PANCREAS ALERTS

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Diagnostic value of CT features of the gallbladder in the prediction of gallstone pancreatitis.

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The aim of this retrospective study was to evaluate the diagnostic value of CT features of the gallbladder in the prediction of gallstone pancreatitis. Eighty-six patients who underwent a diagnostic computed tomography (CT) scan for acute pancreatitis were included. The readers assessed the presence of pericholecystic increased attenuation of the liver parenchyma, enhancement of gallbladder (GB) and common bile duct (CBD) wall, pericholecystic fat strands, GB wall thickening, stone in the GB or CBD, and focal or diffuse manifestations of pancreatitis on abdominal CT scans. In addition, the maximal transverse luminal diameters of the GB and CBD were measured. The presence of pericholecystic increased attenuation of the liver parenchyma, GB wall enhancement and thickening, pericholecystic fat strands, stone in the GB or CBD, and diffuse manifestations of pancreatitis achieved statistical significance for differentiation of gallstone induced pancreatitis from non-biliary pancreatitis ($P<0.05$). The mean values of maximal transverse luminal diameter of GB and CBD were significantly higher in gallstone induced pancreatitis group (39.67±7.26 mm, 10.20±4.13 mm) than non-biliary pancreatitis group (27.01±6.14 mm, 3.85±2.51 mm, $P<0.0001$). In conclusion, gallbladder features of CT in patients with pancreatitis could be the valuable clues for the diagnosis of gallstone induced pancreatitis.

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Fatal acute pancreatitis occurring outside of the hospital: clinical and social characteristics.

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Mortality caused by acute pancreatitis in patients admitted to the hospital has been thoroughly investigated, but knowledge regarding outpatient fatalities is far from complete. The purpose of this study was to assess the incidence and clinical characteristics of patients who have died due to acute pancreatitis occurring outside the hospital. Deaths caused by acute pancreatitis in the southern part of Sweden during 1994-2008 were identified at the Department of Forensic Medicine, Lund. A retrospective review of all cases was performed. A total of 50 patients were included, representing approximately 50 of 292 (17%) of all deaths due to acute pancreatitis in the region during this period of time. Median age was 54 (range: 47-69) years and the majority (37, 74%) were men. The main etiology was alcohol, seen in at least 35 (70%) patients. Twelve (24%) patients were obese. The duration of abdominal pain, in evaluable cases, was 3.0 (range: 1.6-6.2) days. Profound signs of pancreatitis were seen in all patients; 35 (70%) had a necrotising disease according to histopathological examination. Pulmonary changes were common, e.g., bronchopneumonia, pleural effusion, or edema, and all but four had fatty liver. Massive intra-abdominal bleeding was seen in one patient. At least eight patients had a mental disorder, and three were homeless. In conclusion, fatal acute pancreatitis occurring outside the hospital accounts for a substantial part of all deaths due to the disease. The incidence seems to decline, and no variation in season was seen. Alcohol was the predominant etiology. Many of the patients lived alone and in poor social conditions.

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Damage of the interstitial cells of Cajal and myenteric neurons causing ileus in acute necrotizing pancreatitis rats.

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Small intestinal motility is impaired in acute necrotizing pancreatitis (ANP). The present study was designed to detect the impairment in small intestinal motility and to assess the role of interstitial cells of Cajal (ICC), myenteric neurons and the associated mechanism in the pathogenesis of ileus during experimentally induced acute pancreatitis. ANP was induced by intraperitoneal injections of 30% L-ornithine at a dose of 3 g/kg at hourly intervals. The alterations of small intestine electrical activity - migrating myoelectric complexes (MMCs), and slow waves - were measured 24 h after ANP induction. The

spontaneous mechanical activity and the contractile response to ACh, KCl, tetrodotoxin (TTX) and the nitric oxide synthase (NOS) inhibitor NG-nitro-L-arginine (L-NNA) were evaluated by organ bath technique, and the morphologic alterations of the network of ICC, myenteric neurons and neuronal nitric oxide synthase (nNOS) immunoreactive cells were evaluated using the markers of c-Kit, PGP9.5, and nNOS, respectively. To demonstrate the deficiencies in enteric neuronal origin, The authors also measured nNOS expression in the muscular layer of ileum. L-ornithine-induced necrotizing pancreatitis manifests with multiple symptoms, including decreased amplitude of spontaneous contractions in small intestinal smooth muscle, declined contractile response to ACh, TTX, and L-NNA *in vitro*, disrupted MMC cycle length, decreased dominant frequency and dominant power of slow waves *in vivo*. Furthermore, the morphologic studies demonstrated the damage of ICC (ANP group *versus* control; P<0.001), myenteric neurons (ANP group *versus* control; P=0.001) and nNOS immunoreactive neurons (ANP group *versus* control; P<0.001). The authors also observed a substantial loss in the expression of nNOS protein in muscular layer of the small intestine (ANP group *versus* control; P=0.032). In conclusion, these results suggest that the pathogenesis of the small intestinal paralysis in ANP may be related to the deficiencies in ICC and nNOS neurons.

