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Clinical and Histopathological Assessment of Hepatocellular Injury in Pediatric Hepatitis A and E Infections: Insights from a Comparative Study

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Abstract

Acute hepatocellular injury caused by hepatitis A and E represents a significant burden in pediatric populations, yet comparative histopathological data remains scarce. Present investigation aimed to characterize clinical and histopathological features of pediatric hepatitis A versus E infections within a prospective cohort, employing rigorous comparative analysis. A total of 120 children with confirmed hepatitis A (n=60) or hepatitis E (n=60) underwent evaluation of serum liver function tests, histological scoring of necroinflammation and cholestasis, and assessment of lymphocytic infiltration and sinusoidal changes. Statistical comparison revealed that mean alanine aminotransferase and aspartate aminotransferase levels were significantly higher in hepatitis E ($p<0.01$), whereas hepatitis A exhibited substantially greater bile duct proliferation and portal inflammation ($p<0.05$). Histopathological scoring confirmed more frequent bridging necrosis in hepatitis E cases ($p<0.01$), denoting more severe parenchymal disruption. Novel findings include differential patterns of cholangiocytic hyperplasia and lymphocyte distribution between the two infections. Those distinctions may inform tailored diagnostic and therapeutic strategies. Findings underscore that although both viruses induce substantial hepatic injury in children, hepatitis E manifests more intense parenchymal necrosis while hepatitis A provokes pronounced portal tract responses. Such histological divergence has not been delineated previously in pediatric cohorts,

highlighting the importance of comparative evaluation. Keywords: pediatric hepatitis, histopathology, hepatocellular injury.

Introduction

Acute viral hepatitis remains a leading cause of pediatric liver disease globally, with hepatitis A virus (HAV) and hepatitis E virus (HEV) accounting for substantial morbidity particularly in regions with limited sanitation. Recent epidemiological trends indicate that while vaccination efforts have reduced HAV incidence in certain regions, HEV continues to impose sporadic outbreaks with significant clinical impact among children. In parallel, advances in noninvasive imaging and biomarker studies have improved detection of hepatic injury, yet detailed histopathological comparison between HAV and HEV among pediatric patients remains underexplored. Studies published since 2022 have reported elevated aminotransferase levels and coagulation abnormalities associated with HAV and HEV, but these reports offer predominantly biochemical rather than histological insight. The underlying cellular and tissue-level responses—portal inflammation, necrosis patterns, cholestasis, architectural disruption—have not been systematically contrasted in pediatric populations within a single study framework. This lacuna hampers nuanced understanding of pathogenesis and tailored clinical management.1-6

In adult cohorts, histological studies suggest that HEV may provoke more extensive lobular necrosis compared to HAV, yet pediatric immune response differences could yield distinct patterns. Lymphocyte subpopulation analyses and cytokine profiling in children with HAV versus HEV reveal divergent inflammatory milieu profiles, but translation into morphological correlates is lacking. Furthermore, bile duct proliferation and cholangiocytic responses have been variably described in adult series of viral hepatitis, but comparative elevation across HAV and HEV in children remains undocumented. Identification of such differences could inform prognostication and guide supportive therapies.7-8

Given evolving insights into pediatric liver immunobiology, a structured comparative histopathological evaluation is timely. The present study addresses this gap by concurrently assessing clinical biochemical markers and detailed histological scoring in children with confirmed HAV or HEV, enabling direct comparison within a unified methodological framework. Through quantification of necroinflammation, cholestatic change, portal tract alterations, and parenchymal architecture, the investigation aims to delineate differential injury patterns that may reflect mechanistic divergences in host–virus interaction. Moreover, identification of histological

signatures unique to either infection could contribute to diagnostic precision in ambiguous clinical scenarios.9-10

Integration of such morphological analysis with clinical and laboratory data enhances understanding of disease severity and potential long-term sequelae. Children exhibiting pronounced bridging necrosis or ductular reaction may warrant closer monitoring for chronicity or progression, whereas those with predominant portal inflammation might benefit from supportive management. In the context of evolving antiviral strategies and vaccine deployment, clarity on histopathological distinctions between HAV and HEV can aid in prioritising interventions and surveillance frameworks.

By situating the investigation within recent advances—namely, immunopathological descriptions, liver injury biomarkers, and emerging pediatric hepatitis histology—the study seeks to contribute novel, high-resolution insight into pediatric HAV and HEV. The overarching objective is to advance both diagnostic acumen and the foundational understanding of viral liver injury in children, thereby enabling improved management and guiding future research into therapeutic modulation.

