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Evidence of Chronic Allograft Injury in Liver Biopsies From Long-term Pediatric Recipients of Liver Transplants.

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Abstract

BACKGROUND AND AIM: A substantial proportion of **pediatric liver** transplant **recipients** develop subclinical **chronic allograft injury**. We studied whether there are distinct patterns of **injury** based on histopathology features and identified associated immunological profiles.

METHODS: We conducted a cross-sectional study of 157 stable, **long-term pediatric recipients** of transplanted livers (70 boys; less than 6 years old; mean 8.9±3.46 years after **liver** transplant) who underwent **liver** biopsy analysis from August 13, 2012 through May 1, 2014. Subjects received livers from a living or deceased donor and had normal results from **liver** tests for more than 4 years after receiving transplant. **Liver biopsies** were scored by a central pathologist; an unsupervised hierarchical cluster analysis of histologic features was used to sort **biopsies** into 3 clusters. We conducted transcriptional and cytometric analyses of **liver** tissue samples and performed a systems biology analysis that incorporated clinical, serologic, histologic, and transcriptional data.

RESULTS: The mean level of alanine aminotransferase in subjects was 27.6±14.57 U/L and the mean level of gamma-glutamyl transferase was 17.4±7.93 U/L. Cluster 1 was characterized by interface activity (n=34), cluster 2 was characterized by periportal or perivenular fibrosis without interface activity (n=45), and cluster 3 had neither feature (n=78). We identified a module of genes whose expression correlated with levels of alanine aminotransferase, class II donor-specific antibody, portal inflammation, interface activity, perivenular inflammation, portal and perivenular fibrosis, and cluster assignment. The module was enriched in genes that regulate T-cell mediated rejection (TCMR) of **liver** and other transplanted organs. Functional pathway analysis revealed over-representation of TCMR gene sets for cluster 1 but not clusters 2 or 3.

CONCLUSION: In an analysis of **biopsies** from an apparently homogeneous group of stable, **long-term pediatric liver** transplant **recipients** with consistently normal results from **liver** tests, we found **evidence** of **chronic** graft **injury** (inflammation and/or fibrosis). **Biopsies** with interface activity had a gene expression pattern associated with TCMR.