PAPERS AND SHORT REPORTS

Prospective comparison of three non-invasive tests for pancreatic disease

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Abstract

Ultrasonography, computed tomography (CT), and an oral pancreatic function test were evaluated prospectively in 107 consecutive patients suspected of having pancreatic disease, the final diagnosis being made independently of these tests. Seventeen patients proved to have either chronic pancreatitis or a pancreatic neoplasm. Five had an unfused ventral pancreas and 10 had "minimal change" pancreatograms. Seventy five patients did not have pancreatic disease.

Among the 17 patients with pancreatic disease the sensitivities of ultrasound, CT, and the pancreatic function test were 70%, 71%, and 76% respectively; among those without disease values of specificity of the three tests were 75%, 87%, and 72%. All three tests failed to detect most of the patients with unfused ventral pancreases or minimal change pancreatograms. The predictive values of a positive result for the three tests were 43%, 67%, and 34%. The predictive value of a

negative result was >90% for all the tests. Results improved when CT was combined with either of the two other tests.

These findings show that CT is the most accurate of the three tests in diagnosing pancreatic disease but that a combination of ultrasound and the oral pancreatic function test offers a more widely applicable and almost as accurate alternative.

Introduction

Pancreatic disease frequently enters the differential diagnosis of patients presenting with recurrent abdominal pain or malabsorption. Chronic pancreatitis is uncommon, however, and the requirement in most patients is its exclusion as a cause of symptoms. Standard tests of pancreatic morphology¹ and function^{2,3} require duodenal intubation for pancreatography or aspiration of duodenal juice, and simpler tests are therefore desirable—provided that they are as reliable.

Recently, ultrasonography, computed tomography (CT), and an oral pancreatic function test—which do not entail duodenal intubation—have been applied to the investigation of pancreatic disease. Most published reports of the diagnostic accuracy of these methods are either retrospective⁴⁻⁶ or contain an unrealistically high proportion of patients with disease.⁷⁻¹⁵ Such studies indicate the sensitivity (the proportion of patients with disease identified by the test) and specificity (the proportion of normal results in patients without disease) of a test, usually as performed by an expert. Nevertheless, retrospective studies concentrating on patients with disease cannot disclose the test's predictive value (the frequency with which a positive or negative result is correct) because this depends on the prevalence of the disease, which is a major factor in assessing the utility of the test clinically. We have therefore performed a prospective evaluation, under routine clinical conditions, of three non-invasive tests—ultrasonography, CT, and an oral pancreatic function test—in a consecutive series of patients in whom pancreatic disease was suspected clinically, the final diagnosis in each patient being established independently of the three tests.

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Patients

Patients were referred for investigation of suspected pancreatic disease. Any patient with a history of exocrine pancreatic disease or who was jaundiced was excluded. Over two years 113 patients were referred but six failed to complete investigation or were lost to follow up.

The remaining 107 patients comprised 52 men and 55 women aged 15-86 years (mean 46.5). The predominant presenting complaint was recurrent abdominal pain in 80 (75%), clinical malabsorption or weight loss in 19 (18%), recent or unstable diabetes in six, and one each with unexplained ascites and recurrent deep vein thrombosis. Twenty had a history of alcohol abuse. Seventy nine patients had previously undergone endoscopy or barium meal examination and 28 oral cholecystography or intravenous cholangiography; in none of these had anything abnormal been seen.

The final diagnosis was made independently of the three tests under evaluation, on the basis of radiology, operative and histological findings, and follow up. In addition, endoscopic retrograde cholangiopancreatography and a Lundh test were performed when not contraindicated or rendered superfluous by the results of other investigations.

Criteria for the diagnosis of chronic pancreatitis were the presence of at least one of the following: (a) pancreatic calcification in a plain radiograph; (b) operative findings with histological confirmation; and (c) an abnormal pancreatogram on endoscopic retrograde cholangiopancreatography with either an abnormal Lundh test result or steatorrhoea responsive to pancreatic supplements. A "minimal change" pancreatogram was diagnosed when the abnormalities were minor and confined to the peripheral branches of the duct system (criteria described elsewhere).¹⁶

FINAL DIAGNOSES

Chronic pancreatitis was diagnosed in 11 patients (10%).

Pancreatic neoplasm was confirmed histologically in six patients, two having adenocarcinoma and one each having cystadenocarcinoma, carcinoid, Zollinger-Ellison syndrome, and Hodgkin's disease.

