RESEARCH PAPER

The Impact of Interleukin-17 Levels on Recent and Previous Hepatitis A Virus Infections in Pediatric Patients

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Abstract

Background: Infection with the hepatitis A virus (HAV) persist to be a critical issue in pediatrics. Although interleukin-17 (IL-17) is known to have a vital functions in the regulation of the inflammatory responses, the association of IL-17 with the phases of HAV infection in the pediatric population is not well clarified.

Objective: The aim of the study was to evaluate the levels of IL-17 in pediatric who had recent as well as past hepatitis A virus (HAV) infection and to compare it with the IgM and IgG antibody responses.

Methods: In this cross-sectional study, 42 pediatric patient with hepatitis A virus infection and 35 healthy controls were included. The subjects were divided into two groups based on serological evidence of hepatitis A virus infection. Group A comprised patients with evidence of current infection, and Group B comprised patients with evidence of past infections. Serum levels of interleukin-17, anti-HAV IgM, and anti-HAV IgG were measure using an ELISA method.

Results: The patient group had significantly decrease IL-17 levels in compared to the control groups (mean: 33.46 ± 22.29 pg/mL vs. 45.73 ± 20.95 pg/mL; $p = 0.0152$). Patients showed significantly lower anti-HAV IgG levels than controls (mean: 1.685 ± 1.009 vs. 2.909 ± 0.542; $p = 0.0001$), whereas there was no significant differences in IgM levels ($p = 0.4239$). A subgroup analysis revealed no significant differences in IL-17 ($p = 0.3986$), IgG ($p = 0.5277$), or IgM ($p = 0.5273$) between recent and past infection.

Conclusion: When compared to normal control, the pediatrics group of hepatitis A virus-infected individual exhibited decreased levels of interleukin-17. This indicates the immunomodulatory effect of the virus. The significant decrease in the level of IgG in the infected individuals may be an indicator of immune system disturbances. This warrants the need to study the involvement of IL-17 in the pathology and recovery of the disease.

Keywords: Hepatitis A virus, Interleukin-17, pediatric patients, IgG, IgM, immune response

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1.Introduction

Hepatitis A virus is a highly contagious hepatotropic virus causing acute liver inflammation and mainly spreads through the fecal-oral pathway (1). Indeed, despite the availability of effective vaccinations, HAV infection still constitutes one of the most important global health concerns for pediatric patients, mainly in developing countries due to the lack of proper sanitation facilities (2). Children often act as asymptomatic carriers and reservoirs for community transmission of the disease (3).

The immune response against HAV infection involves both innate and adaptive immunity. Anti-HAV IgM antibodies are an indicator of acute or recent infection that typically appears during the first week of symptoms and stays for many months (4) Anti-HAV IgG antibodies, which appear soon after IgM and persist for a lifetime, provide long-lasting protection. Understanding the temporal dynamics of these responses is important for proper diagnosis and estimation of population immunity (5).

T helper 17 cells are the major producers of interleukin-17, a pro-inflammatory cytokine that is critical in host defense against extra-corporeal pathogens and participates in a variety of inflammatory diseases (6). IL-17 enhances the recruitment of neutrophils, triggers the production of antimicrobial peptides, and activates the production of other pro-inflammatory cytokines that

promote inflammation (7). Though the exact role of this cytokine during HAV infection remains to be fully understood, latest research reveals that IL-17 may possibly be involved in the pathophysiology and treatment of viral hepatitis (8).

Current investigations of viral hepatitis diseases have proven to have a complex association with the IL-17 role in the course of these diseases. For hepatitis B and C, increased IL-17 levels are associated with increased inflammation of the liver and the development of fibrosis (9, 10). HAV infection is unique because it causes acute self-limiting hepatitis rather than chronic infection. Thus, the immunity developed to HAV infection is unlike the immunity developed to the hepatitis viruses (11).

