Mitochondrial DNA A3243G Mutation Involved in Familial Diabetes, Chronic Intestinal Pseudo-Obstruction and Recurrent Pancreatitis.


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The authors report on a family with five members who carry the A3243G mutation in mitochondrial tRNA for leucine 1 (MTTL1) and present with diabetes, chronic intestinal pseudo-obstruction (CIPO) and recurrent pancreatitis, and to screen for this mutation in a cohort of 36 unrelated patients with recurrent pancreatitis. The mutation was quantified in several tissue samples from patients. Respiratory chain activity was studied in muscle biopsies and fibroblast cultures. In addition, the thymidine phosphorylase gene (TP) involved in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) and three genes involved in chronic pancreatitis - PRSS1, SPINK1 and CFTR - were sequenced in affected patients. Finally, the MTTL1 gene was examined in 36 unrelated patients who had recurrent pancreatitis, but no mutations in the PRSS1 and SPINK1 genes. Heteroplasmy for the mtDNA A3243G mutation was found in all tissue samples from these patients, but no mutations were found in the genes coding for thymidine phosphorylase, PRSS1, SPINK1 and CFTR. Also, none of the 36 unrelated patients with recurrent pancreatitis were carrying any MTTL1 mutations. In conclusion, the mtDNA A3243G mutation associated with the gastrointestinal manifestations observed in the affected family should be regarded as a possible cause of CIPO and unexplained recurrent pancreatitis. However, the mutation is probably only weakly involved in cases of isolated recurrent pancreatitis.

Eosinophilia Associated with Chronic Pancreatitis.

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Eosinophilia (>0.5 x10/L eosinophils (EOSs) in the peripheral blood) has been overlooked in the study of chronic pancreatitis (CP). The purpose of this study was to investigate the clinical significance and causes of eosinophilia by analyzing the features of CP cases with eosinophilia. The authors retrospectively analyzed the clinical features of CP patients with eosinophilia and compared them with CP patients without eosinophilia. There were 28 cases (15.6%) of CP with eosinophilia among 180 CP patients. The ratio of male to female patients was 8.3:1. The mean patient age at the time of diagnosis was 49.0 (±16.2) years. The peak value of EOSs in the patients' peripheral blood was 0.935 (±0.600) x10/L. The incidence of eosinophilia in autoimmune pancreatitis was significantly higher than in non-autoimmune pancreatitis CP cases. The incidence of pancreatic ascites, pancreatic enlargement, or jaundice in CP cases with eosinophilia was significantly higher than in those without eosinophilia. There was no obvious infiltration of EOSs in the pancreatic tissues of 16 pathology or cytology specimens. In conclusion, the occurrence of eosinophilia during the course of CP is not unusual. This may be related to autoimmune
mechanisms, serous membrane response, or the progression of pancreatic inflammation and fibrosis.

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Histopathological Features of Patients with Chronic Pancreatitis due to Mutations in the PRSS1 Gene: Evaluation of BRAF and KRAS2 Mutations.


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Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis (CP; 1%) and more than 25 mutations in the PRSS1 gene have been detected. HP patients with the p.R122H mutation have a 35% lifetime risk of developing pancreatic cancer, but the oncogenetic process remains unknown. The authors have investigated the histopathological features and frequency of BRAF and KRAS2 mutations in 2 patients with PRSS1 mutations (p.A121T, p.R122H) and patients with CP (n=11). Pancreatic tissue was stained with hematoxylin-eosin and examined by light microscopy. Mutational analysis of the BRAF (exon 5, 11) and KRAS2 (exon 1) genes was performed using PCR and direct DNA sequencing. Results. Histopathological features revealed similar results in both patients, pancreata showed strong fibrosis and ducts with signs of distortion, irregular size and noticeable dilatations. The authors identified one BRAF mutation (p.V600E) in the p.R122H patient and two KRAS2 (p.G12D; p.G12C) mutations in CP controls. The results sustain the knowledge about the clinical phenotype of patients with PRSS1 mutations who have a high risk of pancreatic cancer. Whether the histopathological picture or the BRAF mutation is specific for patients with PRSS1 mutations or plays a specific role in the tumorigenesis of patients with HP needs to be further evaluated.


