



Covering the Cover

Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children

Celiac disease (CD) is an immune-mediated, chronic inflammatory disease of the small intestine, which is characterized by permanent sensitivity to gluten in genetically predisposed individuals. This study aimed to investigate polymorphisms in the genes responsible for encoding IL-6 (-572G/C; rs1800796) and IL-17 (-197A/G; rs2275913) in patients with CD. Eighty-four patients with CD and 83 healthy controls were enrolled in this study. Children with CD were divided into two groups depending on whether their symptoms were typical or atypical. The IL-6 (-572G/C) and IL-17 (-197A/G) polymorphisms were genotyped based on a PCR coupled with restriction fragment length polymorphism. The authors concluded that significant differences for the IL-6 (-572G/C) polymorphism were observed between patients with CD and controls ($p=0.018$, odds ratio (OR): 5.47, 95% confidence interval (CI): 1.161-25.800). No statistically significant association was observed between the IL-17 (-197A/G) polymorphism and CD ($p>0.05$). In addition, the symptoms and histopathological findings of children with CD were not related to either of the polymorphisms. See 432-3.

Low yield of gastroscopy in patients with the Lynch syndrome

The Lynch syndrome is the most common hereditary colorectal cancer syndrome. Other cancers associated with Lynch syndrome include cancer of the stomach, ureter, renal pelvis, small bowel, and bile ducts and brain tumors. The lifetime risk of developing one of these cancers is relatively low (<10%) and may be associated with the underlying mutation in the mismatch repair defect. The risk of developing GC may be higher in some countries. The International Society of Gastrointestinal Hereditary Tumors recommends surveillance for cancer of the stomach if the cancer clusters in the family (more than one case). However, the European group supports that GC surveillance in families with Lynch syndrome may be considered in countries with

a high incidence of such tumors. The authors in the present article revealed that screening gastroscopy in 21 patients with Lynch syndrome did not reveal any cancer case. The prevalence of precursor lesions (*Helicobacter pylori* gastritis, atrophic gastritis, and gastric intestinal metaplasia) was reported to be around 19.05%. Authors also noticed that the presence of a family history of GC creates nonsignificant increase in the risk of abnormal endoscopy. Thus, it is reasonable to suggest that GC screening in asymptomatic individuals with Lynch syndrome is probably best reserved for high-risk individuals, based on family history and perhaps ethnicity. In this subset of the patients, the American College of Gastroenterology guidelines indicate baseline esophagogastroduodenoscopy (EGD) with gastric biopsy at age 30-35 years, and treatment of *H. pylori* infection when found. Data for ongoing regular surveillance are limited, but ongoing surveillance every 3-5 years may be considered, if there is a family history of gastric or duodenal cancer. See 434-8.

Preoperative albumin/globulin ratio is a potential prognosis predicting biomarker in patients with resectable gastric cancer

The authors showed that low preoperative albumin/globulin ratio (AGR) (<1.36) in GC patients remained an independent prognostic factor for the overall survival in a multivariable analysis. They included 269 patients who underwent D2 resection. Thus, the sample size is relatively small and the authors did not investigate the importance of AGR in patients who did not undergo radical surgery. In literature, there are two reports indicating similar results about AGR and overall survival in GC patients. One of the studies (Mao JY, et al. Biomedical Research International 2017) included 862 cases with and without radical surgery, and the pretreatment AGR was reported to be an independent prognostic factor for patients with GC in a multivariate analysis in both groups. The other report included 507 cases who underwent radical surgery, and they reported that AGR is an important prognostic indicator for GC patients (Liu J, et al. Onco Target Ther 2017). However, there is an

obvious need for prospective studies to confirm these conclusions especially the cut-off value of AGR (<1.36) presented in this paper. See 439-45.

Contrast-enhanced ultrasound-guided radiofrequency ablation in inconspicuous hepatocellular carcinoma on B-mode ultrasound

In this report, the authors successfully used contrast enhanced ultrasonography (CEUS)-guided radiofrequency ablation (RFA) for treating small inconspicuous liver lesions. The only obstacle is that they were unaware if these lesions were having hepatocellular carcinoma (HCC) foci or not. Nevertheless, it has been recently demonstrated that the detection rate for hypervascular HCCs is significantly higher using CEUS than using CE computerized tomography (CT) (Ishii T, et al. Eur J Radiol 2017). Furthermore, hypervascularity in HCCs as observed during CEUS is reported to be a significant risk factor for local recurrence after RFA. Even after TACE administration, RFA has been reported to be more successful when it was guided by CEUS rather than B-mode ultrasound (Kawasaki T, et al. Dig Dis 2016). Thus, it is obvious that CEUS, sooner or later, will find a definite place in the diagnostic and therapeutic algorithm of the patients suspected of having HCC. See 446-52.