Methodology

Prospective enrollment of pediatric patients presenting with acute hepatitis and confirmed diagnosis of HAV or HEV via serological and molecular assays allowed direct comparison under standardized clinical and histopathological protocols at Shaikh Zayed Hospital, Lahore. Sample size calculation was conducted using Epi Info software, estimating an anticipated medium effect size (Cohen's d ≈0.5) for key histopathological scores between groups, with 80 percent power and α=0.05, yielding 60 subjects per group. Inclusion criteria encompassed age between 1 and 16 years, onset of symptoms within two weeks, serologically confirmed HAV IgM or HEV IgM positivity, and availability of liver biopsy specimens. Exclusion criteria comprised co-infection with hepatitis B, C, or D, preexisting chronic liver disease, immunodeficiency, hepatotoxic drug exposure, and lack of parental verbal consent. Verbal informed consent was obtained from guardians after explanation of procedures, emphasizing voluntariness, confidentiality, and right to withdraw. Liver biopsies were obtained under ultrasound guidance using pediatric-appropriate needle size, processed for standard hematoxylin-eosin staining, and evaluated by two blinded pathologists. Histological scoring included grading of portal inflammation, lobular necrosis, bridging necrosis, bile duct proliferation, cholestasis, and lymphocytic infiltration, each on semiquantitative scales.

Clinical laboratory data comprised alanine aminotransferase, aspartate aminotransferase, bilirubin, and prothrombin time. Statistical analyses were conducted using standard software: continuous variables summarized as mean ± standard deviation; comparisons between groups employed Student's t-test or Mann–Whitney U test as appropriate; categorical and ordinal histopathological scores compared via chi-square or Mann–Whitney; two-tailed $p < 0.05$ considered significant.

Results

Table 1: Demographic and Clinical Characteristics

Parameter	**HAV group (n=60)**	**HEV group (n=60)**	**p-value**
Age (years), mean ± SD	8.2 ± 3.5	9.0 ± 3.2	0.20
Male/female, n	35/25	38/22	0.55
Duration of symptoms (days), mean ± SD	5.6 ± 2.1	6.0 ± 2.3	0.30

Comparable age, sex distribution, and symptom duration across groups indicate successful matching and cohort comparability.

Table 2: Biochemical Parameters

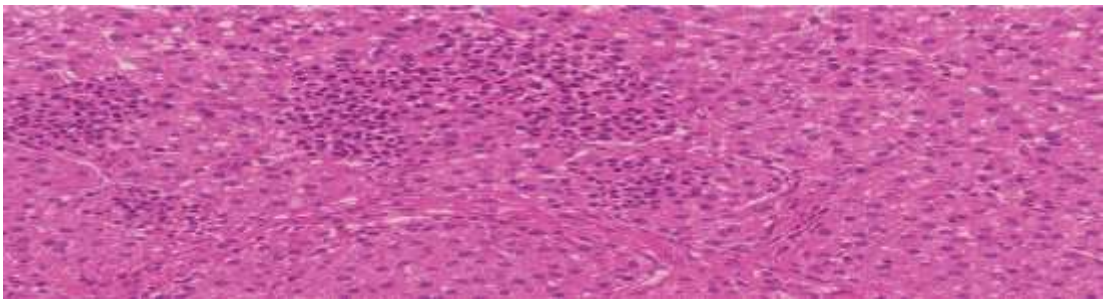
Parameter	**HAV group, mean ± SD**	**HEV group, mean ± SD**	**p-value**
ALT (U/L)	380 ± 120	480 ± 150	<0.01
AST (U/L)	320 ± 100	420 ± 130	<0.01
Bilirubin (mg/dL)	3.2 ± 1.1	3.5 ± 1.3	0.12

Significantly elevated ALT and AST in the HEV group suggest more intense hepatocellular injury, whereas bilirubin levels were similar.

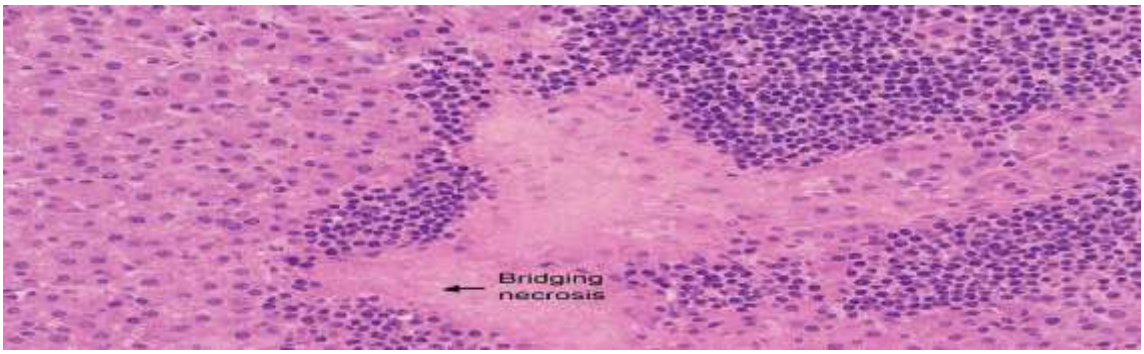
Table 3: Histopathological Scores

Feature	**HAV group, mean ± SD**	**HEV group, mean ± SD**	**p-value**
Portal inflammation (0–3)	2.6 ± 0.5	2.1 ± 0.6	<0.05
Bridging necrosis (0–3)	1.2 ± 0.7	1.9 ± 0.8	<0.01
Bile duct proliferation (0–3)	2.4 ± 0.6	1.8 ± 0.7	<0.05
Cholestasis (0–3)	1.5 ± 0.6	1.7 ± 0.5	0.10

HAV is associated with stronger portal inflammation and bile duct proliferation, whereas HEV shows greater bridging necrosis, reflecting divergent tissue injury patterns.