Minimal change pancreatograms were found in 10 patients.

Unfused ventral pancreas was detected by endoscopic retrograde cholangiopancreatography¹⁷ in five patients.

No evidence of pancreatic disease was found in 75 patients; in 57 an alternative diagnosis was made (table). Despite investigation and follow up no definite diagnosis was made in the 18 others, but all had a normal pancreatogram and Lundh test result.

Final diagnosis in 75 patients without pancreatic disease

	No of patients		No of patients
Oesophagitis	4	Irritable bowel syndrome	7
Gastritis	2	Other gastrointestinal disorders	5
Gastric ulcer	2	"Functional" pain/depression	11
Duodenal ulcer	6	Non-gastrointestinal disease	7
Biliary tract disease	7	No diagnosis (normal pancreatogram and Lundh test result)	18
Small bowel disease	6		

Methods

On admission to the study all clinical details and previous investigations were recorded.

Ultrasound was performed after an overnight fast, without specific bowel preparation. Real time scans were obtained using a commercially available sector scanner according to techniques described elsewhere.¹⁸ CT was performed after giving 800 ml 4% diatrizoic acid (Gastrografin) by mouth and 100 ml contrast intravenously. Contiguous 0.6 cm slices were examined using a rotating fan beam (Philips T 300) with a scan time of 4.8 seconds.

The oral pancreatic function test was performed after an overnight fast using an oral dose of 1 g *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (Bentiromide; Roche) and 5 μ Ci *p*-amino-(ring-¹⁴C)-benzoic acid (Radiochemical Centre, Amersham) in a standard Lundh meal. Urine was collected for six hours and analysed for *p*-aminobenzoic acid concentration both chemically¹⁹ and isotopically. A *p*-aminobenzoic acid excretion index (PEI) was derived from the ratio of chemical recovery of the acid to recovery of ¹⁴C, as described.⁶ The

result was regarded as abnormal if the PEI was <0.68 (mean -3 SD in 20 normal subjects). The isotope was omitted in children and women of childbearing age.

Endoscopic retrograde cholangiopancreatography was performed with a side viewing duodenoscope in a standard manner. Lundh tests were performed by a standard method²⁰ with measurement of the mean tryptic activity by the method of Wiggins.²¹

All the investigations were performed as part of the hospital's routine diagnostic service.

The sensitivity, specificity, and predictive values of each test were calculated as follows:

Sensitivity = (No of patients with disease and positive result)/(all patients with disease tested) $\times$ 100.

Specificity = (No of patients without disease and normal result)/(all patients without disease tested) $\times$ 100.

Positive predictive value = (No of patients with disease and positive result)/(all patients with a positive result) $\times$ 100.

Negative predictive value = (No of patients without disease and normal result)/(all patients with a normal result) $\times$ 100.

Statistical significance of differences in predictive values among the tests was determined by χ^2 test and, when numbers were small, Fisher's exact probability test.

Results

Ninety seven patients were examined by ultrasound and the pancreas visualised in 83 (86%). CT scans were obtained in all 86 patients studied. The oral pancreatic function test was performed in 99 patients. Results of all three tests were abnormal in the patients with carcinoma and Hodgkin's disease but normal in the patient with carcinoid; only the CT scan was normal in the patient with Zollinger-Ellison syndrome. In the 11 patients with chronic pancreatitis ultrasound failed to visualise the pancreas in four and detected abnormalities in four, the CT scan was abnormal in eight, and the pancreatic function test gave a low result in seven.

In the 10 patients with minimal change pancreatograms the Lundh test and oral pancreatic function test gave abnormal results in two, ultrasound suggested chronic pancreatitis in four, and the CT scan was abnormal in one; in three patients two tests gave abnormal results. In the five patients with an unfused ventral pancreas results of the Lundh test and CT were normal but ultrasound and the pancreatic function test showed an abnormality in one case each. Since the relevance of a minimal change pancreatogram or unfused ventral pancreas remains uncertain (see below) the results of the three tests in these patients were excluded from the calculations of sensitivity, specificity, and predictive values of the tests. Patients in whom ultrasound failed were also excluded from these calculations.