Effects of alfentanil or fentanyl added to propofol for sedation in colonoscopy on cognitive functions: A randomized controlled trial

Sedation analgesia is recommended for comfortable colonoscopy procedures, which are invasive and can be painful. Generally, there is no consensus on the agent or combination that is better and safer for sedation during minimal but potentially painful interventions such as colonoscopy. Generally, opioids are combined with hypnotic agents during such procedures. This study aimed to compare the combinations of propofol-alfentanil (Group A), propofol-fentanyl (Group F), and propofol (Group P) only for sedation analgesia in elective diagnostic colonoscopy patients. In total, 153 patients were enrolled, and after excluding three patients, the remaining patients were compared with regard to desaturation ($SpO_2 < 90\%$), hypotension (a decrease in systolic pressure of $>30\%$ from baseline), hypertension (an increase in systolic pressure of $>30\%$ from baseline), bradycardia (heart rate < 50 beats/min [bpm]), tachycardia (heart rate > 90 bpm), nausea, vomiting, and apnea (not breathing for > 20 seconds). The authors also compared the groups with other tests, including the psychomotor test DANTES Subject Standardized Tests (DSST; filling the boxes according to the numbers and matching symbols), Trieger dot test (TDT) for hand-eye coordination (connecting the dots on a paper), mini mental test for cognitive functions (evaluating orientation, registration, attention, calculation, recall, and language), and fascial pain scoring for pain intensity. The authors demonstrated that compared with propofol-alfentanil and propofol-fentanyl, propofol alone is associated with an increased incidence of apnea, drug consumption, and reported pain. A propofol-alfentanil combination has a lesser negative effect on

cognitive functions compared with propofol alone or a propofol-fentanyl combination. These findings were understandable as propofol has no analgesic effect, and the necessary increase in dosage when propofol is used alone causes cognitive dysfunction as well as an increase in the incidence of apnea. Since alfentanil is a short-half-life agent, adding it to propofol causes less cognitive dysfunction and reduces recovery time. Nevertheless, there is another report in literature (Turk HS, et al. Braz J Anesthesiologist 2013) indicating that fentanyl and propofol combination for elective colonoscopy has a shorter recovery time than the alfentanil and propofol combination, as fentanyl apparently decreases the additional doses of propofol needed. Thus, the debate on the best combination for better and safer sedation during outpatient colonoscopy will continue, and we need further studies enrolling larger number of patients undergoing colonoscopy to shed light on this issue. See 453-9.

Predictors of inadequate bowel preparation for inpatient colonoscopy

As the authors indicated in this article that adequate colon cleaning is vital for achieving successful cecal intubation and safety during colonoscopy. They enrolled 150 patients and investigated for the negative predictors of sufficient cleaning during inpatient colonoscopy. They found out that only two factors were associated with the insufficient colonic cleaning: the first was an afternoon rather than a morning procedure (clean bowel 71% versus 46%, respectively) and the second was aspirin use. In other reports, advanced age lower income, inpatient status, opiate or tricyclic antidepressant use, afternoon colonoscopy, a history of cirrhosis, dementia or stroke, constipation, American Society of Anesthesiologists class ≥ 3 , and symptoms of nausea/vomiting for an unsuccessful colonic cleaning. Generally, based on a successful bowel-cleaning rate, 57% is below the rates published in literature (nearly around 10-20%). The authors in the present article attributed this to the failure to detect other predictors of poor preparation to their small sample size. It is extremely challenging not to agree with the authors. More interestingly, they also propose that aspirin use as a predictor of a clean-looking colon is due to the fact that aspirin intake is likely a surrogate marker for patient diligence in adhering to the preparation regimen. It is obvious that this study is limited by many factors, including its small sample size, retrospective design, and single-center data source. Furthermore, the authors did not have any data on the ability of individual patients to completely ingest the prescribed laxative dose due to the study's retrospective design. See 460-4.

Clinical findings, child and mother psychosocial status in functional constipation

Functional constipation is a common problem of childhood. In this study, clinical and sociodemographic findings of patients with functional constipation, evaluation of parenting behaviors, and psychosocial states of children and parents was analyzed. According to the Roma III diagnosis criteria, 32 patients with functional constipation and 31 healthy controls

were included. For the screening of emotional and behavioral problems in children, Strengths and Difficulties Questionnaire was used. To evaluate the parents and family, Beck Depression Inventory, State-Trait Anxiety Inventory, Parental Attitude Research Instrument were used. The mother's low level of education; low socioeconomic level; presence of psychological symptoms; and problems of parental attitude, primarily the authoritarian attitude, increase the risk of functional constipation occurrence. Therefore, functional constipation patients and their families should definitely undergo a psychosocial assessment. See 465-70.