As for pediatric, the relationship between the levels of IL-17 and different stages of HAV infection is still under investigation, yet we already have an obvious correlate for HAV infection and a good understanding of the importance of IL-17 in the inflammation process. It is still not well understood how the expression of IL-17 relates to immune responses to HAV infection, involving both IgM and IgG antibodies, and how it does so during different phases of HAV infection.

2. Methods

Study Design and Participants

This cross-sectional study was conducted between 2025/07/16 to 2025/11/15 at Children's Welfare Teaching Hospital \ Medical City. The study included 42 pediatric patients diagnosed with HAV infection and 35 age-matched healthy controls. Patients were recruited from the pediatric gastroenterology and infectious disease clinics, while controls were selected from children attending the hospital for routine check-ups with no history of hepatitis or acute illness.

Inclusion criteria for patients were: (1) age between 1 and 16 years, (2) confirmed HAV infection based on positive anti-HAV antibodies, and (3) absence of other concurrent infections or chronic diseases. Exclusion criteria included: (1) co-infection with other hepatotropic viruses (HBV, HCV), (2) immunosuppressive therapy, (3) autoimmune disorders, and (4) chronic liver disease from other causes.

Patients were subdivided into two groups based on serological profiles:

- **Group A (Recent infection):** Patients with positive anti-HAV IgM indicating acute or recent infection (n = 28)
- **Group B (Previous infection):** Patients with positive anti-HAV IgG and negative IgM indicating past infection (n = 14)

Similarly, control participants were divided into:

- **Control Group A:** Healthy children age-matched to patient Group A (n = 18)
- **Control Group B:** Healthy children age-matched to patient Group B (n = 17)

Ethical approval was obtained from the institutional review board, and written informed consent was obtained from parents or legal guardians of all participants.

2.1 Sample Collection and Processing

Five milliliters of venous blood were collected from each participant following standard aseptic techniques. Blood samples were allowed to clot at room temperature for 30 minutes before centrifugation at 3000 rpm for 10 minutes. To prevent protein and antibody degradation, the serum was separated and stored in aliquots at -80°C until analysis.

2.2 Laboratory Measurements

IL-17 Measurement: Serum IL-17 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions. All samples were test in duplicate, and the average value was recorded. The results were represented as picograms per milliliter (pg/mL).

Anti-HAV Antibodies: Anti-HAV IgM and IgG antibodies were tested with ELISA kits designed specifically for HAV serology. The examines followed the manufacturer's instructions. Result were classified as positive or negative using determined cutoff values, with quantitative data collected for statistical analysis.

2.3 Statistical Analysis

The statistical analysis was carried out using the GraphPad Prism software (10.6.1). The statistical relationships among the clinicopathological variables associated with HAV infection were assessed using a t-test to analyze quantitative data. ROC curve analysis was performed to evaluate the diagnostic performance of IL-17 levels. Curve, examine the curve's area under the curve (AUC), as well as the particular sensitivity and specificity values at several threshold points. Pearson correlation analysis was used to investigate the relationship between the variables, yielding a correlation coefficient (r) that quantifies the interrelations between two continuous variables. In all statistical analyses, a p-value less than 0.05 is considered statistically significant.

3.1 Results

3.2 Clinical and Demographic Considerations

A total of 77 study participants took part in the study: 42 patients with hepatatis A virus infections and 35 controls. There are clear demographic similarities between the two groups with respect to age and sex.

3.3 IL-17 Levels in Patients versus Controls

Analysis of IL-17 levels revealed a statistically significant difference between the patient group and control group(figure 1, table 1).

