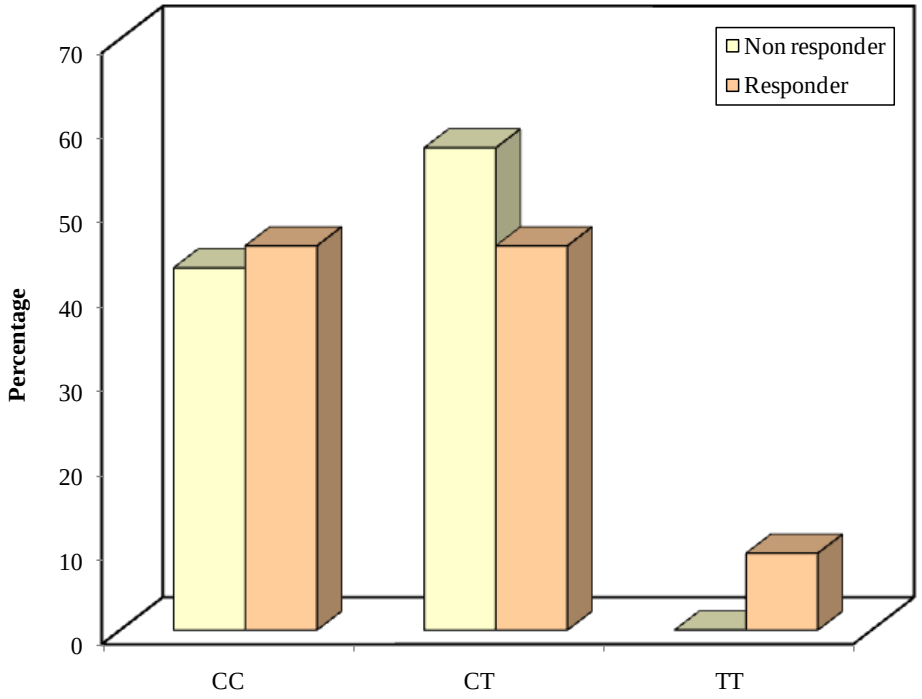


Figure (7): Comparison between non-responding and responding patients according to IL 10 -819 polymorphism.

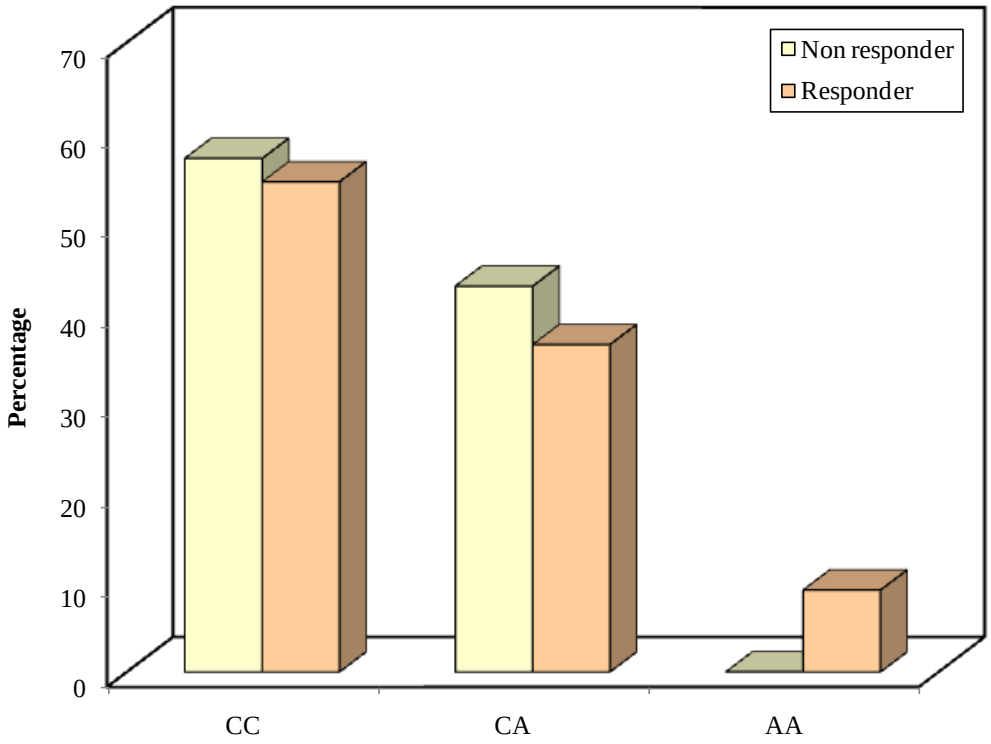


Figure (8): Comparison between non-responding and responding patients according to IL 10 -592 polymorphism.

