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Studying Polymorphism Of Toll-Like Receptor-6 And HADV7 In Childhoodwith Acute Respiratory Tract Infections

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Abstract

Background: Infection wih HAdV 7 develops serious illness with many complicationsduring childhood. As part of innate immune response, recognition of pathogen associated molecular patterns is mediated by pattern recognition receptors including Toll-like receptors (TLRs).

Method: One hundred cases included in the study; 75 with acute respiratory tract infection (ARTI),diagnosed medically by specialist clinician, their mean age was (40.56±8.31 months) and 25 apparent healthy controls (AHC) with mean age (43.6± 10.96 months). DNA extracted from blood specimens, nasopharyngeal and throat swabs from patients and controls for further extraction of human adenovirus (HADV7) genome and total genomic DNA. Detection of Toll-like receptor 6 (TLR-6) polymorphism detected by using ARMS PCR technique.

Results:HADV7 nucleic acid detected in 66.7% of ARTI cases, while no viral nucleic acid was detected in AHC group (P=0.03). In ARTI, the most commonly affected age stratum infected with DNA –HADV7 was (6-44 months) which constituted 34% (P< 0.05).

The results of TLR-6 (rs5743557) amplification appeared that frequency of GG and AG genotypes in patients with ARTI and AHC groups was significantly increased in patients than controls, in which GG genotype increased as rate OR=2.489 compared with GA and AA genotypes in studied groups.

Conclusions:HADV7 that recently identified in Iraq causes acute respiratory tract infections in children and more specific in infants. In addition, TLR 6polymorphism in patients could point for its possible roles in pathogenesis of acute respiratory tract infection.

Keywords: HADV-7, Toll-like receptor-6, Acute respiratory infections,

Introduction:

The family Adenoviridae comprises genus members called human adenoviruses with linear ds DNA, virus species and types classification done by using sequencing techniques (1). These viruses cause infections throughout the year (2). Human adenovirus-7 (HADV-7) causes serous respiratory problems in children. In comparison with other types, HADV-7 showed more severe cases (3).A case study in 2014 reported the role of the virus in causing fatal outcome and nosocomial transmission (4).The virus capsid genes studied in China during 2020 to know the genetic variability of the virus (5).Toll-like receptors (TLR) play an important role in recognition and bind with pathogen associated molecular patterns to activate immune components against viral and bacterialinfections (7,26-43)(8). Many studies indicated the genetic map related to TLR-6 to understand and explain its role in immune responses (9) (10).However, this research work is a new studyabout HADV7 and TLR6 polymorphism in relation to a set of acute respiratory tract infection of childhood patients in Iraq.

Materials and Methods

Study population:

Seventy-five children and infants having acute respiratory tract infections (ARTI) with age range (6-120) months and 25 apparent healthy controls(AHC) with age range (8-120) months were included in the study. Out of the total studied population (ARTI and AHC); 58 were males and 42 were females. The medical diagnosis was done by specialist clinician.

Extraction ofDNA from clinical specimens:

Peripheral blood specimen, nasopharyngeal and throat swabs were taken from the study population. Specific viral DNA/RNA extraction kit used for extraction, the total genome DNA extraction was done according to the protocol of G-SPIN^{TM}Total Extraction kit, Intron/Korea). Then DNA was quantified, purified and detected by gel documentation.

PCR for Human Adenovirus 7 (HADV7) Fiber Gene:

Amplification of HADV 7 fiber gene done by using Qiagen amplification mixture. The amplification steps as follow; 35 cycles (94^{o}C for 1 minute then 50 ^{o}C for 1 minute, 72 ^{o}C, 2 minutes and the final step, 72 ^{o}C, 7 minutes.

Detection of TLR-6 polymorphism:

The extracted total genome DNA from peripheral blood, nasopharyngeal and throat swabs was used in amplification of the target region using ARMS-PCR technique.

Results:

I.Distribution of Patients with Acute Respiratory Tract Infection (ARTI) and Apparently Healthy Control (AHC) Groups According to Their Age

The mean age of the patients with ARTI was (40.56±**8.31**months) was less than the mean age of the AHC(43.6± **10.96** months). There are non-significant statistical differences (p=0.47) between ARTI and AHC (Table 1).