Duodenum-Preserving Total Pancreatic Head Resection without Segment Resection of the Duodenum for Chronic Pancreatitis.


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The purpose of this study was to describe a duodenum-preserving total pancreatic head resection procedure without segment resection of the duodenum for the treatment of chronic pancreatitis with an enlarged pancreatic head. Between January 1999 and December 2006, 35 patients with chronic pancreatitis were operated on by duodenum-preserving total pancreatic head resection procedure without segment resection of the duodenum. These patients were followed up to estimate the outcomes of the surgical procedure. The mortality of the surgical procedure was 0. The overall morbidity was 17%. One patient developed pancreatic fistula, three patients developed bile leakage, and no patient developed duodenal fistula. Twenty-one patients who suffered abdominal pain in preoperative stage obtained complete pain relief, the mean European Organization for Research and Treatment of Cancer QLQ-C30 pain scale decreased from $59\pm27$ to $13\pm21$. In the postoperative stage, the endocrine function of the patients compared equally to the preoperative stage. In conclusion, the modified procedure obtains acceptable postoperative outcomes and benefits on extirpation of inflammatory lesions and avoidance of the anastomosis of the residual pancreatic head and the jejunal.


A Rapid, Endoscopic Exocrine Pancreatic Function Test and the Lundh Test: A Comparative Study.
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The diagnosis of chronic pancreatitis is often difficult in the early stages of the disease. Morphological tests may be normal, and reliable methods for the evaluation of the exocrine pancreatic function are time-consuming and troublesome. A new test for exocrine pancreatic function, using endoscopic aspiration of secretin-stimulated pancreatic juice, has been developed. The authors evaluated the test using the Lundh meal test as reference. The endoscopic secretin stimulation test (ESST) was performed in a consecutive row of 24 patients referred for pancreatic function testing because of clinical suspicion of chronic pancreatitis and in 23 healthy volunteers. The participants fasted overnight and secretin was given intravenously (1 CU/kg) as a bolus the following morning. Thirty minutes after administration of secretin, the tip of the duodenoscope was placed close to the ampulla of Vater and duodenal aspirate was drawn for 10 min. Intraduodenal concentrations of lipase, bicarbonate, elastase and zinc were measured. The concentration of lipase during the Lundh test (4x20 min aspiration) was used as reference test in the patients. Judged from the Lundh test, the exocrine pancreatic function was nearly abolished in 5 patients (<10% of lower normal limit), reduced in 6 patients and normal in 13 patients. ESST failed in 1 patient (no aspirate). Lipase concentrations (KU/L) were significantly lower in the patients with nearly abolished function compared to patients with reduced or normal exocrine pancreatic function (NEPF; Mann-Whitney U test: P<0.05). Pancreatic elastase concentration was significantly lower in the group with nearly abolished exocrine function compared to patients with NEPF (Mann-Whitney U test: P<0.05), but there was no difference between elastase concentrations among the other groups. The authors found significant correlation between lipase and bicarbonate concentrations during ESST and lipase concentrations during the Lundh test in all 23 patients (Spearman's rank test: rho=0.597 and 0.683, respectively, P<0.01). By using receiver operating characteristic curves, best cut-off point for bicarbonate was estimated. Lipase and bicarbonate results in the healthy volunteers were not statistically different from results in patients with NEPF. No side effects were observed except for worsening of nausea and abdominal pain in 2 of the patients. In conclusion, the ESST is safe, and by combining the estimation of lipase and bicarbonate concentrations this test is a rapid, easy and useful diagnostic test for exocrine pancreatic function.

Role of Oxidative Stress in Pancreatic Inflammation.

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Reactive oxygen and reactive nitrogen species (ROS/RNS) have been implicated in the pathogenesis of acute and chronic pancreatitis. Clinical and basic science studies have indicated that ROS/RNS formation processes are intimately linked to the development of the inflammatory disorders. The detrimental effects of highly reactive ROS/RNS are mediated by their direct actions on biomolecules (lipids, proteins, and nucleic acids) and activation of proinflammatory...
signal cascades, which subsequently lead to activation of immune responses. The present article summarizes the possible sources of ROS/RNS formation and the detailed signaling cascades implicated in the pathogenesis of pancreatic inflammation, as observed in acute and chronic pancreatitis. A therapeutic ROS/RNS-scavenging strategy has been advocated for decades; however, clinical studies examining such approaches have been inconsistent in their results. Emerging evidence indicates that pancreatitis-inducing ROS/RNS generation may be attenuated by targeting ROS/RNS-generating enzymes and upstream mediators.

