Plexiform neurofibroma mimicking a pancreatic cystic tumour

Pancreatic neurogenic tumours are extremely rare. Among benign neurogenic tumours, schwannoma is more frequently encountered. We report here the case of a plexiform neurofibroma, a type of neurogenic tumour in the pancreas, to our knowledge previously unreported.

History
A 44 year old Caucasian female patient was hospitalised for epigastric and right abdominal pain lasting for seven months. Abdominal ultrasound and computed tomography showed a cystic lesion located in the superior and anterior part of the pancreatic isthmus, with a maximal diameter of 3.5 cm (fig 1A, B). T2 magnetic resonance imaging demonstrated a trilobar cystic lesion with strong hyperintensity (fig 1B); no communication with the main pancreatic duct was noted at magnetic resonance cholangiopancreatography (fig 1C). Endoscopic ultrasound (EUS) showed a cystic lesion containing heterogeneous fluid (fig 1D). EUS guided fine needle aspiration provided mucoid fluid with no epithelial cells. Fluid pancreatic enzyme concentrations were 423 and 1204 U/l for amylase and lipase, respectively, while CEA, CA 19.9, and CA 72.4 were 17 ng/ml, 9 U/ml, and 140 U/ml, respectively. Despite the low CA 19.9 concentration and lack of mucinous cells in cystic fluid, other findings were consistent with a diagnosis of mucinous cystadenoma. Surgical exploration confirmed a cystic lesion of the superior part of the main pancreatic duct (fig 1A, B). Tumour enucleation was performed. On macroscopy there was a well delineated, trilobated, translucent, oedematous mass, measuring 3.5 cm (fig 1E). The tumour consisted of aggregates of benign spindle cells embedded in a fibrillar matrix (fig 1F). These aggregates formed a thin rim around a central low cellular zone of oedema and myxoid degeneration. The tumour cells expressed neurofilaments and S100 protein on immunohistochemistry. P53 immunostaining was negative and sparse nuclei were Ki67 positive. These features were consistent with a benign plexiform neurofibroma (PNF).

Discussion
The presence of PNF in the pancreas has several clinical implications, as indicated by the present case. Firstly, PNF may mimic a pancreatic cyst, as was hypothesised in this case before surgery. The cystic appearance of pancreatic neurogenic tumours is frequently encountered, with intratumoral oedematous and myxoid changes probably being the underlying lesions. A bright appearance on T2 weighted magnetic resonance images is a characteristic of PNF. Secondly, surgical...
resection was necessary to exclude malignancy which is more frequently encountered in PNF compared with classical neurofibromas. In addition to classical benign features, similar to published data on benign PNF, a high cell proliferation and p53 protein expression were absent in our case. Thirdly, PNF is a morphological variant of neurofibroma, generally considered pathognomonic for an NF1 syndrome. When diagnosed in adult patients, it is frequently a solitary tumour and is considered a mosaic isolated form of NF1 syndrome. The absence of detectable genetic abnormalities and other clinical NF1 syndrome associated lesions in the present case could be explained by such a mechanism. For these patients, there is a low risk of developing other diseases associated with NF1 syndrome.

In conclusion, we have reported an uncommon case of PNF, unique in its pancreatic location. Intratumoral myxoid and oedemaous changes that develop in this type of neurofibroma give a cystic appearance which may lead to a misdiagnosis of a pancreatic cyst. Such lesions should be added to the list of benign pancreatic tumours with a cystic appearance.

A Handra-Luca
Department of Pathology, Jean Verdier and Beaujon Hospitals, Assistance Publique-Hôpitaux de Paris, France

D Vidaud
Department of Biochemistry, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, France

M-P Vullierme
Department of Radiology, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, France

N Colnot
Department of Pathology, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, France

D Henin
Department of Pathology, Bichat-Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, France

P Ruszniewski
Department of Gastroenterology, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, France

P Bedosa, A Couvelard
Department of Pathology, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, France

Correspondence to: Dr A Handra-Luca, MD PhD, Service d’Anatomie Pathologique, Assistance Publique-Hôpitaux Paris, Hôpital Jean Verdier, Avenue du 14 Juillet, 93143 Bondy, France; adriana.handra-luca@vr.ap-hop-paris.fr
doi: 10.1136/gut.2005.074609
Conflict of interest: None declared.