Table1 : Distribution of Patients with ARTI and AHC according to Their Age.

Study groups	No.	Mean of age (Months)	S. D	S. E	Range		(P-value)
					Minimum	Maximum	
ARTI	75	40.56	8.31	2.304	6 months	120 months	P=0.47 N S (P>0.05)
AHC	25	43.6	10.96	4.59	8months	120 months	
	100						

II.Distribution of Patients with ARTI and AHCAccording to Their Age Stratum And Gender.

Figure 1 showsthe distribution of male patients in this study were 31%, 6% and 7% for ARTI patients with age group 6-44 months, 45-83 months and 84-122 months, respectively; while the distribution of male AHC 10%,3% and 3% with the same previously age groups ,respectively. Furthermore, the distribution of female patients in this study were 16%,10%,1% with age group 6-44 months, 45-83 months and 48-122 months, respectively.While, the distribution of female AHC were 6%, 4%, 3% with the same previously age groups,respectively.

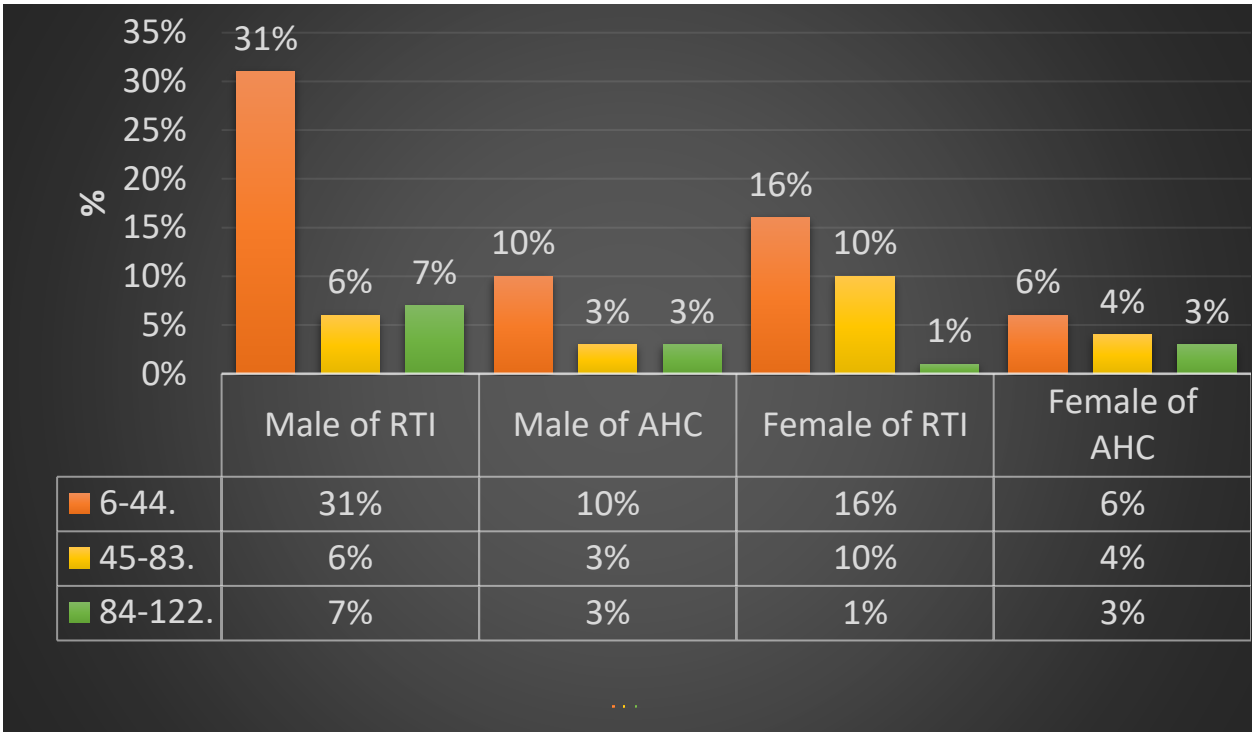

Figure 1: Distribution of Children and Infant and Children Population III.Study According to Their Age Stratum and Gender.