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Justifying Multidetector CT in Abdominal Sepsis: Time for Review?

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The further development of multidetector row CT (MDCT) has led to changes in the application and examination technique, leading to a need to justify the level and frequency of radiation exposure associated with MDCT. A literature review of how the use of modern scanners has affected diagnosis was undertaken, followed by a year-long retrospective study of MDCT scans of patients presenting with symptoms of abdominal sepsis. The diagnostic accuracy of detecting causes of abdominal sepsis using this technology was sought. Scans were performed using a LightSpeed 16 system (GE Healthcare Medical Systems, Slough, UK and Milwaukee, WI). Clinical diagnoses were based upon surgical and histopathological findings, treatment outcome and follow-up scans. System dose parameters recorded were the dose-length product (DLP) and volume CT dose index. The literature on investigating suspected abdominal sepsis has not been updated significantly since the time of conventional CT. Ninety-four patients were included in the study; causes of abdominal sepsis could be detected with a sensitivity of 0.95 and a specificity of 0.91. Repeat examination and cumulative exposure was a key finding. Patients with abscesses and acute pancreatitis had the highest number of scanner visits; patients with diverticular disease had the lowest number of visits, lowest cumulative DLP and shortest stay in hospital. Cumulative DLP was affected by scan length, number of scans and patient size. In conclusion, diagnostic accuracy data for MDCT scans using 16 slices confirm that CT remains a suitable modality for imaging abdominal sepsis but scope for dose constraint exists.


Cardiovascular Homeostasis In Hypotension Associated with Initial Stages of Severe Acute Pancreatitis.

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The authors aimed to identify the mechanisms underlying hypotension during the early phase of severe acute pancreatitis (SAP) by analyzing whether an impaired response to vasoactive substances occurs in this pathological process. Experimental SAP was induced by infusing 5% sodium taurocholate through the main pancreatic duct in rats. Once mean arterial pressure (MAP) in animals with pancreatitis was reduced, different vasoactive substances and inhibitors were administered. Administration of the nonspecific nitric oxide synthase inhibitor N omega-nitro-L-arginine methyl ester caused a similar increase in MAP in rats with pancreatitis and control rats, whereas inducible nitric oxide synthase inhibition did not cause changes in MAP.
Moreover, the hypertensive response to endothelin and angiotensin II was lower in pancreatitis. Inhibition of angiotensin II synthesis by the angiotensin-converting enzyme inhibitor perindopril in animals with pancreatitis caused severe hypotension, causing death in 40% of them. Finally, pressor hyporesponsiveness to angiotensin II in animals with pancreatitis was avoided by previous administration of perindopril and N-omega-nitro-L-arginine methyl ester. The SAP-induced hypotension is associated with a deficient pressor responsiveness to angiotensin II and endothelin-1. The renin-angiotensin system plays an important role in the control of MAP in animals with pancreatitis.


What Is the Outcome for Patients Presenting with Severe Acute Pancreatitis Requiring a Hospital Stay of More than One Month?

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The aim of this study was to investigate the clinical progression of patients who had severe acute pancreatitis (AP) and a stay in hospital of more than a month. A total of 24 patients (median age: 57 years) were included in this eight-year retrospective study. Cure was defined as the restoration of the pancreatic parenchyma, and the disappearance of all pseudocysts and pancreatic fistulae. Data including the duration of hospital stay, disease severity and pancreatic sequelae were also collected. Results. The median total duration of the hospital stay was 67 days. The overall mortality rate was 20.8%, whereas the mortality rate due to AP was 12.5%. The average healing period was 7.7 months. On univariate analysis, patients who also had respiratory diseases, chronic alcoholism, necrotizing superinfection, pseudocyst, food intolerance and/or hospital-acquired infection took significantly longer to heal. After cure, the authors observed pancreatic and/or hepatic duct stenoses in 50% of cases, and the onset or aggravation of diabetes in 25%. In conclusion, in patients hospitalized for more than one month because of necrotizing AP, the rate of mortality is around 20%, with a final hospital stay of two months and a healing period of more than seven months. In addition, half of the patients presented with pancreatic or biliary sequelae.


