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ORIGINAL ARTICLE

Incidence and characteristics of chronic and lymphoplasmacytic sclerosing pancreatitis in patients scheduled to undergo a pancreatoduodenectomy

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Abstract

Background: The determination of the exact nature of a pancreatic head mass in a patient scheduled to undergo a pancreatoduodenectomy can be very difficult. This is important as patients who suffer from benign disease such as pancreatitis do not always require surgery. The aim of the present study was to analyse the incidence of pancreatitis and the signs and symptoms associated with these tumours mistaken for pancreatic cancer and the diagnostic procedures performed.

Methods: A consecutive group of patients who underwent a pancreatoduodenectomy between 1992 and 2005 with histopathologically proven pancreatic adenocarcinoma (PCA) and pancreatitis were analysed.

Results: The incidence of pancreatitis after pancreatoduodenectomy is 63 out of 639 patients who underwent a pancreaticoduodenectomy (9.9%). Of these patients, 24 patients (38%) had lymphoplasmacytic sclerosing pancreatitis (LPSP) and 31 patients (49%) had focal chronic pancreatitis. Eight patients (13%) had an intermediate form with characteristics of both. Pancreatic adenocarcinoma occurred in 227 patients (36%). The presence of pancreatitis without a discrete mass on endoscopic ultrasonography (EUS) seemed to have clinical relevance with a positive likelihood ratio of 5.1. Mortality after resection was nil in both groups.

Conclusion: The incidence of pancreatitis is 9.9% for patients scheduled to undergo a pancreatoduodenectomy. Of these patients, 38% had LPSP, 13% had a intermediate form and 49% had focal chronic pancreatitis. The determination of the exact nature of a pancreatic head mass remains difficult.

Keywords

pancreatoduodenectomy, pancreatitis, pancreatic adenocarcinoma

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Introduction

Pancreatic adenocarcinoma (PCA) is the 4th leading cause of death from cancer in the western world and complete resection by pancreatoduodenectomy (PD) is the only potential curative treatment.[1,2] Although mortality has decreased significantly throughout the last decade post-operative morbidity remains substantial.[3] In contrast, chronic pancreatitis is generally treated conservatively and surgery is only indicated when the quality of life is compromised by major pain symptoms or deterioration of the nutritional status, when adjacent organs, most commonly the duodenum, are compressed by an inflammatory mass and when the clinician is unable to determine the exact nature of the lesion. The treatment of choice is a duodenum-preserving pancreatic head resection or PD.

Despite improvements in radiological imaging modalities, some patients will still undergo PD with a presumptive diagnosis of PCA only to be found to have pancreatitis on final pathologic review.[4–8] In 1961, Sarles *et al.* was the first to describe a condition called primary inflammatory sclerosis of the pancreas also known

as 'autoimmune sclerosing pancreatitis' or simply 'autoimmune pancreatitis'.[9] Nowadays this condition is commonly know as lymphoplasmacytic sclerosing pancreatitis (LPSP).[10–12] The disease is characterized histologically by diffuse lymfoplasmacytic infiltrate centred around pancreatic ducts and ductules, accompanied by obliterative phlebitis, acinar athrophy and interstitial fibrosis.[5,9,11,13–17] Another commonly found benign disease is chronic focal pancreatitis characterized by duct dilation, fibrosis, calcifications, fat necrosis and pseudocyst formation. This is often associated with gallstone pancreatitis, pancreas divisum and excessive alcohol ingestion.

The purpose of the present study was to determine the incidence of pancreatitis and specifically the incidence of chronic focal pancreatitis and lymphoplasmacytic sclerosing pancreatitis in patients who underwent PD for suspected pancreatic adenocarcinoma and to analyse the presenting signs and symptoms and findings during diagnostic work-up.

Patients and methods

From January 1992 to December 2005, 639 consecutive patients underwent a pancreatoduodenectomy in the Academic Medical Center in Amsterdam, the Netherlands. For analysis, all patients with pancreatitis and pancreatic adenocarcinoma (PCA) who underwent a pancreatoduodenectomy were selected from the prospective database.

A standardized staging protocol was used which consists of an orienting transabdominal ultrasonography (US) followed by a helical computed tomography (CT) according to a dedicated protocol of the pancreas and liver.[18,19] If a tumour was suspected but could not be visualized by CT, an endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) was performed. In the Netherlands, most patients undergo endoscopic retrograde cholangiopancreatography (ERCP) with placement of an endoprosthesis for alleviation of jaundice, although this remains controversial.[20] Tumour location and size, local ingrowth, lymphadenopathy and distant metastases were all determined. All findings were analysed by experienced radiologists and subsequently presented in a multidisciplinary team which also included gastroenterologists and surgeons. Finally, the most likely diagnosis was registered in the patient's chart.