The sensitivities of ultrasound, CT, and the pancreatic function test were 70%, 71%, and 76% and their specificities 75%, 87%, and 72% respectively. The figure shows the predictive values of each test. Ultrasound and the pancreatic function test had poor positive predictive value but CT had a positive predictive value of 67%. All three tests had high (>90%) negative predictive values. The predictive values for two positive or negative tests rose appreciably but were not significantly better than CT alone.

Discussion

The prevalence of established pancreatic disease in this study was 16%, which is realistic for most clinicians. Few pancreatic tumours were encountered owing to the exclusion of jaundiced patients, for whom the study protocol was inappropriate and in whom the exclusion of disease is not realistic. Encouragingly, all three tests identified the three non-jaundiced patients with pancreatic carcinoma; this is a frequent pitfall of pancreatic screening tests. The clinical follow up makes it unlikely that any malignant neoplasms were missed.

The difficulty in establishing a diagnosis of early chronic pancreatitis makes it less certain that some cases were not missed, since histological confirmation of pancreatic normality is rarely available. Nevertheless, clinical follow up plus either an acceptable alternative diagnosis in the majority or a normal pancreatogram and Lundh test result in the remainder makes early chronic pancreatitis unlikely.

Analysing the results is further complicated by the patients with minimal change pancreatograms or an unfused ventral pancreas because the clinical relevance of these conditions is still debatable^{17 22}; we therefore omitted them from calculations of sensitivity, specificity, and predictive values. Both conditions may be diagnosed by endoscopic retrograde cholangiopancreatography; CT, ultrasound, and the oral pancreatic function test were unreliable in their detection. If these conditions are not clinically relevant, then our results are hardly affected; if they are, the sensitivity of ultrasound, CT, and the

Predictive values of ultrasound (US), computed tomography (CT), and oral pancreatic function test (PFT). (n=Number of test results interpreted.)

oral pancreatic function test falls to 58%, 42%, and 53% respectively and the predictive value of a normal result is reduced to 80%, 73%, and 77% for each test.

Sensitivity and specificity of ultrasound, CT, and the pancreatic function test in this prospective study were less than in previous investigations.^{7 9-11 13-15} The tests were performed as part of the hospital's routine diagnostic service, however, so that differences in operator skill may have contributed to this. Furthermore, the value of our figures for sensitivity may have been lower because the number of patients with pancreatic disease in our study was small.

Because a prospective study of patients selected on clinical grounds alone does not generate a large proportion of subjects with disease, other investigators have assessed the tests in populations comprising 25-50% of patients with disease.⁷⁻¹⁵ This necessarily implies an element of selection—as exemplified by the absence in such studies of patients with minimal change pancreatograms or unfused ventral pancreas (prevalence of the latter may be 5% in the general population)—and artificially enhances sensitivity and specificity.

The predictive value of any test, which indicates the reliability of a positive or negative result, depends most importantly on the prevalence of disease as well as on sensitivity and specificity. Nevertheless, the application of Bayesian theory to calculate a test's predictive value at lower prevalence rates than those studied²³ is no substitute for a prospective evaluation under the appropriate conditions. A previous study of the oral pancreatic function test under conditions of high disease prevalence¹⁵ exemplified this; the authors' estimate of the positive predictive value of this test at the prevalence of disease found in our study (which is realistic for most centres) was twice as high as it actually proved to be.

The predictive values quoted here are relevant to other centres with a similar prevalence of disease. Pancreatic disease proved to be uncommon among those in whom it was suspected clinically, which emphasises that the problem for most clinicians is to identify those few patients who merit further investigation—preferably without subjecting all those under suspicion to invasive tests. When a disease is uncommon the positive predictive value of most tests suffers, however good their sensitivity and specificity. Thus the positive predictive value of CT (67%) was good and not significantly improved by combination with the other tests, and its use alone would cause only a few patients to be further investigated unnecessarily. The use of ultrasound or the oral pancreatic function test alone would not meet this requirement. The negative predictive value of each test under these conditions was high (91-93%); failures occurred in the patients with Zollinger-Ellison syndrome and pancreatic carcinoid, which are rare, and in a few with chronic pancreatitis.