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Major haemorrhagic complications of acute pancreatitis.

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Haemorrhage is a rare, potentially fatal complication in acute pancreatitis (AP). The aim was to investigate the incidence, management and outcome related to this complication. The medical records of all patients with AP who presented to a single hospital between January 1994 and July 2009 were reviewed retrospectively. Patients who developed at least one in-hospital episode of major haemorrhage were selected. The aetiology, patient characteristics, occurrence of sentinel bleeding, clinical management and outcome were recorded. Fourteen (1.0%) of 1,356 patients diagnosed with AP developed major haemorrhage. Angiography established the diagnosis in four of six patients. Embolization was successful in one patient. Surgery was performed in two patients. Sentinel bleeding occurred in three of four patients with major postoperative bleeding. The overall mortality rate was 36% (5 of 14 patients). Haemorrhage presenting after more than 7 days was associated with a higher mortality rate of 80% (4 of 5 patients). A fatal outcome was at least three times more likely in patients with severe AP and haemorrhagic complications than in those with severe AP but no bleeding. In conclusion, major haemorrhagic complications of AP are rare, but clinically important. Major postoperative bleeding is often preceded by sentinel bleeding. Intra-abdominal haemorrhage presenting more than 1 week after disease onset is a highly fatal complication.

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Glucagon suppression during OGTT worsens while suppression during IVGTT sustains alongside development of glucose intolerance in patients with chronic pancreatitis.

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The authors aimed to examine plasma glucagon responses to oral and intravenous (i.v.) glucose in patients with chronic pancreatitis (CP) and either normal glucose tolerance (NGT), secondary impaired glucose tolerance (IGT) or secondary diabetes mellitus (DM). Eleven patients with CP and NGT, 6 patients with CP and secondary IGT, 7 patients with CP and secondary non-insulin requiring DM, and 8 healthy subjects were examined with an oral glucose tolerance test (OGTT) and an i.v. glucose tolerance test (IVGTT). In the CP groups, significant differences (increasing with the degree of glucose intolerance) in glucagon responses during the first hour of OGTT compared to IVGTT were observed (CP+NGT: -13±22 *vs.* -88±17, P=0.02; CP+IGT: 3±17 *vs.* -87±19, P=0.01; CP+DM: 94±27 *vs.* -78±16 1hxpmol/L (mean±SEM), P<0.001). Glucagon was suppressed equally following OGTT and IVGTT in the healthy subjects (-103±22 *vs.* -131±19 1hxpmol/L; P NS). IVGTT suppressed glucagon similarly in all groups except for a slightly impaired suppression in the CP+DM-group compared to healthy subjects. These results suggest that along with the development of secondary glucose intolerance in patients with CP, the suppression of glucagon by oral glucose is gradually lost and substituted by a paradoxical stimulation of secretion, while the suppression by i.v. glucose is maintained. This might indicate a glucagon stimulatory mechanism of gastrointestinal origin in CP patients.

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Autoimmune pancreatitis: the clinicopathological characteristics of the subtype with granulocytic epithelial lesions.

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Autoimmune pancreatitis (AIP) has been established as a distinct form of chronic pancreatitis that is distinguishable from other types such as alcoholic, hereditary or obstructive chronic pancreatitis. AIP seems to be a global disease, since it has been reported in many different countries, especially from Japan, USA and Europe (Germany, Italy, United Kingdom). Typical histopathological findings in the pancreas in AIP include a periductal lymphoplasmacytic infiltration with fibrosis, causing narrowing of the involved ducts. The typical clinical features include presentation with obstructive jaundice/pancreatic mass and a dramatic response to steroids. However, while the reports from Japan describe uniform changes called lymphoplasmacytic sclerosing pancreatitis (LPSP) in the pancreas from AIP patients, the reports from Europe and USA distinguish two histopathologic patterns in AIP patients: one with the characteristics of LPSP and another with slightly different histological features, called idiopathic duct centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesions (GELs). This article reviews the evidence that GEL-positive AIP or IDCP is a second type of AIP, distinct from LPSP, in regard to pancreatic pathology, immunology and epidemiology.

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Autoimmune pancreatitis and IgG4-related sclerosing disease.