References


No genetic association between EPHX1 and Crohn’s disease

In a case control study on the associations between functional genetic polymorphisms in biotransformation enzymes and Crohn’s disease, we found a strong association between the Tyr113His (348T>C) polymorphism in exon 3 of the microsomal epoxide hydrolase (EPHX1) gene and Crohn’s disease.1 The three referees all agreed that the study was interesting and should be published so that other groups can attempt to replicate the results in independent study cohorts. This was done recently by Cuthbert and colleagues (Gut 2004;53:1386) who investigated 334 controls and 107 patients with Crohn’s disease, and who were unable to reproduce our results. In addition, they reported that our data for the EPHX1 exon 3 polymorphism in the control group were not in Hardy-Weinberg equilibrium (HWE), as also noticed previously by Györfy and colleagues.2 Our data on EPHX1 exon 3 genotyping were obtained by restricted fragment length polymorphism (RFLP) analyses by applying the method described by Lancaster and colleagues.3 However, recently it was reported that a silent substitution polymorphism (G to A) at codon 119 of the EPHX1 gene may exist, which may flaw the polymerase chain reaction (PCR) RFLP method applied by us, as the presence of this polymorphism may disturb proper binding of the reverse primer, covering the 119 G>A and therefore under-classification of His113 alleles.4 Therefore, we developed a dual colour allele specific discrimination assay for genotyping the polymorphism at codon 113 of the EPHX1 gene. EPHX1 genotypes were detected with the iCycler iQ Multicolour Real Time Detection System (Bio-Rad Laboratories, Veenendaal, the Netherlands) using molecular beacons. PCR was performed with the forward primer 5’-CAAGATCCAATCTGGAAGCTG-3’ and the reverse primer 5’-TGA CAT ACG TCC TCT GCT G-3’ in the presence of the FAM labelled wild-type base (5’-CCG GAT GAT TCA CAG ATG CCT GTC G-3’ and the HEX labelled mutant base (5’-CCG GAT ATT CAC AGA CAC CCT GCT TAT CAG G-3’). The 25 μl reaction mixture contained 200 ng of genomic DNA, 10 mM Tris/HC1 (pH 9.0), 50 mM KCl 0.1% Triton X-100, 4 mM MgCl2, 0.25 mM dNTPs, 50 ng of each primer, 200 nM of each beacon, and 2.5 U Taq-DNA-polymerase. The PCR conditions were three minutes at 95°C, then 40 cycles of 30 seconds at 95°C, 30 seconds at 59°C, and 30 seconds at 72°C. Fluorescent signals were measured at 585 nm, were assigned using the iCycler iQ Optical System, software version 3.1. At each PCR run (in 96 well plates) sterile H2O instead of genomic DNA was added in several wells as a negative control for amplification. As the PCR-RFLP analyses were performed in the first half of 1999, only some of the samples were still available (125 of 149 controls and 149 of 151 cases) and these were re-evaluated by the iCycler method.

Genotype distribution of the EPHX1 Tyr113His polymorphism in patients with Crohn’s disease and controls was now in HWE (χ2 = 2.47, p = 0.12 and χ2 = 0.82, p = 0.37, respectively) and genotype distribution was not significantly different between cases and controls (χ2 = 3.5, p = 0.17). The Tyr allele frequencies of 0.70 and 0.68 obtained for cases and controls, respectively, were very similar to the corresponding values of 0.71 and 0.70, as reported by Cuthbert et al.1 Thus in answer to the question as posed by Cuthbert et al.: “Genetic association between EPHX1 and Crohn’s disease: population stratification, genotyping error, or chance?”, we can conclude that a genotyping error was responsible for our earlier published association between the EPHX1 Tyr113His polymorphism and Crohn’s disease cases. Similar genotyping errors may also be present in several other studies on the EPHX1 exon 3 polymorphism in association with a variety of diseases, as many studies were based on methods using a reverse primer covering the “119 silent mutation area” of the EPHX1 gene.1 Into this may also have consequences for interpretation of results in the cited papers. However, a rapid literature search by Pubmed revealed more than 100 papers on EPHX1 polymorphisms over the past 10 years, suggesting that many more papers may deal with genotyping problems, as outlined above.

In addition, Cuthbert et al. also reported that another polymorphism tested in our study, the CPY1A1 exon 7 Ile5Val polymorphism, was not in HWE in the control group. This is correct but this deviation from HWE may be attributed to random chance, due to the rarity of the Val allele in our population, which makes the χ2 test inappropriate, under such conditions. In any instance, genotype distribution is in accordance with HWE when only two individuals less would have been classified as Val/Val homozygotes.

We thank Cuthbert et al. and Györfy and colleagues for their interest in our work. In addition, we conclude that (interpretation of) data in many other published studies on the EPHX1 Tyr113His (exon 3) polymorphism should be critically re-evaluated.