Is Complicated Gallstone Disease Preceded by Biliary Colic?

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Cholecystectomy in cases of "warning" episodes of biliary colic may prevent biliary pancreatitis. The authors aimed to determine which proportion of patients with biliary pancreatitis, compared to other complicated and uncomplicated symptomatic gallstone disease, experienced "warning" episodes of colic and why these episodes did not lead to early cholecystectomy. One hundred seventy-five patients with complicated gallstone disease (pancreatitis (n=53), symptomatic common bile duct (CBD) stones (n=64), and acute cholecystitis (n=58)) and 175 patients with symptomatic uncomplicated gallstones were interviewed at admission. Fifty-seven percent (100 of 175) of patients with complicated disease (95% confidence interval: 50-65%) experienced "warning" episodes of colic and why these episodes did not lead to early cholecystectomy. One hundred seventy-five patients with complicated gallstone disease (pancreatitis (n=53), symptomatic common bile duct (CBD) stones (n=64), and acute cholecystitis (n=58)) and 175 patients with symptomatic uncomplicated gallstones were interviewed at admission. Fifty-seven percent (100 of 175) of patients with complicated disease (95% confidence interval: 50-65%) experienced "warning" episodes of biliary colic (pancreatitis 58%, CBD stones 67%, cholecystitis 45%) vs. 96% (164 of 175) in uncomplicated disease. Eighty-seven percent of patients with
"warning" episodes and complicated disease experienced patient's and general practitioner's delays. General practitioner's delay was more frequent if pain was located in the epigastric region compared to the right upper quadrant (51% vs. 38%, P=0.03). Half of patients with biliary pancreatitis experience "warning" episodes of biliary colic, similar to other gallstone complications. In symptomatic patients, complications are often not prevented because of significant delays in diagnosis and treatment.


The Value of Endoscopic Ultrasonography in Predicting Resectability and Margins of Resection for Periampullary Tumors.

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Cure of pancreatic head and other periampullary neoplasms continues to be infrequent and is unattainable unless clear surgical margins are achieved during Whipple pancreaticoduodenectomy. Endoscopic ultrasonography (EUS) is a relatively recent gastrointestinal tumor imaging modality and may be superior to other techniques used in locoregional staging. The authors hypothesized that EUS can accurately predict not only tumor resectability, but also negative resection margins with Whipple resection. A retrospective review was undertaken of 81 consecutive patients with periampullary tumors who underwent preoperative CT and EUS followed by surgical exploration for intended Whipple resection. A retrospective review was undertaken of 81 consecutive patients with periampullary tumors who underwent preoperative CT and EUS followed by surgical exploration for intended Whipple resection. Correlations among preoperative EUS results, successful resection, and surgical margins on final histopathology were investigated. Of the 81 patients, 61 (75%) underwent successful Whipple resection, and 20 (25%) were found to be unresectable at laparotomy. Resection was achieved in 57 (86%) of 66 patients predicted to be resectable by EUS. Of the 61 resected patients, 52 (85%) had negative margins and nine (15%) had positive margins on final pathology. Margins were determined to be negative in 50 (88%) of 57 resected patients predicted to have negative margins by EUS. In conclusion, EUS is a powerful and desirable imaging modality in the preoperative assessment of periampullary neoplasms.

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Predicting Prognosis in Gastroenteropancreatic Neuroendocrine Tumors: An Overview and the Value of Ki-67 Immunostaining.

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Gastroenteropancreatic neuroendocrine tumors (GEP-NETS) are unusual and rare neoplasms for which prognostic assessment and the diagnosis of malignancy, on the basis of histology alone, represent considerable challenges for the pathologist. To date, many molecular markers have been identified with a view to providing accurate and timely prediction of response to treatment and long-term survival. Proliferation remains a key feature of tumor progression, which has been widely estimated by the immunohistochemical use of the Ki-67 nuclear antigen. Given the continued difficulties inherent in prediction of malignancy in pancreatic neuroendocrine tumors (PETs) in particular, it has become unclear whether Ki-67 is truly a reliable prognostication marker. This review seeks to better establish what the consensus is on the role of the Ki-67 proliferation index as a prognostic indicator of long-term outcome in pancreatic neuroendocrine tumors. The authors conclude that most studies favor the utility of the Ki-67 proliferation index despite different critical percentages and in concert with other pathological parameters in the routine work-up of PETs.