Clinical characteristics

Thirty-three (44%) of patients were present with pneumonia, while bronchiolitis ; bronchitis and asthma accounted for (20) 27% ;(9)12% and (13) represented 17%, respectively of respiratory illness.Through the medical diagnosis by the specialist physician as well as the laboratory diagnostics of the patients participating in these study, it was found that there are 44% of patients suffering from pneumonia followed by 20%, 17% and 12% of patients suffering from bronchiolitis, asthma, and bronchitis, respectively.The majority of children (55%) had a hospital stay for less than 3 days, and about half of them had a medical history especially pneumonia, cough and seizure were (7%), (10%) and (7%), respectively as shown in (Table 2).

Table 1:Clinical Characteristics of Infant and Young Children Patients Included in This Study.

Variables	No. (%)
No. days prior to admission to hospital ≤ 3	

days	41 (55 %)
4-14 days	24(32 %)
> 14 days	10 (13 %)
Diagnosis	
Pneumonia	33 (44%)
Bronchiolitis	20 (27%)
Asthma	13 (17%)
Bronchitis	9 (12%)
Duration of hospital stay	
1-3 days	42 (56 %)
> 3 days	20 (27 %)
Variables	13 (17 %)
Medical history	
None	41 (54%)
Pneumonia	5 (7 %)
Sepsis	4 (6%)
meningitis	3 (4%)
Cystitis	2 (2%)
Jaundice	1 (1%)
Seizure	5 (7%)
Cardiac septal defect	3 (4%)
Cough	8 (10%)
Mixed	3 (4%)

IV.Detection of Human Adenoviruses 7 (HADV7) by Polymerase Chain Reaction Technique(PCR)

1. Extraction Nucleic Acid by Specific Viral DNA/RNA Extraction Kit:

Out of 100 nasopharyngeal swab ;throat swab and blood specimens involved in this study 50 (50%) were found to have a viral infection; including (50) patients equivalent to 66.7% of the total (75) patients with ARTI who were sampled in this study, more than 25 patients who did not show have a viral genome, had an equivalent 33.3% of the total number of patients as shown in Figures (2). While,no viral nucleic acid was detected among all the examined apparently healthy

specimens (25) as control group.There were statistically significant differences (p = 0.03) between patients with the viral genome and those without the Viral genome (Table 3).

Table 2: Percentage of Viral Genome Extraction of Patients with ARTI And AHC Groups.

Viral Genome		Study Groups		
		AHC No. (25)	ARTI No. (75)	Chi-Square (P-value)
Positive	N	0	50	
	%	0%	66.7 %	
Negative	N	25	25	P=0.03
	%	100%	33.3%	S.
Total	N	25	75	(P<0.05)
	%	100%	100%	