Department of Gastroenterology, University Medical Centre Nijmegen, the Netherlands

Correspondence to: Dr W H M Peters, Department of Gastroenterology, University Medical Centre Nijmegen, PO Box 9101, Nijmegen, the Netherlands; w.peters@md.umcn.nl

Conflict of interest: None declared.

www.gutjnl.com
Transcriptional downregulation of the lactase (LCT) gene during childhood

Adult-type hypolactasia, characterised by bloating, gas formation, and diarrhoea after ingestion of lactose containing foods, affects half of the world’s population. The molecular background of lactase non-persistence/persistence trait has been shown to associate with the very low lactase activity (4–9 U/g protein) in those with the C/C type.

We are grateful to the children and their families for their participation. Ms Sari Näsman and Mervi Mannonen at the Day Surgery Unit, Hospital for Children and Adolescents, are acknowledged for coordinating and managing the sample collection. Funding was provided by the Sigrid Juselius Foundation, Helsinki, Finland, the Helsinki University Hospital Research Funding, Helsinki, Finland, the Finnish Cultural Foundation, the Maud Kuistila Foundation, and The Research Foundation of Orion Pharma, Espoo, Finland.

H Rasinperä
Department of Medical Genetics, University of Helsinki, Finland

M Kuokkanen
Department of Medical Genetics, University of Helsinki, Finland, and National Public Health Institute, Department of Molecular Medicine, Helsinki, Finland

K-L Kolho, H Lindahl
Hospital for Children and Adolescents, University of Helsinki, Finland

N S Ennolah
Department of Medical Genetics, University of Helsinki, Finland, and National Public Health Institute, Department of Molecular Medicine, Helsinki, Finland

E Savilahti
Hospital for Children and Adolescents, University of Helsinki, Finland

References


9. Tranh GJ, Giovannucci E, Ma J, et al. Expression from C allele (%) 18 16 14 12 10 8 6 4 2 0

10. Table 1 Lactase activity, L/S ratio, and allelic ratio of the study subjects

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>C/T 13910 genotype</th>
<th>Lactase activity (U/g protein)</th>
<th>L/S ratio</th>
<th>Allele ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>CT</td>
<td>85</td>
<td>1.11</td>
<td>48/52</td>
</tr>
<tr>
<td>1.1</td>
<td>CT</td>
<td>113</td>
<td>1.02</td>
<td>52/48</td>
</tr>
<tr>
<td>4.0</td>
<td>CT</td>
<td>31</td>
<td>0.49</td>
<td>48/52</td>
</tr>
<tr>
<td>4.3</td>
<td>CT</td>
<td>53</td>
<td>0.48</td>
<td>42/58</td>
</tr>
<tr>
<td>4.7</td>
<td>CT</td>
<td>40</td>
<td>0.62</td>
<td>40/60</td>
</tr>
<tr>
<td>4.9</td>
<td>CT</td>
<td>6</td>
<td>0.08</td>
<td>48/52</td>
</tr>
<tr>
<td>0.8</td>
<td>CT</td>
<td>6</td>
<td>0.08</td>
<td>48/52</td>
</tr>
<tr>
<td>0.6</td>
<td>CT</td>
<td>22</td>
<td>0.28</td>
<td>18/82</td>
</tr>
<tr>
<td>7.1</td>
<td>CT</td>
<td>6</td>
<td>0.08</td>
<td>48/52</td>
</tr>
<tr>
<td>11.1</td>
<td>CT</td>
<td>29</td>
<td>0.54</td>
<td>13/87</td>
</tr>
<tr>
<td>14.9</td>
<td>CT</td>
<td>21</td>
<td>0.40</td>
<td>17/83</td>
</tr>
<tr>
<td>17.0</td>
<td>CT</td>
<td>29</td>
<td>0.62</td>
<td>24/76</td>
</tr>
<tr>
<td>1.1</td>
<td>CT</td>
<td>24</td>
<td>0.28</td>
<td>51/49</td>
</tr>
<tr>
<td>5.0</td>
<td>CT</td>
<td>6</td>
<td>0.08</td>
<td>49/51</td>
</tr>
<tr>
<td>22.8</td>
<td>CT</td>
<td>6</td>
<td>0.08</td>
<td>49/51</td>
</tr>
</tbody>
</table>

*Defined by assessing cSNP G/A 593 in exon 1 of the lactase LCT gene.

