Digest

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Two distinct aetiologies of cardia cancer

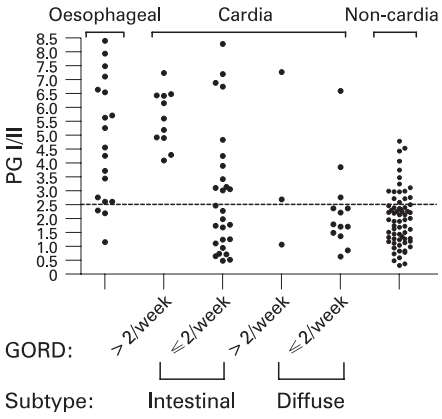
Although atrophic gastritis is a well recognised risk factor for non-cardia gastric cancer and gastro-oesophageal reflux disease (GORD) for oesophageal adenocarcinoma, the roles of atrophic gastritis and GORD in the aetiology of adenocarcinoma of the cardia is less clear. In this case–control study, Derakhshan *et al* evaluated risk factors for upper gastrointestinal adenocarcinoma. Non-cardia cancer was associated with atrophic gastritis but not with GORD symptoms, whereas the opposite was true for oesophageal adenocarcinoma. Cardia cancer was positively associated with both severe gastric atrophy and with frequent GORD symptoms, although the latter was only apparent in the non-atrophic subgroup and in the intestinal subtype. The association of cardia cancer with atrophy was stronger for the diffuse versus intestinal subtype and this was the converse of the association observed with non-cardia cancer. Based on their findings, the authors suggest there seem to be two distinct aetiologies of cardia cancer and propose that gastric atrophy, GORD symptoms and histological subtype can be used to distinguish between a gastric or oesophageal origin for cardia cancer. ***See page 298***

Brain-derived neurotrophic factor enhances enteric nervous system signalling

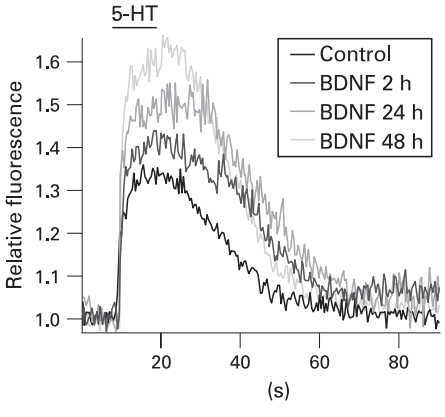
Brain-derived neurotrophic factor (BDNF) regulates growth, survival and differentiation of central and peripheral neurons. However, it is also involved in the control of peristalsis and has been shown to accelerate colonic transit and relieve constipation in humans. Boesmans *et al* evaluated the cellular mechanisms behind the effect of BDNF on gastrointestinal motility using primary myenteric neuron cultures and whole-mount preparations from guinea pig ileum. Immunohistochemistry revealed the presence of BDNF and its tropomyosin-related kinase B (TrkB) receptor in mucosa, submucosal plexus and myenteric ganglia. BDNF did not affect Ca^{2+} transients in myenteric neurons by itself but caused an enhancement of Ca^{2+} transients induced by serotonin and the neuropeptide substance P. This was reversed by a TrkB receptor blocker. BDNF exposure also amplified the spontaneous network activity and facilitated the release of synaptic vesicles from the enteric nervous system. This study demonstrated that BDNF enhances rather than directly activates enteric nervous system signalling. Based on that, the promotility effect of BDNF seems to result from its modulating role on enteric neuronal activity and synaptic communication. ***See page 314***

NOD2 mutations associated with failure of small intestinal transplantation

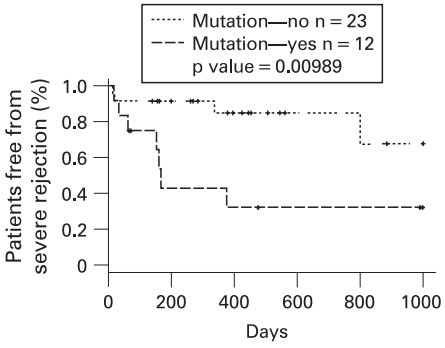
Small intestinal transplantation for intestinal failure is an evolving treatment, although development is limited by graft rejection in 30–40%. Fishbein *et al* describe the geneotype of 34 consecutive patients transplanted primarily for short bowel syndrome. Surprisingly, 35% had one or more of three Crohn's associated NOD2 mutations (R720W, G908R and 302insC) compared with 8.6% of donors. Twelve patients with a NOD2 mutation had a 4.5-fold increased risk of developing a severe rejection, compared with the 22 patients with wild-type NOD2 alleles. Other covariates, including age, gender, viral status (cytomegalovirus and Epstein-Barr virus) and combined liver transplant, had no effect on outcome. As NOD2 mutation is thought to impair mucosal antimicrobial peptide expression, the authors studied the expression of human defensins (HD) at baseline and 3–4 weeks after transplantation. Patients with NOD2 mutations showed a significant decrease in the defensins HD5 and hBD-2, while wild-type recipients showed no decline. This impairment of innate immunity appears to represent a significant risk factor for rejection of the graft and reversing it may be a way of improving outcome in the future. ***See page 323***



Pepsinogen I/II values as an indicator of gastric atrophy (<2.5) in patients with upper gastrointestinal adenocarcinoma.