Parameter	Control	Patients	P-value
IL-17 (pg/mL)			
Mean ± SD	45.73 ± 20.95	33.46 ± 22.29	**0.0152***
Median (IQR)	38.59 (30.72-58.26)	25.03 (20.11-39.05)	-
Range	2.85-89.06	11.97-105.9	-
Anti-HAV IgG			
Mean ± SD	2.909 ± 0.542	1.685 ± 1.009	**0.0001*****
Median (IQR)	2.964 (2.46-3.40)	1.892 (0.72-2.46)	-
Range	1.83-3.78	0.14-3.66	-
Anti-HAV IgM			
Mean ± SD	1.255 ± 0.912	1.411 ± 0.810	0.4239
Median (IQR)	1.062 (0.51-1.63)	1.304 (0.62-2.08)	-
Range	0.16-3.41	0.16-2.96	-

Table 1: Summary Statistics of IL-17 and Antibody Levels

***P < 0.05; ***P < 0.001. Data presented as mean ± standard deviation or median (interquartile range). Statistical comparisons performed using Student's t-test or Mann-Whitney U test as appropriate.**

The mean IL-17 concentration was significantly lower in patients (33.46 ± 22.29 pg/mL) compared to healthy controls (45.73 ± 20.95 pg/mL), with a p-value of 0.0152. The median IL-17 level in patients was 25.03 pg/mL (IQR: 20.11-39.05), while controls showed a median of 38.59 pg/mL (IQR: 30.72-58.26).

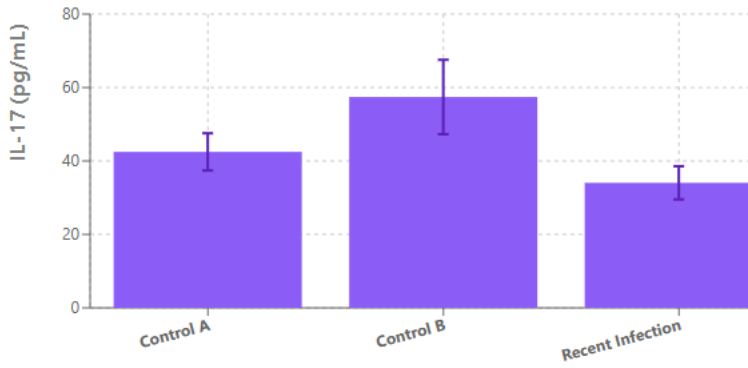

Figure 2: IL-17 levels stratified by infection stage. Recent infection (Group A) vs. Previous infect matched controls. Error bars represent SEM. No significant differences between subgroups (Co

IL-17 levels demonstrated considerable inter-individual variability in both groups, spanning 93.91 pg/mL in

patients (11.97-105.9 pg/mL) and 86.21 pg/mL in controls (2.846-89.06 pg/mL), indicating substantial inter-individual variability.

3.4 IL-17 Levels by Infection Stage

When the data from the recent infection group (Group A) was compared to the previous infection group (Group B) through a subgroup analysis, there was no significant difference in the amount of IL-17 ($p = 0.3986$). Patients with recent infection had a mean value of 34.05 ± 23.94 pg/mL of IL-17 (median = 26.07 pg/mL), while the patients with previous infection had a mean value of 27.36 ± 23.73 pg/mL (median = 22.14 pg/mL). This indicates that the amount of IL-17 is suppressed regardless of the stage of HAV infection.

There was no significant difference in the means of Control Group A (mean = 42.48 ± 21.54 pg/mL) and Control Group B (mean = 57.42 ± 41.75 pg/mL), as the p-value was found to be 0.199.

3.5 Anti-HAV IgG Levels

A highly significant difference was observed for the Anti-HAV IgG levels between the patient group and the control group. The patient group showed lower levels of IgG when compared to the control group. The mean for the patient group was 1.685 ± 1.009, and the mean for the control group was 2.909 ± 0.542. The results were statistically significant with a p-value of 0.0001. The median for the patient group was 1.892 in patients versus 2.964 in controls.

The subgroup analysis's results showed no significant differences in the levels of IgG antibodies between patients with a recent infection, whose mean was 1.796 ± 1.127, and patients with a previous infection, whose mean was 1.596 ± 0.9533, as the p-value was 0.5277.

The unexpected result may have been influenced by the different immune responses in individuals or the timing of the collection of the sample in relation to the start of the infection. As for the levels of IgG in the control group, these values were almost the same for both Control A and Control B, i.e., 2.937 ± 0.460 and 2.938 ± 0.754, respectively; $p = 0.9978$.