†Carrier of a CLD mutation (unpublished data).
Table 1  Comparison of CFTR mutation frequencies detected in the young onset pancreatic cancer cohort versus the clinical database

<table>
<thead>
<tr>
<th>CFTR mutation</th>
<th>Mayo Clinic clinical database reference group (n=5349)</th>
<th>Young onset pancreatic cancer cases (&lt;60 y old at diagnosis, n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>CFTR mutation non-carriers</td>
<td>152</td>
<td>91.6</td>
</tr>
<tr>
<td>CFTR mutation carriers</td>
<td>14</td>
<td>8.4</td>
</tr>
<tr>
<td>Mutation distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF508</td>
<td>12</td>
<td>85.7</td>
</tr>
<tr>
<td>R177H</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>G551D</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>2789G&gt;5&gt;</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>G542X</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>N1303K</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>1717G&gt;T</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>3849T&gt;10kbC&gt;T</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>A455E</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>R162X</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>R347H</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>R553X</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>3905T</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>621&gt;T&gt;1G</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>1282X</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>1988T&gt;G&gt;</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>R560T</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Young onset pancreatic cancer cases were more frequent carriers of the CFTR mutations compared with patients in the control database (odds ratio 2.18 (95% confidence interval 1.24–3.29); p = 0.006).

This represents a substantial improvement over population based pancreatic cancer epidemiological studies, with participation rates ranging from 34.6% to 45.6%.

Cystic fibrosis transmembrane regulator gene carrier status is a risk factor for young onset pancreatic adenocarcinoma

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the USA. Although predominantly a cancer of the elderly, approximately 20% of patients are diagnosed under the age of 60 years. Younger patients are likely the best candidates for early surgical intervention, and patients at risk for young onset cancer comprise a logical focus for screening or prevention.

Carriers of mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) are associated with chronic idiopathic pancreatitis. Chronic pancreatitis, in turn, increases the risk for pancreatic cancer by 26-fold. Therefore, we hypothesised that mutations in CFTR may confer a higher risk of pancreatic cancer.

From October 2000 to April 2004, pancreatic cancer patients seen at the Mayo Clinic were ultra rapidly recruited to our study, with more than 75% of all such patients seen at the Mayo Clinic enrolled in the registry. This represents a substantial improvement over population based pancreatic cancer epidemiological studies, with participation rates ranging from 34.6% to 45.6%.

We thank the patients in this study and the contributions of Tammy Dahl, RN, Kathy Liffrig, Cynthia Nixa, Diane Batzel, Que Lau, Suresh Chari, MD, and Thomas Smyrk, MD.

Funding for this research was provided by the Mayo Clinic SPOR in Pancreatic Cancer (P50 CA102701), R25T CA 92049, Lustgarten Foundation for Pancreatic Cancer Research, NCI GRANT (R01 CA97075).

R McWilliams
Department of Oncology and Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

W E Highsmith
Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

K G Rabe, M de Andrade, L A Tordsen
Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

Conflict of interest: None declared.

References

Cystic fibrosis transmembrane regulator gene carrier status is a risk factor for young onset pancreatic adenocarcinoma

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the USA. Although predominantly a cancer of the elderly, approximately 20% of patients are diagnosed under the age of 60 years. Younger patients are likely the best candidates for early surgical intervention, and patients at risk for young onset cancer comprise a logical focus for screening or prevention.

Carriers of mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) are associated with chronic idiopathic pancreatitis. Chronic pancreatitis, in turn, increases the risk for pancreatic cancer by 26-fold. Therefore, we hypothesised that mutations in CFTR may confer a higher risk of pancreatic cancer.

From October 2000 to April 2004, pancreatic cancer patients seen at the Mayo Clinic were ultra rapidly recruited to our study, with more than 75% of all such patients seen at the Mayo Clinic enrolled in the registry. This represents a substantial improvement over population based pancreatic cancer epidemiological studies, with participation rates ranging from 34.6% to 45.6%.

We thank the patients in this study and the contributions of Tammy Dahl, RN, Kathy Liffrig, Cynthia Nixa, Diane Batzel, Que Lau, Suresh Chari, MD, and Thomas Smyrk, MD.

Funding for this research was provided by the Mayo Clinic SPOR in Pancreatic Cancer (P50 CA102701), R25T CA 92049, Lustgarten Foundation for Pancreatic Cancer Research, NCI GRANT (R01 CA97075).