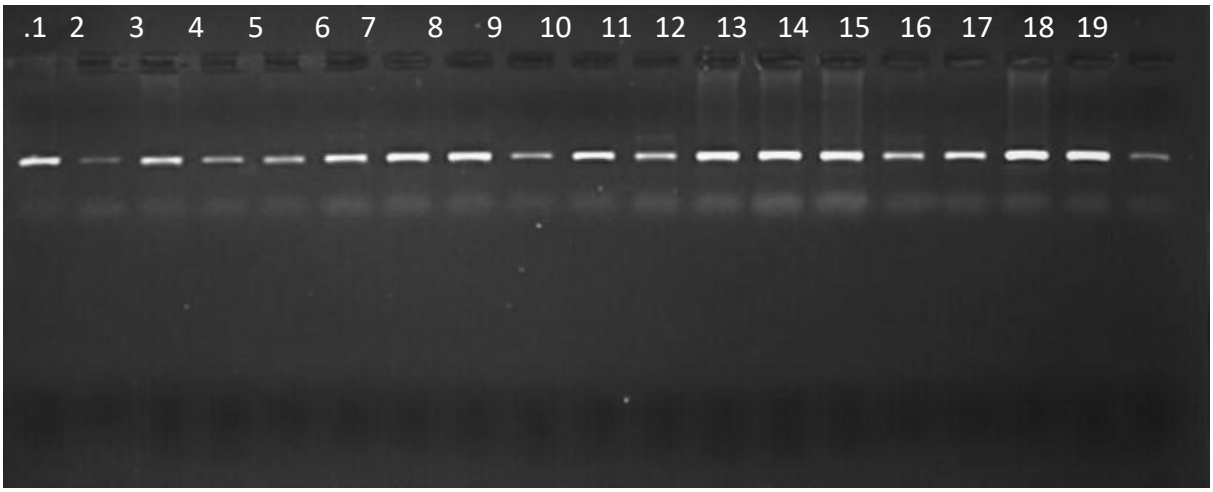

Figure 2: Extraction of Viral Genome from Patients with ARTI ,1 % Agarose Gel Electrophoresis , TBE 1X ,at Voltage 75 Volt for 45 min, Lanes (1-19) were Positive.

2. Detection ofHADV7 Genome By PCR:

The positive result according to PCR shows 56% (28 out of 50 cases) as positive while 44% (22 out of50 cases) as negative, as shown in (Table 4) as well as Figures (3).Statistically significant differences (p = 0.04) among patientsgroup.

Table 4: Percentage of HADV7Positive Signals in Patients with ARTI by Using qRT.PCR Technique.

Total Viral genome	No.	%	P value
Positive	**28**	56	**P=0.04** **S** **>0.05**
Negative	22	44	
Total	50	100	

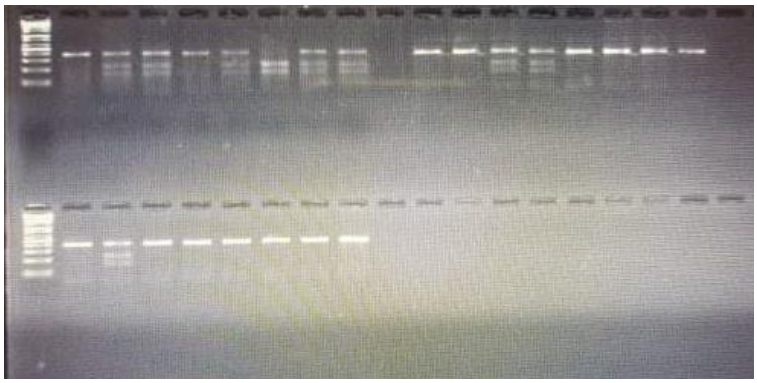

Figure 3:Detection ofHADV7 Genome By PCR

V.The Results of HADV7 in the Patients with ARTI According to the Age Stratum.

In ARTI, the most commonly affected age stratum infected with DNA –HADV7 was (6-44 months) which constituted 34% (17 out of 50 cases), while the age stratum (45-83 months) was constituted 12% (6 out of 50 cases), followed by 10 %(5 out of 50) in age stratum (84 – 122 months). Statistical comparison of these age stratum revealed significant differences ($p< 0.05$), (Table 5).

Table 3 Frequency of HADV7-PCR Signal Among The Patients With ARTI According to the Age Stratum

Age Stratum	Months	HADV7			P value
		No.	Positive	Negative	

	6-44	32	17	15	
		64%	34%	30%	
	45-83	11	6	5	Anova test
		22%	12%	10%	P=0.04
	84-122	7	5	2	S.
		14%	10%	4%	(P<0.05)
Total		50	28	22	
		%100	56%	44%	

VI.The Results of HADV7 in the Patients with Viral DNA According to the Gender.

Table (6) illustrated the positive results of HADV7-PCR detection from patients with ARTI according to their gender where 64% (18 out of 28) were males and 35.7% (10 out of 28 cases) were females. The statistical analysis found significant differences among gender with positive HADV7-PCR in ARTI group (P <0.05).

Table 6.: Percentage of HADV7 in ARTI Patients According to Their Gender.

