

More Diagnostic Use for MMP-7?

The finding of direct hyperbilirubinemia in a neonatal infant is a significant concern as cholestatic disorders, especially biliary atresia, need diagnostic and therapeutic interventions quickly. However, other causes of cholestasis can occur in neonates, especially in those infants receiving total parenteral nutrition (TPN) with resultant cholestasis. Serum matrix metalloproteinase-7 (MMP-7) has shown tremendous promise in helping to diagnose biliary atresia in neonates. Thus, the authors looked at the ability of MMP-7 to differentiate cholestasis caused by biliary atresia versus cholestasis caused by TPN in neonates.

The authors of the retrospective study evaluated MMP-7 levels in infants less than 6 months of age with conjugated hyperbilirubinemia (defined as a direct hyperbilirubinemia ≥ 1 mg/dL). Infants were defined as having TPN-associated cholestasis if they received TPN in the first 30 days of life, had no other identified cause of cholestasis, had an improvement in cholestasis after stopping TPN, or were found to have normal biliary anatomy upon death and subsequent autopsy. MMP-7 levels were obtained while patients had active cholestasis. A total of 15 patients with TPN-associated cholestasis then were compared to 4 patients with biliary atresia status post hepatportoenterostomy surgery. Of note, none of the patients with biliary atresia had exposure to TPN.

There was no significant difference in age at which time MMP-7 levels were obtained. The median time of TPN exposure was 50 days (interquartile range: 40-67 days). Infants with TPN-associated cholestasis had a significantly lower gestational age compared to patients with biliary atresia, likely due to their history of prematurity. The authors found that total serum bilirubin levels, direct serum bilirubin, and gamma-glutamyl transferase levels were not significantly different between infants with biliary atresia and infants with TPN-associated cholestasis. However, infants with biliary atresia had a significantly higher MMP-7 level compared to patient with TPN-associated cholestasis (112.3 versus 37.8 ng/mL, $P = 0.03$). Only one patient with TPN-associated cholestasis had an MMP-7 level in a range similar to patients with biliary atresia. Overall, a serum MMP-7 cutoff level of 52.8 ng/mL in this patient cohort

had a sensitivity of 100%, specificity of 93.3% (95% confidence interval 68.1% - 99.8%), positive predictive value of 80% (95% confidence interval 28.4% - 99.5%) and negative predictive value of 100% in identifying cholestasis from biliary atresia versus cholestasis from TPN. No association between time duration of TPN and MMP-7 levels was noted.

Thus, it appears that MMP-7 testing is becoming an important tool in determining the presence of biliary atresia in infants. An elevated MMP-7 level would warrant a quicker intervention (i.e., potential hepatportoenterostomy) to prevent complications from a delay in a biliary atresia diagnosis. The ability to obtain MMP-7 levels in children's hospitals and newborn intensive care units is warranted.

Pooja S, Fawaz R, Cowles R. Comparing serum matrix metalloproteinase-7 in parenteral nutrition-associated liver disease and biliary atresia. *Journal of Pediatrics* 2022; 249: 97-100.

Changes in Outcomes of Pediatric Crohn's Disease Over Time

Crohn's disease (CD) in children is increasing in incidence worldwide for reasons that are not clear. Immunosuppressant (azathioprine, 6-mercaptopurine, methotrexate) and anti-tumor necrosis factor alpha (anti-TNF- α) medications (infliximab, adalimumab, etc.) are being used much more frequently in pediatric patients with CD, and the authors evaluated changes in outcomes in pediatric patients with CD over time via a population study using a pediatric cohort of patients with CD. Patients for this study came from EPIMAD, which is a longitudinal and prospective study of patients with inflammatory bowel disease (IBD) in northern France. All patients diagnosed with CD between 1988 and 2011 that were younger than 17 years of age were evaluated in this database to see if immunosuppressant and anti-TNF- α therapy reduced pediatric CD complications. Patients were evaluated from 1988 to 1993 (the period before immunosuppressant use), 1994 to 2000 (the period before anti-TNF- α use), and 2001

to 2011 (the period when anti-TNF- α therapy was used). Outcomes, including CD disease behavior, intestinal resection, and hospitalization due to CD flares were compared during these three time periods.

A total of 1007 pediatric patients with CD were evaluated using the EPIMAD registry. Females comprised 44.8% of the study with the median age at diagnosis being 14.5 years (IQR (interquartile range), 12.0–16.1 years) and the median duration of patient follow-up being 8.8 years (IQR, 4.6–14.2 years). Ileocolonic disease was present in 54.9% of patients. There were 167 pediatric patients (16.7%) enrolled during the time period before immunosuppressant use, 260 patients (25.8%) enrolled during the time period before anti-TNF- α use, and 580 patients (57.5%) enrolled during the time period when anti-TNF- α therapy was used. The authors noted that a 5-year cumulative exposure rate to exclusive enteral nutrition increased significantly throughout the three time periods while the 5-year cumulative exposure rate to any type of corticosteroid did not significantly change. The 5-year cumulative exposure rate to immunosuppressant therapy and anti-TNF- α significantly increased throughout the study while age in years at first exposure to immunosuppressant therapy and anti-TNF- α decreased significantly throughout the study. The exposure rate to a combination of these two types of CD therapies increased significantly throughout the study.

Progression to CD-associated stricturing

complications decreased significantly over time while progression to CD-associated penetrating disease did not significantly change over time. The authors also noted that the cumulative 5-year intestinal resection rate decreased significantly throughout the study while the 5-year cumulative hospitalization rate for CD-related flares did not significantly change.

This study appears to show that new therapies for pediatric CD may be affecting disease outcomes with the encouraging effects of less stricturing disease and less requirement for intestinal resection. Since children with CD appear to have a higher rate of identifiable genetic causes for immune dysfunction in the setting of CD compared to adults, the long-term use of immunosuppressant therapy and anti-TNF- α in this scenario is still unknown. However, the results of this study suggest that the introduction of new therapies for CD in children appear to be clinically effective.

Ley D, Leroyer A, Dupont C, Sarter H, Bertrand V, Spyckerelle C, Guillon N, Wils P, Savoye G, Turck D, Gower-Rousseau C, Fumery M, on behalf of the Epimad Group. New therapeutic strategies have changed the natural history of pediatric Crohn's disease: a two-decade population-based study. *Clinical Gastroenterology and Hepatology* 2022; 20: 2588-2597.

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