R McWilliams
Department of Oncology and Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

W E Highsmith
Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

K G Rabe, M de Andrade, L A Tordsen
Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

www.gutjnl.com

Downloaded from http://gut.bmj.com/ on April 14, 2017 - Published by group.bmj.com
Distal intestinal obstruction syndrome in the early postoperative period after lung transplantation in a patient with cystic fibrosis: morphological findings on computed tomography

Distal intestinal obstruction syndrome (DIOS) occurs in 19.9% of adults with cystic fibrosis (CF). Usually the diagnosis is based on history, physical examination, and plain abdominal roentgenogram. The increased risk of gastrointestinal complications such as DIOS is well known after lung transplantation. Due to the added risk of gastro-intestinal surgery in the postoperative period and the generally good response to conservative treatment, it is necessary to distinguish DIOS from other gastrointestinal complications. Nevertheless, descriptions of computed tomographical patterns of DIOS in the international literature are rare.

We present the case of a 34 year old male suffering from end stage CF. Because of gastrointestinal manifestations of CF, the patient had exocrine pancreas insufficiency. As a consequence of deterioration in respiratory function, lung transplantation was performed. Despite enzymatic and propulsive medical treatment the patient developed an acute abdomen during the postoperative period. To determine the cause of his symptoms abdominal radiographs and computed tomography were performed. Abdominal plain films showed remarkably little abdominal gas and poor delineation of the abdominal organs (fig 1A). Contrast enhanced computed tomography showed massive dilatation of the small bowel and proximal colon with marked swelling of the intestinal wall (fig 1B, C). The lumen of the small intestine and proximal part of the ascending colon were filled with a homogenous mass (fig 1B) with increasing roentgen opacity from the duodenum (approximately 19 HU) to the right hemicolon (approximately 39 HU). Isolated air fluid levels were seen in the small bowel. The transverse, descending, and sigmoid colon were thin with only little faeces. There was no evidence of external compression. Based on these findings a diagnosis of DIOS was made. laparotomy, performed due to failure of medical treatment, confirmed the diagnosis.

DIOS is unique to patients with cystic fibrosis. Intestinal obstruction developed due to accumulation of highly viscous mucofaeculent material in the terminal ileum and right hemicolon. Pancreatic insufficiency is a prerequisite for DIOS but is not its only pathophysiological cause. Other factors such as reduced intestinal water content, lower luminal acidity of the foregut, accumulation of intraluminal macromolecules, dehydration of the mucus layer due to altered intestinal secretion, and slow intestinal transit contribute to the development of DIOS.

Plain films are only of limited value in differentiating DIOS from other causes of acute abdomen. In the case of DIOS, they usually show typical signs of a small bowel ileus but other frequent reasons for ileus in patients with CF (for example, adhesions, intussusception, paralytic ileus due to perforated appendicitis, or Crohn’s disease) cannot be excluded without further investigation. In our case, abdominal plain films showed no typical signs of small bowel ileus but little abdominal gas with poor delineation of the abdominal organs leading to the differential diagnoses of ascites, colitis, mesenteric infarction, and proximal bowel obstruction. In contrast with the plain abdominal radiograph, computed tomography showed the criteria of DIOS. The small bowel was completely filled with a homogenous mass with increasing roentgen opacity from the duodenum (approximately 19 HU) to the right hemicolon (approximately 39 HU), suggesting increasing viscosity of the intestinal content due to water absorption. In accordance with previous descriptions of DIOS, obstruction occurred in the right hemicolon.

Our case showed that abdominal plain films, as used in previous studies, are not adequate for the diagnosis of DIOS. Computed tomography can reveal the characteristic signs of DIOS and exclude inherent differential diagnoses. We have demonstrated for the first time that DIOS causes increasing opacity of intestinal contents during small intestinal passage, suggesting increasing viscosity.

References
Association of a new cationic trypsinogen gene mutation (V39A) with chronic pancreatitis in an Italian family

Predisposition to hereditary pancreatitis has been associated with mutations in three genes: protease, serine, 1 (PRSS1), which is responsible for inherited chronic pancreatitis in 10% of the cases, and cystic fibrosis transmembrane conductance regulator (CFTR), and serine protease inhibitor Kazal type 1 (SPINK1).9

We have identified a novel PRSS1 mutation in seven subjects with chronic pancreatitis (CP) from three generations of an Italian family. The index patient was a 57 year old man with CP referred to our hospital for ductal adenocarcinoma of the pancreatic head. Eleven relatives were examined, and an uncle, also with CP, had died in an accident. Congenital malformations and alcoholic, biliary, obstructive, and autoimmune pancreatitis were ruled out. Eleven subjects gave their written consent to the study.