ARTI Patients	HADV7- Infection	
	+	%
Male	18	64.3
Female	10	35.7
Statistical analysis	(P <0.05) = 0.03 S	

VII. Resultsof Gene Polymorphism of Toll Like Receptors 6(TLR.6):

1.Extraction Total Genome DNA from theNPA&TS Swabs as well as Blood Specimens:

The whole genomic DNAwas extracted ,purifying and migrated using agarose gel from the NPA&TS swabsas well as blood specimens of infants and adult children patients with respiratory tract infection as well as apparently healthy control groups as a first step to amplify the target the tow single nucleotide polymorphisms (SNPs) TLR.6 gene polymorphism.After used the gel electrophoresis technique the result was almost the appearance of the DNA in 75 patients with ARTI and 25 as AHC samples as shown in Figure (4).

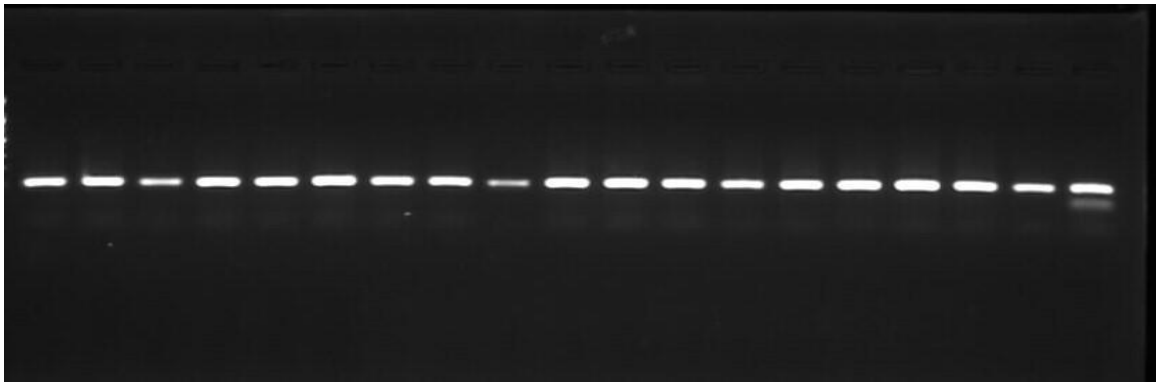

Figure 4: Extraction Human Total Genome DNA From ARTI & AHC, 1% Agarose Gel Electrophoresis, TBE 1X, at Voltage 75 volt for 45 min.

VIII.Genotyping of TLR.6 Gene Polymorphisms

The amplified of TLR-6 (rs5743557) target sequences of studied groups were by ARMS technique are summarized in table (7) and figures (4) .Two bands (G Allele=108 bp and A Allele=162 bp) due to the presence of the G>A mutation. Whereas the wild type was identified by a single bp fragment. It can be seen that the frequency of GG and AG genotypes in patients with ARTI and AHC groups which reached 42.9%, 28.6%, 25%, and 14.3% respectively. It was significantly increased in patients than control, in which GG genotype increased as rate OR=2.489 compared with AG and AA genotypes in studied groups. On the other hand, the frequency of AA genotype in patients with ARTI and AHC groups was 32.1% and 57.1% respectively, that decreased in patients.From the table(7) showed the statically analysis found a high significant in TLR.6 gene polymorphism of that Iraqi patient**.**

Table 7: Genotype Distribution and Odd Ratio of TLR.6 GenePolymorphisms Between the ARTI Patients and AHC.