3.6 Anti-HAV IgM Levels

Anti-HAV IgM levels showed no statistically significant difference between the overall patient group (mean: 1.411 ± 0.8102) and controls (mean: 1.255 ± 0.9124), with a p-value of 0.4239. The median values were also comparable (1.304 for patients vs. 1.062 for controls).

Subgroup comparisons revealed no significant differences. The group of patients who suffered a recent infection showed a level of 1.503 with a standard deviation of 0.9122. The patients who suffered a past infection showed a level of 1.328 with a standard deviation of 0.8737 (p-value of 0.5273). The levels of IgM of these two groups of control are also very low with a high p-value of 0.7548.

4. Discussion

This study shows significant immunological changes that may have consequences for understanding disease pathogenesis and host immune response, offering novel perspectives relationship between IL-17 levels and HAV infection in pediatric patients.

The main result of this study was that pediatric patients with HAV infection had lower levels of serum IL-17 than healthy controls ($p = 0.0152$). This finding contrasts with data from HAV patients, where elevated IL-17 levels have been linked to the development of hepatitis and hepatic fibrosis (9, 10).

Patients with HAV infection may have lower levels of IL-17 due to a specific immunopathological mechanism common to acute hepatotropic viral infections.

The population's reduced IL-17 production could be due to a variety of factors. First, HAV may inhibit Th17 cell differentiation, resulting in reduced IL-17 production. Viral infections, including HAV, have developed a variety of techniques through the course of evolution to evade the host immune system (12). Interference with the cytokine network is a well-known immune evasion mechanism employed by viruses. This includes the suppression of the production of pro-inflammatory cytokines, which could otherwise cause liver damage (13). Indeed, the immune suppression observed during an HAV infection could be a protective mechanism, as excessive liver damage could otherwise be observed. Additionally, the liver dysfunction during an HAV infection could also play a role. This could, in turn, affect the production of IL-17 (14).

The lack of a significant difference in the amount of IL-17 produced by recent and past infections ($p = 0.3986$) suggests that suppression of the cytokine may extend beyond the initial phase or that the timepoints sampled were not sufficient to observe the dynamic changes in the cytokine. Future studies that include multiple timepoints after the onset of HAV infection are warranted to better understand the pattern of change in

the amount of IL-17 produced over the course of the infection.

The significantly lower level of anti-HAV IgG in infected patient compare to controls ($p = 0.0001$) are an unexpected result that warrants careful consideration. Traditionally, IgG antibodies have been known to occur in the convalescent stage of the disease and last a lifetime, providing immunity against the hepatitis A virus (5). The lower IgG levels in our patient population could be explained in several ways.

Firstly, the patient group may have still been within the initial phase of the acute infection, during which the IgG antibody response may not have developed or peaked. The time elapsing between the onset of symptoms and the collection of the samples is of prime importance when considering the antibody levels. Secondly, the control group may have naturally elevated IgG antibody levels due to previous exposure to HAV, vaccination, or the transfer of maternal antibodies to their children. The patient group may have other factors affecting the production of these antibodies, such as genetic or nutritional deficiencies, contributing to the low IgG antibody levels (15).

The lack of significant differences in IgM levels between the patient and the control groups ($p = 0.4239$) is intriguing, especially in the case of the Group A patients, since they are expected to have high IgM as a consequence of a recent infection. This phenomenon could imply that the individuals included in the “recent infection” group were actually in a post-infection status with declining IgM concentrations or that the ELISA test was not sufficiently sensitive to pick up the changes in the IgM concentrations.

The simultaneous decrease in levels of both IL-17 and IgG in infected patients may point towards a potential immunological association between the two, as it has been established that IL-17 has a significant role in modulating B cell responses in a number of contexts (16). Th17 has been shown to play a significant role in B cell activation as well as in switching to produce antibodies such as IgG, which are a part of the Th17 subset itself; hence, a decrease in levels of IL-17 in hepatitis A virus infections may point towards a defective IgG response, which needs to be investigated in this context as well (17).