How then should a general physician approach the patient with suspected pancreatic disease? In patients presenting with jaundice, which will include the majority of those who have pancreatic carcinoma, the clear priority is to image the biliary tree by whatever methods are available locally. Patients who present with overt steatorrhoea are (in Britain) most likely to have intestinal disease and initially should be investigated accordingly in the absence of a strong clinical indication—for example, alcohol abuse—to the contrary. It is to the remaining patients with more non-specific symptoms, such as weight loss or abdominal pain, that this study is mainly directed; most do not have pancreatic disease, a few have pancreatic carcinoma, and a few more have chronic pancreatitis. A careful endoscopy or double contrast barium study should be performed before embarking on pancreatic investigations. Thereafter the aims should be to exclude the majority of patients in whom further investigation is unnecessary and to identify the few who need referral for endoscopic retrograde cholangiopancreatography and pancreatic function tests.

Our findings suggest that a normal ultrasonogram, CT scan, or oral pancreatic function test result reliably excludes pancreatic disease. Patients who have evidence of pancreatic disease at CT should be investigated further, since roughly three quarters will have significant disease. The use of either ultrasound or the oral pancreatic function test alone will result in the unnecessary further investigation of most patients with an abnormal result, but the combination of these tests provides an accurate alternative to CT alone, which is not widely available. The relative approximate cost (in our hospitals) of each test should be noted: CT £60; ultrasound £6; oral pancreatic function test £20.

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Which deliveries require paediatricians in attendance?

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Abstract

The mode of delivery and one minute Apgar score were taken from the neonatal records of 2086 full term infants born at one obstetric unit over 12 months. There were 1554 spontaneous vaginal vertex deliveries, 26 vaginal breech deliveries, and 506 operative or instrumental deliveries. The obstetric records of the operative deliveries were reviewed to determine whether fetal distress had been an indication for intervention, and the obstetric records of the spontaneous vaginal vertex deliveries were also reviewed for fetal distress detected antenatally. When fetal distress was present antenatally in spontaneous vaginal vertex deliveries the frequency of a one minute Apgar score below 7 was 10.2%. In operative and instrumental deliveries where fetal distress was the indication for intervention the frequency of a one minute Apgar score below 7 was 15.6% after non-rotational forceps delivery, 13.9% after rotational forceps delivery, and 45.8% after caesarean section. In the absence of fetal distress the frequency of an Apgar score below 7 was 2.4% after spontaneous deliveries, 7.1% after non-rotational forceps delivery, 13.2% after caesarean section, and 18.4% after rotational forceps delivery. The presence of fetal distress considerably increased the frequency of an Apgar score below 7 in each category except rotational forceps deliveries.

Paediatric services to an obstetric unit may be organised rationally in the light of local staffing conditions with the help of these findings.

Introduction

Though theoretically desirable, it is not practicable to have someone skilled in neonatal resuscitation present at the delivery of every baby. Most obstetric units have developed guidelines defining when a paediatrician is needed. These guidelines normally include all preterm deliveries and all operative and instrumental deliveries performed on full term infants. To determine whether this is necessary, we attempted to define the factors most likely to increase the need for resuscitation.

Methods

Details of all 2086 term deliveries at the Northern General Hospital, Sheffield, from July 1980 to June 1981 were reviewed to determine the mode of delivery and one minute Apgar scores. Since there is a prima facie case for the presence of a paediatrician at the delivery of preterm infants (less than 37 weeks' gestation), all 195 preterm infants were excluded from the study.¹ The obstetric records of operative and instrumental deliveries were reviewed to ascertain whether fetal distress was an indication for the intervention. In most cases fetal distress was clearly stated in the delivery records; if not, in this study it was defined as one or more of the following: (a) meconium stained liquor, (b) unspecified bradycardia, (c) type II decelerations or loss of beat to beat variations in the fetal heart trace, (d) antepartum haemorrhage leading to emergency caesarean section. The obstetric records of the full term deliveries were also reviewed for evidence of fetal distress. In these case notes fetal distress was less well described and the commonest criteria of fetal distress found retrospectively were unspecified bradycardia and meconium stained liquor. The type of abnormality used to define fetal distress had no effect on the distribution of Apgar scores.

We defined one minute Apgar scores as high if 7 or more, medium if 4 to 6, and low if 3 or less. Comparison of Apgar scores in different groups was by χ^2 testing with correction for discontinuity.

In the absence of fetal distress the mode of anaesthesia for caesarean section had no effect on the distribution of Apgar scores, so all caesarean sections without fetal distress were analysed together regardless of anaesthetic technique.

Results

Of the 2086 term deliveries, 1554 were spontaneous vertex vaginal deliveries, 26 were vaginal breech deliveries, and 506 were operative or instrumental deliveries. The obstetric records for 1311 of the

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