Genotype TLR-6 (rs---------)		Study Groups		Total	P. Value	OR	95% C.I for OR	
		ARTI	AHC				Lower	Upper
AA	N	9	4	13	0.02	0.551	0.371	0.812
	%	32.1	57.1	37.1				
GG	N	12	2	14	0.03	2.489	1.342	1.630
	%	42.9	28.6	40				
AG	N	7	1	8	0.02	0.234	0.493	0.459
	%	25	14.3	22.9				
TOTAL	N	28\75	7\ 25	35				
	%	37.3	28	100				

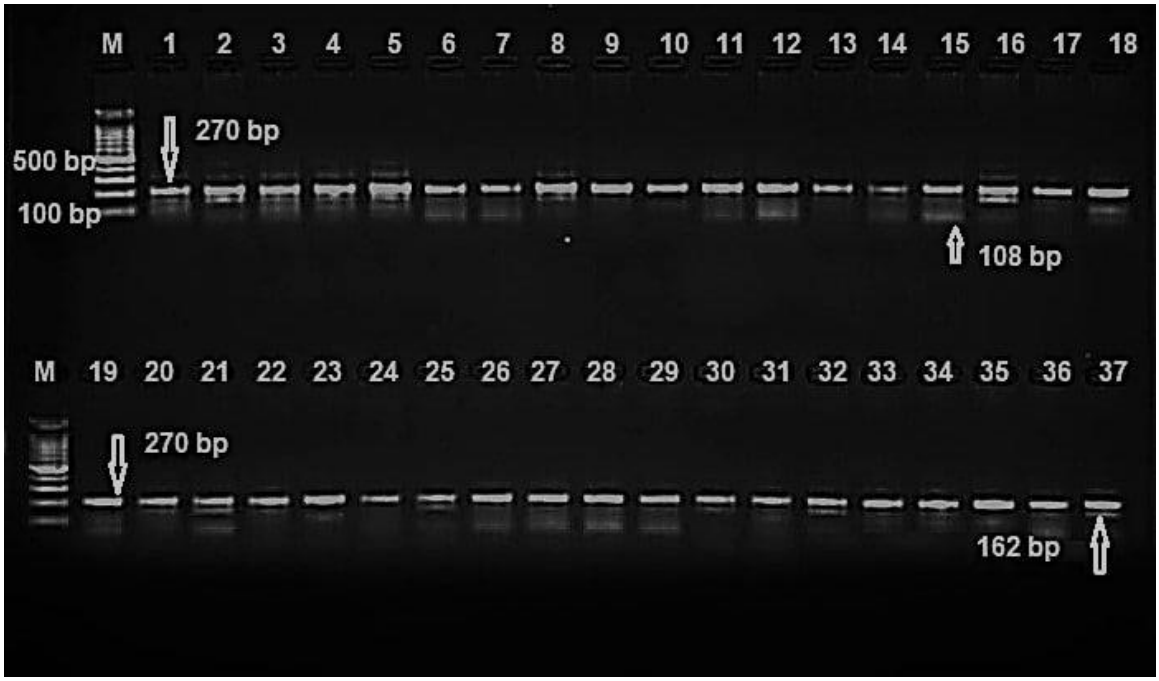

Figure 7: Allelo typing patterens of TLR.6 gene using PCR-ARMS; Showed a heterozygous allele (GA) had a two band (108and 162pb) molecular size in ARTI. While ,homozygous allele had a single band with ---- bp molecular size.M: DNA ladder 100-1100 bp .The amplified products using PCR-ARMS migrated into 3% agarose, 75V, 20 mA for 120 min; 15 µl in each well; stained with ethidium bromide.

Discussion

These results could reflect that age is a very important factor in developing acute respiratory infections and increase the possibility of finding viral infections, especially rhinoviruses, RSV, Advs and HBoVs. In general, the lower of age, the greater the risk of respiratory infections (11). The current study agreed with other studies that revealed the gender, specifically in male children might play a role as a risk factor in respiratory morbidity (12). A study mentioned that there is difference between male and female regarding to airway growth and parenchymal growth (13). Type of specimen is an important factor in detection of HADV7, especially nasopharyngeal aspirate (14). The severity and morbidity of disease caused by HADV 7 comparing with other HADVs was proved in many studies(15-19). Fatel outcomes due to infections with this virus in many countries in Asia aned Europe have been proved (20,21). Differential diagnosis for pneumonia as a result of HADV infection from other etiological viral infections seems very difficult (22). Many studies

proved the association between TLRs genetic variants and many respiratory diseases in children including asthma and atopic dermatitis (23,24,25).

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