The cystic fibrosis assay (CF-OLA; Applied Biosystems, California, USA) was used to look for 31 frequent CFTR mutations in all subjects. The five exons of the PRSS1 gene were sequenced with the oligonucleotides described by Nishimori and colleagues.3 The four SPINK1 exons were investigated by denaturant gradient gel electrophoresis (DGGE). No CFTR or SPINK1 mutations were found although subject III-8 (with CP) carried the N1303K mutation in heterozygosis in the cystic fibrosis gene.

The PRSS1 exon 2 sequence of the index patient revealed a T>C change at nucleotide 116 (c.116 T>C) causing a valine to alanine substitution at codon 39 (V39A). This mutation was present in another six subjects with CP, diagnosed from exocrine insufficiency and computer tomography and magnetic resonance imaging demonstrations of typical ductal alterations and parenchymal calcifications. Two of these patients were also diabetic. In a further two patients, the genetic analysis was not performed, but CP was confirmed by clinical and morphological findings. The remaining four subjects had a normal pancreas and did not carry the V39A mutation (fig 1).

The lod score calculated for the association between V39A and CP was z = 3.0 at 0 = 0.0. This mutation was not found in a DGGE investigation of 130 patients with sporadic CP. Mean age of the patients was 47.22 (± 13.64) years (median 54 (range 25–60)). Mean age at onset was 30.0 (± 7.35) years (median 32 (range 19–40)) whereas in patients displaying other PRSS1 mutations, onset was typically during childhood or adolescence.3

An acute attack requiring hospitalisation formed the clinical overture in six of the nine CP patients. The other three (III-4, III-5 and IV-2) presented morphological and functional evidence of CP at the time of the study but were asymptomatic. It is clear therefore that damage to the pancreas may occur prior to the clinical onset of CP.

In hereditary CP, the mechanism of the R122H mutation has been elucidated.1 This substitution removes a hydrolysis start site and makes both trypsin and trypsinogen autolysis resistant. A similar mechanism has been proposed for the N291 mutation which alters protein conformation and masks the R122 site.7 Valine 39 is evolutionarily conserved in the trypsinogen gene of all terrestrial vertebrates8 and would thus seem of importance in the protein’s structure and function. As V39 is only 10 amino acids distant from N29, its replacement by alanine may result in abnormal conformation of the peptide and mask arginine 122 against enzymatic degradation. Further work is needed to define the mechanism and confirm this interpretation.

In conclusion, the presence of the V39A mutation in seven of the CP patients, its absence in their healthy relatives, the 3.0 lod score, and the strong evolutionary conservation of V39, all indicate that the novel mutation is the cause of CP in this family.

Acknowledgements

We would like to thank Professors J P Neoptolemos and DC Whitcomb for their valuable assistance and Mr J Illife. This work was supported by Compagnia di San Paolo and Regione Piemonte.

C Arduino
SC Genetica Medica, ASOS Giovanni Battista, Torino, Italy

P Salcone
SC Gastroenterologia, ASO San Luigi Gonzaga, Orbassano (TO), Italy

B Pasini, A Brusco
Università di Torino, Dipartimento di Genetica, Biologia e Biochimica, Torino, Italy
ITPA genotyping is not predictive for the development of side effects in AZA treated inflammatory bowel disease patients

We read with interest the letter by Colombel et al on the non-predictive value of ITPA genotyping for the development of myelosuppression after azathioprine (AZA) treatment (Gut 2005;54:565).

The level of thiopurine methyltransferase (TPMT) activity is determined by a common genetic polymorphism. It was shown that low TPMT activity is linked to a higher relative risk of development of myelosuppression after AZA treatment. 8 Testing for TPMT genotype before the start of AZA treatment is of limited clinical value as myelosuppression resulting from TPMT mutations occurs in less than one third of patients with myelosuppression.

Polymorphisms in genes encoding inosine triphosphate phosphoribosyltransferase (ITPase), another enzyme involved in metabolism of AZA, have also been suggested to be associated with the development of side effects in AZA treatment. 9 Colombel et al show that there was no difference in the frequency of ITPA polymorphisms in 41 patients who developed AZA related myelosuppression in comparison with a previously published control population. Unfortunately, this leaves the question of other side effects such as flu-like symptoms, rash, and pancreatitis unanswered. In addition to the TPMT genotype, we determined the 94C>A ITPA polymorphism. All 109 patients with inflammatory bowel disease who started AZA treatment from January 2003 onwards were included, and side effects were determined. There was a mean follow up time of 13 months (range 4–24). The frequency of side effects was compared with the frequency of side effects in AZA treated patients without any (ITPA or TPMT) polymorphism. Notably, for patients with a heterogenous TPMT or ITPA polymorphism, no preventive adjustments of AZA dosing were made.