Furthermore, the relationship between natural and acquired immunity in HAV infection could potentially include IL-17 as a "bridging" molecule. The early stages of natural immunity to HAV infection require activation and production of natural killer cells and interferon to limit viral replication (18). If the inhibition of IL-17 represents a component of a general immune regulatory system, it could potentially influence the development and quality of acquired immunity, including antibody formation.

Understanding the dynamics of IL-17 in HAV infections has potential clinical implications. If the suppression of IL-17 levels is evident in all patients with HAV infections, then the levels of IL-17 have the potential to act as a biomarker for the disease. Patients with higher suppression levels of IL-17 have different clinical outcomes compared to those with lower levels of suppressed IL-17.

Moreover, the observation that IgG titers are low in infected individuals also raises important questions regarding the effectiveness of the vaccines used. If the HAV infection does not produce adequate antibody titers, post-infection surveillance and the administration of booster shots may be necessary.

5. Conclusion

The present study establishes a significant decrease in the levels of serum Interleukin-17 in pediatric patients with hepatitis A virus infection when compared to healthy controls, which could point to a potential immunomodulatory consequences of the hepatitis A virus. The parallel reduction in anti-HAV IgG levels in hepatitis A patients also points to an immune response worthy of examination.

In addition, IL-17 inhibition seems to be a non-phase-dependent phenomenon, based on the fact that IL-17 inhibition happens in the existence as well as the absence of recent infection. The lack of significant difference in anti-HAV IgM levels between patients groups and controls, despite expected increases during acute infections, demonstrates the difficulties of antibody kinetics.

The study provides more clues in understanding how HAV infection influences the immune system in children and leads to some relevant questions about the role of IL-17 in viral hepatitis. The association of suppressed levels of IL-17 and antibody responses might point to a potential relationship between innate and acquired limbs of immunity.

Future research will be focused on longitudinal evaluation of the functional importance of IL-17 level modifications in the context of HAV infection. This will

possibly guide the discovery of novel approaches in the diagnosis and/or therapy of pediatric hepatitis A virus infections.

In conclusion, while it has been widely accepted that the infection from the HAV virus tends to be a self-limiting illness with a good prognosis, it has become essential to elucidate the immunological mechanisms, such as the levels of IL-17, in order to effectively care for patients, as well as prevent such infections in vulnerable populations of children.

6. Recommendations

Based on the findings and limitations of this study, we propose the following recommendations for future research and clinical practice:

1. Longitudinal Studies: Prospective studies to measure serial samples for the levels of IL-17, IgM, and IgG at different stages after HAV infection, such as during the acute phase, early and late convalescence, and long term, to define the temporal profile of these immune responses during HAV infection and recovery.
2. Mechanistic investigations: Investigate the mechanisms of the suppressed levels of IL-17 in HAV-infected patients by performing in vitro and ex vivo studies, including the assessment of the frequencies and functions of Th17 cells and the transcription profiles of infected patients.
3. Comprehensive Cytokine Profiling: Extending the scope of immunology investigations with the inclusion of more cytokines like IL-6, IL-21, IL-22, IL-23, IFN-γ, TNF-α, and the inclusion of the regulatory cytokines like IL-10 and TGF-β,
4. Correlation with Clinical Parameters: Examine the correlation of IL-17 levels with clinical parameters such as the severity of clinical symptoms, the duration of illness, the degree of elevation of liver enzymes (ALT and AST), the level of bilirubin in the blood, and the viral load in order to ascertain the prognostic ability of IL-17.
5. Larger Multi-Center Studies: Multi-center studies involving large numbers of subjects need to be carried out to confirm the findings of the present study among diverse populations and from varied geographical locations, considering all the influencing factors like genetics, nutrition, and environment.
6. Comparison with Other Hepatotropic Viruses: IL-17 responses in HAV infections need to be compared with those in hepatitis B, C, and E infections, which would reveal virus-specific versus general hepatotropic viral immune signatures.

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