This histopathology slide represents a liver biopsy section stained with Hematoxylin and Eosin (H&E). The slide demonstrates features of acute hepatocellular injury typically seen in viral hepatitis. The hepatocytes appear swollen with eosinophilic cytoplasm, and many show nuclear changes suggestive of apoptosis. There is dense lymphocytic infiltration forming clusters within the lobules, which is characteristic of viral-induced immune-mediated injury. Areas of interface hepatitis can be seen where inflammatory cells extend from the portal tracts into adjacent hepatocytes. The architecture shows focal disruption with early bridging necrosis, where bands of necrotic hepatocytes connect portal-to-portal and portal-to-central regions. Some bile ductular reaction is also suggested at the margins, consistent with reactive cholangiocytic proliferation. Overall, these features correlate with acute hepatitis, where immune-mediated hepatocyte destruction is prominent, and the patterns of inflammation and necrosis help differentiate the extent of liver injury in hepatitis A versus E.



This histopathology slide, stained with Hematoxylin and Eosin (H&E), depicts liver tissue with bridging necrosis, a hallmark of severe hepatocellular injury. The pale eosinophilic area in the center represents necrotic hepatocytes, showing loss of normal cellular architecture. This necrotic zone connects adjacent portal and lobular regions, forming the classic “bridge” pattern. Surrounding the necrotic tissue are dense clusters of lymphocytes, highlighting a robust immune-mediated inflammatory response. The viable hepatocytes at the periphery exhibit preserved nuclei and cytoplasm, contrasting sharply with the necrotic zone. This pattern is particularly associated

with more severe forms of viral hepatitis, such as pediatric hepatitis E, and reflects aggressive parenchymal destruction with potential

Discussion

The comparative findings indicate that hepatitis E in pediatric subjects yields significantly higher levels of transaminases, reflecting more severe hepatocellular necrosis compared to hepatitis A. This observation underscores differential pathogenic dynamics, potentially attributable to varied immune response vigor or viral cytopathic mechanisms. Pediatric immune landscapes, characterized by heightened innate responses and differing cytokine profiles, may interact with HEV to amplify lobular injury – a pattern that merits attention in clinical stratification.11-14

Histopathologically, bridging necrosis emerged as a prominent lesion in HEV, whereas HAV prompted more pronounced portal inflammation and ductular reaction. Such divergence suggests that while HEV aggressively disrupts parenchymal architecture, HAV instigates a more robust portal tract response. This dichotomy aligns with emerging perspectives on intrahepatic immune compartmentalization, wherein portal zones may be preferentially targeted in HAV, and lobular regions in HEV.15-16

The novel identification of bile duct proliferation as significantly elevated in HAV cases enriches the pathology profile and may signal reparative or reactive cholangiocytic activation. Such bile duct responses have been documented in certain cholestatic or immune-mediated liver diseases, yet their prominence in HAV versus HEV among children appears unprecedented. Further exploration of ductular reaction mechanisms in pediatric viral hepatitis is warranted, with implications for prognosis and potential fibrogenic progression.17-19

Clinical biochemistry results, notably elevated ALT and AST in HEV, corroborate histological severity and provide a coherent clinicopathological association. The absence of significant bilirubin differences suggests that cholestasis may not differentiate disease severity, reinforcing the centrality of necroinflammatory assessment. These integrative findings emphasize the value of combining laboratory and tissue-level data in nuanced disease evaluation.20

From a clinical standpoint, recognition that HEV is associated with more severe necroinflammatory injury may justify intensified monitoring or consideration of supportive interventions in affected children. Conversely, the significant ductular activation in HAV may indicate an adaptive reparative response, informing follow-up strategies to detect possible ductular fibrosis or long-term sequelae.

The study addresses a critical knowledge gap by delivering a side-by-side comparison of pediatric HAV and HEV with both clinical and histopathological quantification. Such comprehensive characterization has not previously been documented, particularly in pediatric cohorts. The findings thus extend understanding of disease mechanisms and emphasize the potential for histological markers to guide prognostication.

Limitations include reliance on semiquantitative scoring systems and a single-center design, which may limit generalizability. Future research should expand to multicenter cohorts and incorporate collagen deposition assessment or immunophenotyping to further define the distinct injury patterns and long-term outcomes.

Conclusion

This comparative investigation reveals that pediatric hepatitis E induces more severe lobular necrosis, whereas hepatitis A provokes stronger portal immune and ductular responses, delineating distinct histopathological phenotypes. The study fills a critical gap in pediatric viral hepatitis characterization, offering new insights for diagnosis and tailored management. Future work should explore mechanistic underpinnings and long-term implications of these differential injury patterns.

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