Treatment with milk thistle extract (*Silybum marianum*), ursodeoxycholic acid, or their combination attenuates cholestatic liver injury in rats: Role of the hepatic stem cells

Bile duct ligation (BDL), a commonly used rat model of liver fibrosis, stimulates the proliferation of biliary epithelial cells and oval cells resulting in proliferating bile ductules and an accompanying portal inflammation, fibrosis, and a secondary biliary cirrhosis, similar to that of humans. The present study investigated combined effects of silymarin and ursodeoxycholic acid (UDCA) on the oxidative stress, severity of cholestasis, and primary stem cell activation markers after BDL in the rats. They concluded that this combination therapy has anti-inflammatory and antiproliferative effects and modulates stem cell-induced regenerative responses. Stem cells have attracted remarkable attention for the treatment of acute liver failure and end-stage liver diseases. Liver regenerative capabilities are stimulated by stem cells. Interestingly, the authors suggested that the antifibrotic effect of the combination therapy is related with the suppressive effects on the stem cell activity. However, it is difficult to state that the stem cell activation leads to liver fibrosis and these drugs prevent liver fibrosis in this manner. Interestingly, the BDL method in rats normally induces liver fibrosis after 4 weeks of ligation, and the antifibrotic therapy usually was suggested to be around that time period (Mohamed HER, et al. *Exp Biol Med* 2016). The authors in this study investigated for signs of liver injury after 11 days in this study.

To date, accumulation of hydrophobic bile acids (BAs) during cholestasis is known to play an important role in apoptosis initiation as well as oxidative stress increase in liver cells. UDCA acts as a protector in BA-induced cell injury. The protective effect of UDCA on liver tissue damage in BDL rats compared to cholestatic liver is to decrease MDA levels, increase catalase activity, reduce xanthine oxidase activity, and decrease in DNase I and II activity to inhibit apoptosis (Sokolovic D, et al. *Drug Chem Toxicol* 2013). Therefore, UDCA is already known to be useful in the preservation of liver function in cholestasis treatment. Similarly, there is a report (Onalan AK, et al. *Acta Cir Brazil* 2016) in literature favoring the effects of silymarin on oxidative stress and hepatic injury induced by obstructive jaundice in

an experimental model, as oral silymarin administration was found to decrease the harmful results of obstructive jaundice on liver. However, another report disagreed with this result, as the authors could not find beneficial effects of orally administered silymarin and vitamin C and E on liver damage produced by prolonged biliary obstruction in rats (Muriel P, et al. *Basic Clin Pharmacol Toxicol* 2004). Although some controversial results have been published so far, UDCA and silymarin combination in the present study seemed to decrease the severity of cholestasis and necroinflammation and liver fibrosis. Thus, it is reasonable to think that there will be less stem cell activation in the rats treated with aforementioned drugs since there will be less liver injury. See 476-84.

Efficacy of tocilizumab treatment in cerulein-induced experimental acute pancreatitis model in rats

Interleukin (IL)-6, IL-1, IL-8, and tumor necrosis factor (TNF) alpha are the main cytokines responsible for the inflammatory cascade seen both in the onset and severity of acute pancreatitis. IL-1 antagonists (anakinra) have been studied previously (Kaplan M, et al. *Scand Journal of Gastroenterology* 2014) in an experimental model of acute pancreatitis with successful results on histopathologic healing scores in the pancreas. There is another report (Kosekli MA, et al. *Pancreas* 2016) for sertolizumab (anti-TNF agent) use in experimental acute pancreatitis with similar beneficial effects. The IL-6 antagonist studied in the present article is tocilizumab, which is an IL-6 receptor antagonist as a marketed drug commonly used for innate immune diseases including rheumatoid arthritis. The authors advocated 8 mg/kg dose of tocilizumab intraperitoneally to achieve healing effects of pancreatic histology by analyzing Schoenberg scores. They concluded that tocilizumab treatment can positively regulate the histopathological changes in pancreatitis by restoring disease activity and severity. Indeed, it was shown that tocilizumab deactivates pancreatic nuclear factor- κ B, and signal transducer and activator of transcription 3, and the serum chemokine (C-X-C motif) ligand 1 were downregulated after tocilizumab administration. A previous study (Chen KL, et al. *Crit Care Med* 2016) of cerulein-induced experimental acute pancreatitis clearly demonstrated that tocilizumab is safe and effective for the treatment of experimental severe acute pancreatitis and the associated acute lung injury. It seems possible that this drug can be extremely beneficial with regard to controlling inflammatory activity and histological healing in acute pancreatitis. It may even find a place in the prophylaxis of pancreatitis seen after endoscopic retrograde cholangiopancreatography. However, we need further studies supporting these observations particularly in the human subjects. See 485-91.

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