In a patient group of a total of 109 patients, we found 10 who had a TPMT polymorphism and 12 who had a 94 C>A ITPA polymorphism. Eighty eight patients had none of the studied polymorphisms in TPMT or ITPA genes. Of the 12 patients who had an ITPA heterozygous polymorphism only two had side effects (17%). One had a rash and the other had complaints of arthralgia. In patients without any of the investigated polymorphisms, 34 of 88 (39%) had side effects (summarised in table 1). There was one patient, receiving a normal dose of AZA, who had both a TPMT*3A and an ITPA 94 C>A heterozygous polymorphism. Interestingly, this patient did not develop any side effects.

Our data confirms the results of Colombel’s research by showing that an ITPA heterozygous polymorphism is not associated with an increased risk for the development of leucopenia. Additionally, we also found that there was no increased risk for the development of other side effects.

No conclusions can be drawn for patients who are homozygous for the ITPA 94 C>A polymorphism as none was included either in our study or in Colombel’s. Marinaki et al included three patients with a homozygous 94 C>A polymorphism for ITPA and all three had side effects. 9 Therefore, further research on the risk of developing side effects in homozygous 94 C>A ITPA patients is desirable.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No polymorphisms (88 of 109)</th>
<th>TPMT polymorphisms (10/109)</th>
<th>ITPA polymorphisms (12/109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3A</td>
<td>1/3C</td>
<td>WT/94C&gt;A</td>
</tr>
<tr>
<td></td>
<td>3/3A</td>
<td>3/3A</td>
<td>94C&gt;A</td>
</tr>
<tr>
<td></td>
<td>3/3B</td>
<td>3/3B</td>
<td>94C&gt;A/94C&gt;A</td>
</tr>
</tbody>
</table>

One patient was included in both the TPMT polymorphisms column and in the ITPA polymorphisms column as he was heterozygous for the TPMT*3A polymorphism and heterozygous for the ITPA 94 C>A polymorphism. Side effects categorised as “other” included rash, renal function disorders, vertigo, myalgia, and arthralgia.

References
Lack of serum antibodies to membrane bound carbonic anhydrase IV in patients with primary biliary cirrhosis

Nishimori et al have recently reported the presence of autoantibodies against carbonic anhydrase IV (anti-CA IV) in patients with autoimmune pancreatitis (Gut 2005;54:274–81). Furthermore, serum antibodies to CA II (anti-CA II) were observed in several autoimmune conditions. We have now investigated the presence of anti-CA IV and anti-CA II in a large series of sera from patients with primary biliary cirrhosis (PBC) and controls. CA II is known to be expressed in the cytoplasm of various types of epithelial cells, including those lining bile ducts, renal tubules, and salivary ducts. For this reason, CA II was suggested as a common antigen in conditions characterised by an autoimmune aggression against epithelia. In autoimmune pancreatitis, serum anti-CA II are useful diagnostic tools while in PBC they were first detected by Gordon et al in 5/6 sera from patients with antimitochondrial antibody (AMA) positive PBC. Subsequent studies however demonstrated prevalence rates as high as 46% in PBC sera but failed to confirm their specificity for AMA negative sera.

Interestingly, anti-CA II were also shown to inhibit enzyme activity.

Apart from cytosolic CA II, the CA family also includes a highly active membrane bound enzyme that was coined CA IV. Both CA II and CA IV are abundantly expressed in human bile duct epithelial cells. Interestingly, mainly due to the sequence homology between CA II and CA IV and CA IV localisation on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might localise on cell membranes, Nishimori et al hypothesised that the exposed CA IV might.

In summary, we submit that the hypothesis that antibodies against the membrane bound CA IV may play a role in PBC should be rejected, based on experimental data on a large series of sera. Our finding may be secondary to a different cellular expression of CA IV in the target organ (that is, pancreatic and bile ducts) but only specific tissue studies can provide these answers. At present, therefore, anti-CA IV should be regarded as specific to autoimmune pancreatitis and research should focus on better defining their possible role in this condition.

P Invernizzi, C Selmi, M Zuiin, M Poddà
Department of Internal Medicine, San Paolo School of Medicine, University of Milan, Italy

Correspondence to: Dr P Invernizzi, Division of Internal Medicine, Department of Medicine, Surgery, and Dentistry, University of Milan, Via di Rudinì 8, 20142 Milan, Italy; pietro.invernizzi@unimi.it

Conflict of interest: None declared.