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Although pancreatic cystic neoplasms are widely recognized, practice habits among physicians and awareness of consensus guidelines are currently unknown. The authors assessed the awareness of guidelines and described variability in practice habits among 2 groups: (1) "general group" of gastroenterologists and surgeons and (2) "EUS group" of specialists in EUS. An online survey was sent to randomly selected gastroenterologists and surgeons and e-mailed to members of the American Society for Gastrointestinal Endoscopy (ASGE) Special Interest Group in EUS (EUS-SIG). Response rate for the general group was 8.8% (220/2500) and 9.7% for the EUS group (42/431). EUS specialists were mostly in academic practice (66.7% vs. 36.3%, P<0.001) and reported seeing 21 to 50 cysts per year (54.8% vs. 12.3%, P<0.001). The majority of the general group (64.1%) was unaware of any published practice guidelines, compared with 33.3% of EUS specialists (P<0.001). Awareness of ASGE guidelines was more frequently reported than other guidelines in both groups and yet was still <50% for each group. Both demonstrated moderate consistency with the International Association of Pancreatology guidelines, appropriately answering 66.7% of the questions. For 9-mm lesions, only 25% of the questions were correctly answered in each group. EUS specialists were less likely to refer main-duct intraductal papillary mucinous neoplasms (IPMN) for surgery and more likely to opt for EUS-guided FNA (compared with high-resolution CT, MRCP, or surgery) for 9-mm, 22-mm, and 34-mm branch-duct IPMNs (P<0.001 or P=0.001). Limitations. Low response rate and recall bias. In conclusion, awareness of practice guidelines about the management of suspected pancreatic cystic neoplasms is lower among general GI physicians compared with EUS specialists. Among all physicians, the greatest variability in practice is in small (<1 cm) lesions.

Management of Suspected Pancreatic Cystic Neoplasms Based on Cyst Size.


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Intraductal papillary mucinous neoplasms (IPMN) are distinct precursor lesions that can progress to pancreatic adenocarcinoma; thus, it has been of particular interest to cancer prevention researchers. The authors set out to do a population-based analysis of malignant IPMNs compared with other pancreatic subtypes to better delineate its characteristics and explore implications for prevention and management. The authors conducted a case-only analysis of California Cancer Registry data (2000-2007), including descriptive analysis of relevant clinical variables. Overall survival univariate analyses were conducted using the Kaplan-Meier method. Multivariate survival analyses were conducted using the Kaplan-Meier method. Multivariate survival analyses were done using Cox proportional hazards ratios. Overall, 15,296 pancreatic cancer cases were identified, including incident cases of 10,186 adenocarcinomas, 880 mucinous tumors, 568 endocrine tumors, 3,619 carcinoma not otherwise specified tumors, and 43 malignant IPMNs. Thirty-three (80.5%) IPMN cases had localized disease at presentation, eight had regional disease (19.5%), and no IPMNs were
identified with distant disease (two were unstaged). Five-year overall survival was better for malignant IPMN cases (65%) compared with pancreatic endocrine tumors (30%), mucinous tumors (5%), carcinoma not otherwise specified (2%), and adenocarcinoma cases (2%). Compared with adenocarcinoma cases, malignant IPMN cases (hazard ratio: 0.19; 95% CI: 0.10-0.35), endocrine tumors (hazard ratio: 0.28; 95% CI: 0.25-0.32), and mucinous tumors (hazard ratio: 0.84; 95% CI: 0.77-0.90) had higher overall survival in a multivariate survival analysis after adjustment for age, gender, stage, race, socioeconomic status, surgery, chemotherapy, and radiation therapy. In conclusion, pancreatic malignant IPMNs represent an uncommon pancreatic tumor subtype, uniquely characterized by early stage at presentation and better survival.