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Autoimmune pancreatitis (AIP) is a unique form of pancreatitis in which the pathogenesis is suspected to involve autoimmune mechanisms. AIP sometimes mimics pancreatic cancer in its presentation, but as AIP responds dramatically to steroid therapy, accurate diagnosis is necessary. AIP is currently diagnosed on the basis of a combination of characteristic clinical, serological, morphological and histopathological features. However, its diagnosis remains a clinical challenge and there are no internationally agreed diagnostic criteria. Another type of AIP called 'idiopathic duct-centric chronic pancreatitis' or 'AIP with granulocytic epithelial lesion' has been reported in Western countries. IgG4-related sclerosing disease is a systemic disease in which IgG4-positive plasma cells and T lymphocytes extensively infiltrate various organs. Organs with tissue fibrosis and obliterative phlebitis, such as the pancreas, salivary gland and retroperitoneum, show clinical manifestations; AIP seems to represent one manifestation of IgG4-related sclerosing disease. As a mass is formed in most cases of IgG4-related sclerosing disease, a malignant tumor is frequently suspected on initial presentation. Clinicians should consider IgG4-related sclerosing disease in the differential diagnosis to avoid unnecessary surgery.

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Implications of enhancer of zeste homologue 2 expression in pancreatic ductal adenocarcinoma.

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Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer deaths in the United States. Single-agent gemcitabine remains the standard treatment of advanced pancreatic adenocarcinoma. A recently discovered histone methyltransferase termed enhancer of zeste homologue 2 (EZH2) was found to be overexpressed in a variety of carcinomas including pancreatic adenocarcinoma. Silencing of E-cadherin was proposed as a mechanism by which enhancer of zeste homologue 2 mediates tumor aggressiveness, and enhancer of zeste homologue 2 depletion has been found to sensitize pancreatic cancer cells to gemcitabine. In this study, the authors correlated enhancer of zeste homologue 2 with E-cadherin expression in pancreatic adenocarcinoma and evaluated response to gemcitabine in relation to enhancer of zeste homologue 2 expression in tumor cells. Fifty-four pancreatic adenocarcinomas, 13 intraductal papillary mucinous neoplasms, and 6 chronic pancreatitis cases were stained with antibodies against enhancer of zeste homologue 2 and E-cadherin. Enhancer of zeste homologue 2 staining was scored from 1 to 4+ and classified as either low (1-2+ in <25% of tumor nuclei) or high (3-4+ in >25% of tumor nuclei). E-cadherin expression was scored on membrane positivity as follows: 0 (0%-10%), 1 (10%-25%), 2 (25%-75%), and 3 (>75%). High enhancer of zeste homologue 2 expression in pancreatic adenocarcinoma was significantly associated with decreased E-cadherin expression and more aggressive disease. There was significantly longer survival in gemcitabine-treated patients with low *versus* high enhancer of zeste homologue 2 expression. High enhancer of zeste homologue 2 expression was detected in intraductal papillary mucinous neoplasms with moderate to severe dysplasia, but not in chronic pancreatitis. This study suggests that E-cadherin down-regulation may lead to enhancer of zeste homologue 2-mediated invasion and metastasis.

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RGS16 and FosB underexpressed in pancreatic cancer with lymph node metastasis promote tumor progression.

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Lymph node (LN) metastasis is one of the most important adverse prognostic factors for pancreatic cancer. The aim of this study was to identify novel lymphatic metastasis-associated markers for pancreatic cancer. DNA microarray analysis was used to determine and compare the expression profiles of 17 pancreatic cancer tissues with LN metastasis and 17 pancreatic cancer tissues without LN metastasis. The microarray results were validated by real-time reverse transcription-polymerase chain reaction and immuno-histochemistry. Only 58 genes were differentially expressed between the two groups with a difference in signal intensity ratio greater than a 1.5-fold change. Of these genes, 30 were significantly down-regulated in the LN metastasis group. Among five selected down-regulated genes for validation using real-time PCR, the expression of DST, FosB, RGS16, and CXCL12 was significantly lower in the LN metastasis group. Immunohistochemical analysis confirmed RGS16 and FosB underexpression in pancreatic cancer tissues with LN metastasis. RGS16 and FosB underexpression was associated with poor patient survival. These findings show that RGS16 and FosB are underexpressed in pancreatic cancer with lymph node metastasis and associated with reduced survival, suggesting that RGS16 and FosB might be prognostic markers for pancreatic cancer.

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SNAIL induces epithelial-to-mesenchymal transition in a human pancreatic cancer cell line (BxPC3) and promotes distant metastasis and invasiveness *in vivo*.