Table (11): Comparison between non-responding and responding patients according to IL 6-174 polymorphism

	Response to IFN				FEp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
IL 6 -174					
GG	2	28.6	25	75.8	0.027*
GC	3	42.9	4	12.1	0.088
CC	2	28.6	4	12.1	0.279

FEp: p value for Fisher Exact test
*: Statistically significant at $p \leq 0.05$
In this study we found a statistically significant increase in G/G genotype among responders (75.8/%), while G/C and C/C genotypes were higher among non-responders (42.9% and 28.6% respectively) (P<0.05).

Table (12): The odd's ratio among IL 6 -174 polymorphism

	Non responder	Responder+	OR	95% CI (lower – upper)
IL 6 -174				
GG+	2	25	7.813*	(1.262 – 48.356)
GC+CC®	5	8		

The IL-174G/G genotype was 7.813 fold higher in responding groups than non-responding.

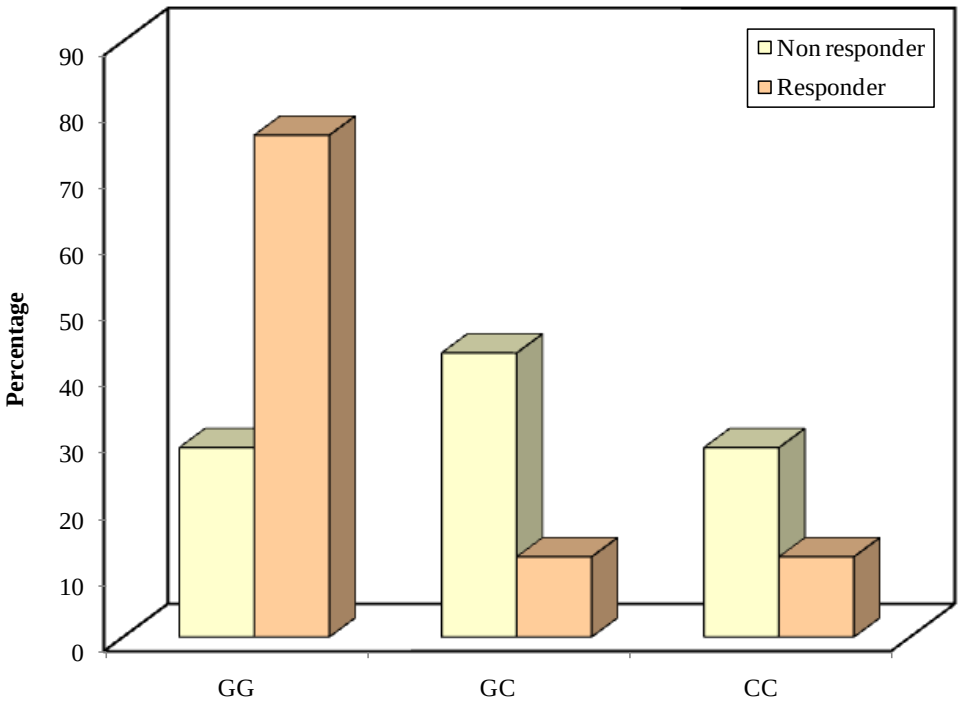


Figure (9): Comparison between non-responder cases and responder cases according to IL 6-174 polymorphism.

Table (13): Comparison between non-responding and responding patients according to IL 10/IL 6

	Response to IFN				FEp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
IL 10/IL 6					
GG/GG	0	0.0	12	36.4	0.081
GG/GC	1	14.3	2	6.1	0.448
GG/CC	0	0.0	1	3.0	1.000
GA/GG	2	28.6	4	12.1	0.279
GA/GC	2	28.6	0	0.0	0.027*
GA/CC	1	14.3	0	0.0	0.175
AA/GG	0	0.0	9	27.3	0.175
AA/GC	0	0.0	2	6.1	1.000
AA/CC	1	14.3	3	9.1	0.552
MCp	0.002*				

MCp: p value for Monte Carlo test
FEp: p value for Fisher Exact test
*: Statistically significant at $p \leq 0.05$
Table shows that combination of IL10-1082 GA and IL 6-174 GC were statistically significant higher among non- responding group (P<0.05).

Table (14): The odds ratio of GA/GC among non-responder

	Non responder +	Responder	OR	95% CI (lower – upper)
IL10 -1082/IL6 -174				
Other combination genotypes ®	5	33	0.132*	(0.058 – 0.298)
GA/GC+	2	0		

The combination genotypes were statistically significant higher among non-responding groups.