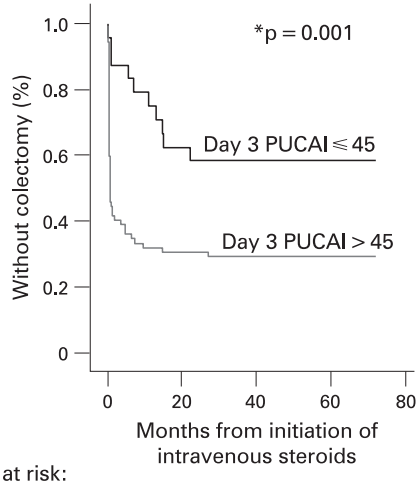
5-Hydroxytryptamine (5-HT)-induced Ca^{2+} signalling was enhanced in brain-derived neurotrophic factor (BDNF)-treated myenteric neurons.



Kaplan-Meier curves of rejection after transplantation and its association with recipient's NOD2 genotype.

Predicting failure of corticosteroid treatment in children hospitalised with severe ulcerative colitis

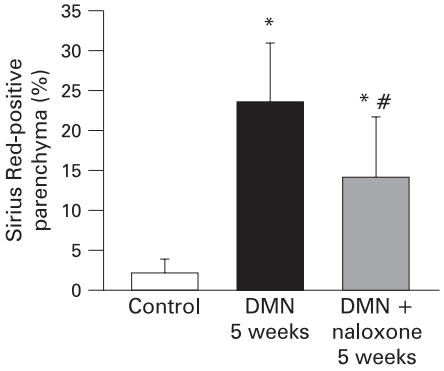
Deciding when to escalate treatment is one of the most important decisions to be made in the management of severe ulcerative colitis (UC) yet there are little data in children, in whom the colitis is often severe. A retrospective review by Turner *et al* of 99 children hospitalised for their first admission with severe UC is, therefore, to be welcomed. Of the 99 children, 53 responded to intravenous corticosteroids, 40% required colectomy and 6% went on to a trial of tacrolimus, of whom four out of six responded. At 1 year, 58% had had a colectomy. A multivariate logistic regression analysis was performed to predict outcome. The best measure was the Paediatric Ulcerative Colitis Activity Index (PUCAI), which combines scores on six items (abdominal pain, rectal bleeding, stool consistency, number of stools per day, number of nocturnal stools and impairment of activity). At day 3, a PUCAI score >45 had a 93% sensitivity to predict treatment failure, while at day 5 a score >70 had a 93% specificity (see fig). Surprisingly, colonic dilatation was not associated with outcome. This provides valuable data to guide treatment in children with severe UC. ***See page 331***



Kaplan Meier survival estimation of time to colectomy stratified by the Paediatric Ulcerative Colitis Activity Index (PUCAI).

Endogenous opioids play an important role in liver fibrinogenesis

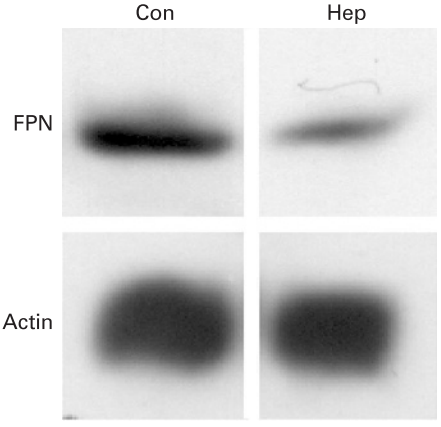
Liver fibrosis is the final result of chronic liver injury and is due to excessive accumulation of extracellular matrix proteins by hepatic stellate cells (HSCs). Levels of endogenous opioids are increased in patients with chronic liver disease and the levels correlate with the degree of liver injury. In this study of rats and humans, De Minicis *et al* evaluated the role of endogenous opioids on liver fibrinogenesis in vitro and in vivo. They demonstrated that HSCs express opioid receptors and the expression pattern differs in quiescent and activated HSCs. The activation of these receptors increased HCS proliferation and collagen accumulation. When liver fibrosis was induced by administration of dimethylnitrosamine the HSC activation and collagen deposition was reduced by the opioid antagonist naloxone. In both dimethylnitrosamine-treated rats and in human liver biopsies opioid receptors were observed in HCSs in areas of active fibrinogenesis and increased expression of the endogenous opioid met-enkephalin was found. These data support an important role for endogenous opioids in the fibrinogenic response to chronic liver injury and may lead to experimental medical treatments and prevention of chronic liver injury. ***See page 352***



Naloxone reduced the fibrinogenic response after administration of dimethylnitrosamine (DMN) in rats.

Acute decrease in serum iron by hepcidin is mediated by the inhibition of ferroportin levels in macrophages

Hepcidin is a key regulator of iron metabolism, with synthesis in the liver rising when iron stores are high and falling when they are depleted. Hepcidin has been shown to bind to the iron transporter, ferroportin, in transfected cells causing internalisation and degradation. Chaston *et al* showed that hepcidin, either released from interleukin 6-stimulated HuH7 hepatoma cells or given as a synthetic peptide, rapidly decreased ferroportin expression in macrophages but did not affect Caco-2 intestinal type cells. Mice injected with synthetic hepcidin peptide showed a rapid decrease in ferroportin levels in the macrophage-rich red pulp of the spleen (see fig). This was associated with a substantial decrease in serum iron but this short term exposure to hepcidin did not alter duodenal iron absorption, although previous studies have indicated that chronic exposure would do so. Macrophages recycle some 20–25 mg of haemoglobin-derived iron per day compared with only 1–2 mgs of iron absorbed from the diet by duodenal enterocytes, clearly indicating that hepcidin's control of the macrophage release of iron is likely, at least in the short term, to have a dominant effect on overall body iron homeostasis. ***See page 374***



Ferroportin levels in the mouse spleen are decreased by hepcidin treatment.