Pancreatoduodenectomy was defined as en bloc resection of the duodenum and pancreatic head and distal bile duct and preferably with preservation of the pylorus.[21] Reconstruction was performed by a retrocolic jejunal loop with an end-to-side pancreaticojejunostomy, hepaticojejunostomy and finally an antecolic gastrojejunostomy or duodenojejunostomy.

All complications were registered during hospital stay or readmission within 90 days after discharge. Complications were divided into surgical complications (intra-abdominal abscess, wound infection, haemorrhage, pancreatic leakage, biliary leakage and delayed gastric emptying) and general post-operative complications (urological, pulmonary and cardiac).

All pathological records of patients with pancreatitis were reevaluated by a senior pathologist (FJWTK) according to the criteria described by various authors.[5,9,11,13–17] Both entities had histological signs of fibrosis. The criteria specific for LPSP were the presence of periductalar inflammation, obliterative phlebitis and acinar atrophy. The criteria for chronic focal pancreatitis were the presence of duct dilation, calcifications, fat necrosis and pseudocysts. The resection specimens were scored as either lymphoplasmacytic sclerosing pancreatitis (LPSP), chronic focal pancreatitis and an intermediate form if characteristics where present specific to both forms. In the present study, IgG4 levels were not measured as it is only recently been found that high IgG4 levels correlate with LPSP, particularly in oriental patients.[22]

Data analyses were performed using SPSS® software (SPSS Inc., Chicago, IL, USA). A *P*-value of less than 0.05 was considered statistically significant. The Kruskal–Wallis and Pearson's χ^2-test were performed where appropriate to analyse differences between the three groups of patients with pancreatitis. The Student's *t*-test, Mann–Whitney, χ^2 test and Fisher's exact test where used to compare PCA and pancreatitis. Because the different diagnostic procedures were not performed in all patients (e.g. EUS in 39% of the patients), it was not seen fit to perform a formal multivariate analysis. Instead the likelihood ratio and the 95% confidence interval were calculated of all the significant data in order to evaluate the impact on the likelihood of disease. The generally accepted values were used to quantify the significance of the likelihood ratio (LR) was used and was defined as 'large' for LR+ of >10 or LR- <0.1, 'moderate' for LR+ 5–10 or LR- 0.1–0.2, 'small' for LR+ 2–5 and LR- of 0.2–0.5, 'minimal' for LR+ of <2 and LR- of >0.5 and 'no effect' for LR = 1.

Results

During the study period, 639 pancreatoduodenectomies were performed. Of these, 63 patients (9.9%) eventually had pancreatitis after histopathological examination. Of the 63 patients only 8 (1%) underwent surgery with the pre-operative diagnosis of having pancreatitis. After pathological reexamination, 24 patients (38%) had characteristics of LPSP, 31 patients (49%) of focal chronic pancreatitis and 8 patients (13%) had an intermediate form which could neither be described as a pure LPSP nor pure focal chronic pancreatitis.

The general characteristics of the patients with pancreatitis are summarized in Table 1. There were some differences within the groups including significantly more patients with diabetes mellitus in the LPSP group. Also, patients with LPSP tended to smoke significantly more often. Jaundice occurred significantly less often in patients with focal chronic pancreatitis and consequently the patients were less likely to be jaundiced during surgery and underwent less pre-operative biliary drainage procedures.

The signs and symptoms and diagnostic work-up are summarized in Table 2. Overall, patients with pancreatitis had a significantly higher male-to-female ratio and were significantly

Table 1 General characteristics of patients with pancreatitis

	LPSP *n* = 24	Intermediate *n* = 8	Focal chronic pancreatitis *n* = 31	*P*
Gender male–female ratio	3.0	1.0	2.1	0.419
Mean age (±SD)	57 (±16)	52 (±12)	58 (±11)	0.537
Diabetes mellitus	7 (29%)	1 (13%)	1 (4%)	0.024
Smokers	20 (85%)	3 (38%)	13 (42%)	0.004
Alcohol use (≤2 units a day)	13 (55%)	3 (38%)	17 (55%)	0.665
Alcohol use (>2 units a day)	3 (13%)	1 (13%)	5 (16%)	0.919
Median duration of symptoms (range)	12 (2–100)	16 (8–100)	13 (0–260)	0.662
Pain	14 (58%)	5 (63%)	26 (84%)	0.086
Jaundice	23 (96%)	7 (88%)	16 (52%)	0.001
Weight loss reported by patients	15 (63%)	6 (75%)	23 (74%)	0.608
Mean BMI	24 (±3.0)	22 (±3.5)	23 (±3.5)	0.359
Jaundice at surgery	9 (38%)	1 (13%)	1 (3%)	0.004
Preoperative biliary drainage	22 (92%)	4 (50%)	14 (45%)	0.001

Kruskal–Wallis and Pearson's χ^2-test were appropriate. LPSP, lymphoplasmacytic sclerosing pancreatitis.