Table (15): Agreement (sensitivity, specificity and accuracy) for GC (IL6)

		Responder	Non responder	Sensitivity	Specificity	PPV	NPV	Accuracy
GC (IL6)	-	29	4	42.86	87.88	42.86	87.88	80.0
	+	4	3					

Table (16): Agreement (sensitivity, specificity and accuracy) for GA (IL10)

		Responder	Non responder	Sensitivity	Specificity	PPV	NPV	Accuracy
GA (IL10)	-	29	2	71.43	87.88	55.56	93.55	85.0
	+	4	5					

Table (16): Agreement (sensitivity, specificity and accuracy) for GA/GC (IL10/6)

		Responder	Non responder	Sensitivity	Specificity	PPV	NPV	Accuracy
GA/GC (IL10/6)	-	33	5	28.57	100.0	100.0	86.84	87.5
	+	0	2					

Data from previous tables (14, 15 and 16) revealed that the highest positive predictive value was present in combination genotypes (IL-1082GA/IL6-174GC) among non-responding groups.

Table (18): Comparison between non responder cases and responder cases according to IFN +874 polymorphism.

	Response to IFN				MCp
	Non responder (n = 7)		Responder (n = 33)		
	No	%	No	%	
IFN +874					
TT	3	42.9	11	33.3	
TA	3	42.9	13	39.4	0.877
AA	1	14.3	9	27.3	

MCp: Monte Carlo test p value

The prevalence of T/T and T/A genotypes were more prevalent among non-responders (42.9% and 42.9% respectively) while the A/A genotype was more prevalent among responders (27.3%), however these results were not significant (P>0.05).

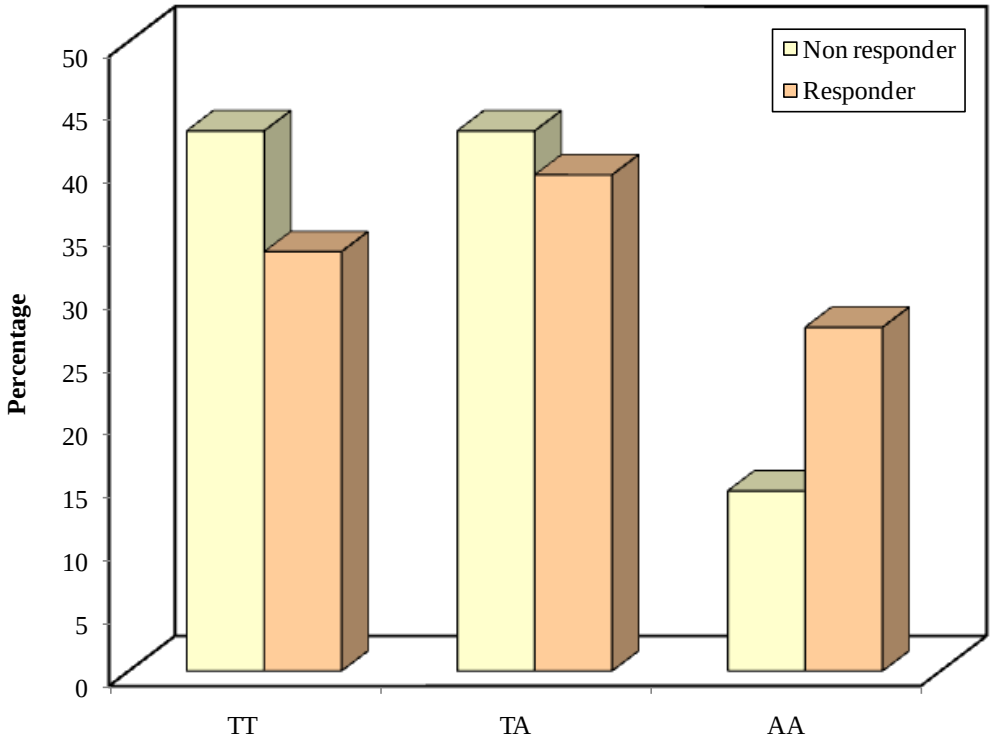


Figure (10): Comparison between non responder cases and responder cases according to IFN γ+874 polymorphism

IV. Discussion

Hepatitis C virus (HCV)is a major public health concern, a leading cause of liver disease and one of the major etiological agents of chronic liver diseases.HCV is encountered worldwide with relatively high prevalence in Africa and the Middle East. (20)The highest prevalence rate of HCV infection has been reported among Egyptian blood donors. (21)

Sequencing of the human genome revealed single differences at specific positions, these normal variations are called single nucleotide polymorphisms (SNPs).(12) Cytokine genetics are polymorphic at targeted positions, and genetic changes within coding/regulatory areas have been demonstrated to directly improve cytokine exclamation and exudation and the response to IFN-based therapy in hepatitis C virus infection (HCV). (9) This effect is probably mediated by the modulation of the immune responses secondary to the change in the cytokine level.

