Biomarkers in Pediatric Liver Disease

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Biomarkers for diagnosis, prognosis, and treatment monitoring have now become an integral part of the modern management of chronic diseases in humans. Liver is the only solid organ that has an inherent regenerative potential depending on the severity and nature of the injury. Chronicity is a common natural history leading to liver failure in most untreated liver diseases. Injury to the liver leads to cell death followed by fibrosis and complications such as synthetic and detoxification failure and the sequel of portal hypertension. Biomarkers in various body fluids continue to be evaluated and put in clinical practice. Standard tests of liver function or dysfunction, namely albumin, prothrombin time, and liver enzymes, are the most commonly used but suffer from being nonspecific. Apart from repeated imaging, liver biopsy continues to be the gold standard to assess the severity of liver disease, which apart from being invasive and expensive is difficult to repeat serially. Great progress is being made in assessing liver cell damage and its (apoptotic or necrotic) mechanisms by serum biomarkers such as cytokeratin (CK)-18 and its fractions. The fragments of CK-18 and the M30:M65 ratio can differentiate between apoptotic and necrotic cell death. Levels of CK-18 have been shown to differentiate between patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis, and have been shown to be associated with fibrosis (and not steatosis) in patients with chronic hepatitis C. Inflammation is usually an essential component of acute and chronic liver disease. Mediators of inflammation like chemokines are small proteins divided into 4 families (CC, CXC, CX3C, and C). Activated Kupffer cells secrete interleukin (IL)-1β and CXC chemokines, which attract neutrophils which release ROS and proteases and induce hepatic necrosis. Some of these inflammation mediators are being increasingly used as prognostic biomarkers in the management of liver disease. Fibrosis is the sequel of liver cell death. Activation of hepatic stellate cells is central in the development of fibrosis. The CCL2/CCR2 pathway is once again implicated in the development of fibrosis. CCL5 is another important chemokine pathway implicated in hepatic fibrosis, as are the interferon-γ-induced chemokines.
CXCL9, CXCL10, and CXCL. Other important cytokines linked with the development of hepatic fibrosis are TGF-β1 and platelet-derived growth factor, both of which stimulate the proliferation of hepatic stellate cells. Identification of procollagen peptides in the serum has served as a biomarker of fibrosis. Such peptides are procollagen type-I carboxy-terminal peptide, procollagen type-III amino-terminal peptide, serum type-IV collagen, laminin, hyaluronic acid, and YKL-40. These biomarkers have been used with clinical parameters to form various formulas or indices to predict the severity of fibrosis in several diseases (e.g. chronic hepatitis C, NAFLD, and biliary atresia) with variable success.

Liver cancer is one of the dreaded complications of chronic liver disease, and these patients are at risk of developing the malignancy during the course of their illness. Early detection is important as advanced cancer could exclude them from liver transplantation. The classic biomarker of liver malignancy is α-fetoprotein, even though it is not specific to liver tumors, as it may be raised in chronic hepatitis and cirrhosis. Other serum biomarkers that may be used in conjunction with α-fetoprotein are des-γ-carboxy prothrombin and Golgi protein 73. Elevated cytokines have also been detected, e.g. IL-6, IL-8, and IL-10. Various microRNA profiles have been described that can detect the presence of hepatocellular carcinoma on a background of chronic liver disease.