References


Association of achalasia and dental erosion

Dental erosion is the dissolution of enamel and dentine caused by acids, like lactic and organic acids. The source of acid is normally either dietary or related to the presence of palatal dental erosion in patients with achalasia strongly suggests that the source of the acid within the oesophagus is lactic acid unlike reflux disease where hydrochloric acid from the stomach is responsible. This study shows that in patients with achalasia, particular attention to the condition of their teeth needs to be addressed. In conclusion, achalasia is related to palatal dental erosion and the cause of the erosion is fermented foods and not regurgitated gastric juice.

R Moaazze Department of Prosthodontics, GKT Dental Institute, London, UK

A Anggiansah, A J Botha
St Thomas’ Hospital NHS Trust, London, UK

D Bartlett
Department of Prosthodontics, GKT Dental Institute, London, UK

Correspondence to: Dr R Moaazze, Department of Prosthodontics, GKT Dental Institute, GKT Dental Tower, St Thomas’ St, London Bridge, London SE1 9RT, UK; Rebecca.moaazze@kcl.ac.uk

www.gutjnl.com
Conflict of interest: None declared.

References


BOOK REVIEW

New Techniques in Gastrointestinal Imaging


Many areas of radiology are rapidly developing new techniques to answer clinical problems or devising ways of refining current imaging techniques. Gastrointestinal imaging is no exception.

New Techniques in Gastrointestinal Imaging has been edited and written by experts in the field from the international community and encompasses the more recent developments in all aspects of gastrointestinal imaging. The book has been divided into chapters that either concentrate on a particular imaging technique (for example, computed tomography (CT) colonography) or those that cover recent developments in the investigation of a particular area (for example, the rectum).

There are very comprehensive chapters covering the new CT and magnetic resonance (MR) techniques available for imaging the colon and small bowel. New CT and MR techniques for hepatic imaging are also included, with special reference to the development of CT angiography. There are excellent chapters on the use of microbubbles in ultrasound (US) and endoscopic US, both of which are good introductions to these techniques for those with limited previous knowledge or experience. Also included is a very useful chapter on positron emission tomography (PET) with a gentle introduction to the physics of the technique and current applications and limitations. New interventional imaging techniques are also covered, with chapters on radiofrequency ablation of liver lesions and on self expanding metallic stents in the colon.

I was however dismayed to find a section on defecating proctography, a technique I had rather hoped had been consigned to history. The current method seems to have changed little from my days as a junior registrar banished to the barium room although new MR techniques are described.

This book has been written to update the general radiologist in areas of gastrointestinal radiology that have changed significantly in recent times. This it does very well, with concise descriptions of the techniques, thorough discussions on clinical use, and handy tips on image interpretation. As such, there are chapters in the book that need some background knowledge of radiological techniques to appreciate the new developments (for example, CT and MR chapters on liver imaging). However, all chapters provide a good setting for each of the new techniques so that the interested gastroenterologist would find useful information on the current role of each investigation, its performance with relation to more established techniques, and future developments.

A Graham

doi: 10.1136/gut.2005.067686

CORRECTIONS

doi: 10.1136/gut.2005.064824

In the Editor’s quiz: GI snapshot on p1272 of the September issue (D Joshi, J Dunga, A James and MM Yaqoob. An unusual case of hepatosplenomegaly. Gut 2005;54:1272; doi:10.1136/gut.2005.064824) the second author’s name should read Dungu not Dunga.

In the Gut Tutorial on p296 of the February issue the author’s name and affiliation was omitted. The details are as follows: Robin Spiller, Professor of Gastroenterology, Wolfson Digestive Diseases Centre, University Hospital, Nottingham NG7 2UH, UK.

In the Gut Tutorial on p555 of the May issue the author names and affiliations were omitted from the original publication. This has been updated on the Gut website. The authors and affiliations are as follows:

S A Khan, A Miras, Liver Unit, Department of Medicine A, Faculty of Medicine, Imperial College London, St Mary’s Hospital Campus, South Wharf Road, London W2 INY, UK; M Pelling, Department of Radiology, Faculty of Medicine, Imperial College London; S D Taylor-Robinson, Liver Unit, Department of Medicine A, Faculty of Medicine, Imperial College London.
Association of achalasia and dental erosion

R Moazzez, A Anggiansah, A J Botha and D Bartlett

*Gut* 2005 54: 1665-1666
doi: 10.1136/gut.2005.067686

Updated information and services can be found at:
http://gut.bmj.com/content/54/11/1665.2

These include:

**References**
This article cites 11 articles, 0 of which you can access for free at:
http://gut.bmj.com/content/54/11/1665.2#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/