In this study, our ultimate goal was to find out a genetic signature to identify the ideal candidates for peg-interferon/ ribavirin therapy based on the genotype polymorphism of those cytokines with a recognized part

in the of the immune reaction modulation, and consequently the viral therapy response. Accordingly, it would be possible to prescribe the combined treatment to those patients who are likely to respond to it, whereas patients expressing the unfavorable genotype will be spared the side effects and the high cost of the treatment. Moreover, they can be directed to an alternative therapy early during the course of the disease.

In this trail we found a significant and interesting relation between GA genotype and to interferon/ribavirin treatment response, the GA genotype was significantly higher by 18 fold among non-responders (FEp = 0.003*) ($p<0.05$), while the GG and AA genotypes were higher among responders to IFN (FEp =0.210 and 0.224 respectively) ($p>0.05$).

Studying the IL-10 -819 SNP showed that the TT and CC genotypes were prevalent among responders while CT genotype was higher among non-responders. Regarding the IL 10 -592 SNP, it was found that the AA genotype was prevalent among the responders while CC and CA genotypes were higher among responders.

In agreement with our result, Branwen Hennig et al., studied the IL-10 promoter polymorphism and its correlation with the outcome of hepatitis C infection, (22)they found that responders to interferon administration indicated a significantly higher rate of the IL-10 (-1082) GGand -592 AA genotype, while the IL-10 -1082 heterozygous form and IL-10 -592 CC genotype were more frequent among non-responders.

In a previous study done by Shi-yong zhang et al. on the effect of IL-10 -1082 polymorphism and IL-10-592 polymorphism on persistence of chronic hepatitis C infection in non-treated patients with IFN. (23) It was found that IL-10 -1082 AA and IL-10 -592 CA were associated with increased risk of persistent HCV infection,but -1082 GA and -592 AA with a reduced risk.

In our study of IFNγ gene polymorphism for association with interferon /ribavirin treatment response in patients with chronic hepatitis C, we found that TT and TA genotypes were prevalent among non-responders while the AA genotype was more prevalent among responders. Likewise Ying Huang, et al., and Yu ML et al.,demonstrated that there was no significant association of the +874 T/A SNP and treatment response. (24,25)Bahget et al., also found that the TA genotype favored a more severe form of liver disease.(26)

Analysis of the association between -308 polymorphism in the TNF-α promoter and IFN/ribavirin tretment response showed that he GG and AA genotypes were prevalent among the responders, while GA genotype was higher among non-responders. Similarly, CL Thio et al. studied the effect of tumor necrosis factor alfa (TNF-α) gene polymorphism on the natural clearance of hepatitis C virus infection. The study showed no significant association between the TNF-α -308 and the response to Interferon-α, the study also found that -863A to be associated with HCV clearance. (27) On the other hand, Kusumoto et al, studied the association between TNF-α-308 and hepatic cirrhosis in HCV patients and found that -308A was associated with increased cirrhosis in HCV patients. (28)

This study demonstrated a significant increase in GG genotype among responders by 7.8 fold (FEp 0.027*), ($P<0.05$). Although GC and CC genotypes were higher among non-responders, they were not significant ($p>0.05$).

Similarly, Fabris et al, studied the outcome of IL-6 promoter polymorphism and consequence of HCV (29)and established that IL-6 G/C genotype was linked to non-responders. On the other hand, Nattermann, et al, studied the outcome of IL-6 -174 polymorphism on the treatment consequence of HCV in its co-infection with HIV among Italians,(30)they established that the IL-6 -174 G/C polymorphism correlated to good response to IFN. This difference can be attributed to the smaller size of our study as they studied 424 Italian patients, different ethnic background and the HCV mono-infection of our studied group.

According to TGF-β codon 10 polymorphism, The T/T and C/C genotypes were higher among non-responders.AlthoughT/C genotype was more prevalent in responders, it was not significant ($P>0.05$). Rodart, et al, studied the relation of TGF-β1 Polymorphism with HCV infection (31), and found that the infection became more severe when T/T and T/C genotypes in codon 10 were combined with G/G genotype in codon 25 TGF-β1 in untreated patients, he also found that the G allele of TGF-β codon 25 was expressively increased in hepatic C infected patients than in wellbeing.

V. Conclusion

The findings of this study suggest that the gene polymorphisms of TNF-α, TGF-β, IL-10, IL-6, and IFN-γwere accompanying with vulnerability to the progress of chronic disease of hepatitis C virus among children. This study was the first to reveal this interesting finding and to be performed on a pediatric age group to verify if the studied SNPs, either in isolation or grouped affect the outcome of IFN-ribavirin therapy in chronic HCV infection. It is recommended to study this association on a larger scale and study other cytokine polymorphisms (as IL-28B C/C) to predict response to IFN, which is a predictive of HCV RNA clearance in adults.

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