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SNAIL, a potent repressor of E-cadherin expression, plays a key role in inducing epithelial-to-mesenchymal transition (EMT) in epithelial cells. During EMT, epithelial cells lose cell polarity and adhesion, and undergo drastic morphological changes acquiring highly migratory abilities. Although there is increasing evidence that EMT is involved in the progression of some human cancers, its significance in the progression of pancreatic cancer remains elusive. In Panc-1, a well-known human pancreatic cancer cell line in which EMT is triggered by TGF-beta1 treatment, SNAIL and vimentin are highly expressed, whereas E-cadherin expression is scant. In contrast, another human pancreatic cancer cell line, BxPC3, in which SNAIL expression is not detected, has high levels of E-cadherin expression and does not undergo EMT upon TGF-beta1 treatment. After transfecting the SNAIL gene into BxPC3, however, the cells undergo EMT with remarkable alterations in cell morphology and molecular expression patterns without the addition of any growth factors. Furthermore, in an orthotopic transplantation model using SCID mice, SNAIL-transfected BxPC3 displayed highly metastatic and invasive activities. In the immunohistochemical analysis of the tumor derived from the SNAIL-expressing BxPC3, alterations suggestive of EMT were observed in the invasive tumor front. SNAIL enabled BxPC3 to undergo EMT, endowing it with a highly malignant potential *in vivo*. These results indicate that SNAIL-mediated EMT may be relevant in the progression of pancreatic cancer, and SNAIL could be a molecular target for a pancreatic cancer intervention.

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Long-term impact of a structured group-based inpatient-education program for intensive insulin therapy in patients with diabetes mellitus.

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Structured patient education aiming to improve self-management strategies might be beneficial for insulin-treated diabetic patients. However, in previous studies the extent of the benefit has been inconsistent in different subgroups of patients. The aim of the present study was to assess the potential benefit of a structured inpatient-education program for intensive insulin therapy according to the basal-bolus concept with particular emphasis on self-management strategies. The authors included 81 diabetic patients (59 with type 1, 14 with type 2, eight with other forms) in this retrospective longitudinal study; all had completed the training program on eight consecutive days at a university clinic between 2003 and 2005. Data assessment included HbA1c, LDL-cholesterol, HDL-cholesterol and BMI at baseline (0-15 months before the training) and after 0-5, 5-10 and 10-20 months. A transient decrease of HbA1c (0.2%, 95% CI: 0.04-

0.37%, P=0.017) and LDL-cholesterol levels (9.95 mg/dL, 95% CI: 2.24-17.76 mg/dL, P=0.013) between baseline and the first follow-up examination was observed in the group overall. Thereafter, HbA1c and LDL-cholesterol were similar to baseline, whereas a persistent increase in HDL-cholesterol (P=0.025) was evident in the multivariable analysis. No changes in BMI were observed. A significant type-by-time interaction (P=0.008) in HbA1c suggests a long-term benefit in glycemic control in patients with type 2 diabetes. In conclusion, a diabetes training program for intensive insulin therapy with particular emphasis on self-management skills was followed by a moderate and transient improvement of glycemic control and LDL-cholesterol and by a persistent increase in HDL-cholesterol. Long-term improvement in glycemic control was observed only in patients with type 2 diabetes.

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The GCKR rs780094 polymorphism is associated with susceptibility of type 2 diabetes, reduced fasting plasma glucose levels, increased triglycerides levels and lower HOMA-IR in Japanese population.

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It was recently reported that GCKR rs780094 was associated with fasting plasma glucose (FPG) and triglyceride (TG) levels in various ethnic populations (A allele for low FPG and high TG). An association between GCKR rs780094 and type 2 diabetes mellitus (T2DM) (A allele for low risk) has also been reported. The authors examined the association between GCKR rs780094 and T2DM in Japanese subjects by analyzing 488 cases and 398 controls. A meta-analysis was performed involving two previous association studies. The authors also analyzed the association between the single-nucleotide polymorphism and clinical parameters in the general Japanese population (n=1,854). In the case-control study, the A allele of GCKR rs780094 was associated with a reduced risk of T2DM (odds ratio: 0.711; 95% confidence interval: 0.589-0.859; P=0.00042). A meta-analysis confirmed the association of GCKR rs780094 with T2DM susceptibility. In the general Japanese population, subjects with the A/A genotype had lower levels of FPG, fasting plasma insulin and homeostasis model assessment of insulin resistance than those with the G/G genotype. Conversely, subjects with the A/A genotype had higher levels of TG than those with the G/G genotype. The authors replicated GCKR rs780094 as a marker of T2DM susceptibility in Japanese subjects. This suggests that GCKR rs780094 is a common variant for T2DM susceptibility in various ethnic groups.

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