Table 2 Characteristics, signs and diagnostic work-up comparing patients with pancreatitis with pancreatic adenocarcinoma

	Pancreatitis *n* = 63	PCA *n* = 227	*P*
Gender male/female ratio	2.15	0.96	0.006
Mean age (±SD)	57 (±13)	66 (±9)	<0.001
Median duration of symptoms in weeks (range)	13 (0–260)	12 (0–104)	0.053
Pain	45 (71%)	102 (45%)	<0.001
Jaundice			
US performed	*n* = 54	*n* = 198	
Neoplasm seen	32 (59%)	148 (75%)	0.026
Size of neoplasm	3.0 (0.6–8.0)	2.7 (0.3–7.0)	0.014
ERCP performed	*n* = 59	*n* = 220	
Double duct sign	20 (34%)	95 (42%)	0.198
Suspicious brush	3 / 16	36 / 42	<0.001
CT available for analysis	*n* = 56	*n* = 178	
No discrete mass	26 (46%)	53 (28%)	0.022
Size of neoplasm	2.6 (1.5–5.5)	2.5 (1.0–7.0)	0.514
Head focally enlarged	24 (43%)	118 (67%)	0.002
Diffusely enlarged	6 (11%)	5 (3%)	0.025
Both ducts normal caliber	39 (70%)	58 (33%)	<0.001
Pancreatic duct dilatation	4 (7%)	51 (29%)	0.001
CBD dilatation	5 (9%)	19 (10%)	0.707
Double duct sign	7 (13%)	50 (26%)	0.018
EUS performed	*n* = 31	*n* = 78	
Discrete mass	24 (77%)	56 (72%)	0.549
Signs of pancreatitis	6 (19%)	3 (4%)	0.015

Analysis comprised Mann–Whitney, χ^2 test and Fisher's exact test were applicable. US, ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; CBD, common bile duct; EUS, endoscopic ultrasonography.

Table 3 Value of various findings in predicting the presence of pancreatitis in patients scheduled for pancreatoduodenectomy

Variable	LR+	95% CI	Impact on Likelihood	LR–	95% CI	Impact on Likelihood
Gender	1.6	1.0–2.6	minimal	0.7	0.5–1.0	minimal
Age (median; <65)	2.0	1.2–3.4	small	0.6	0.5–0.9	minimal
Pain	1.9	1.2–3.2	minimal	0.6	0.5–0.9	minimal
Neoplasm seen on US	1.3	1.0–1.7	minimal	0.6	0.4–1.1	minimal
Brush during ERCP	4.6	1.7–13.3	small	0.2	0.08–0.5	moderate
No mass on CT	1.5	1.2–2.5	minimal	0.6	0.2–0.7	minimal
Head focally enlarged on CT	1.5	1.1–2.3	minimal	0.6	0.4–0.9	minimal
Diffusely enlarged pancreas on CT	1.1	1.0–1.3	minimal	0.3	0.09–1.2	small
Both ducts normal on CT	2.2	1.5–4.4	small	0.5	0.3–0.7	small
Pancreatic duct dilatation on CT	4.0	1.4–12	small	0.8	0.7–0.9	minimal
Double duct on CT	2.5	0.9–5.8	small	0.8	0.7–1.0	minimal
Signs of pancreatitis on EUS without discrete mass	5.1	2.5–12	moderate	0.05	0.02–0.2	large

LR+ positive likelihood ratio; LR– negative likelihood ratio; 95% CI: 95% confidence interval. Theoretical example pancreatitis occurs in 11% of all scheduled pancreatoduodenectomies. However, in 22% it remains difficult to differentiate pancreatic adenocarcinoma from pancreatitis. This prevalence leads to pretest odds of 1:5. In the case of negative brush during ERCP the post-test odds is 0.2*1:5 = 0.04. This leads to a post-test risk of pancreatitis in 4% of these patients.
Impact on likelihood was defined as large for LR+ of >10 or LR– <0.1, moderate for LR+ 5–10 or LR– 0.1–0.2, small for LR+ 2–5 and LR– of 0.2–0.5, minimal for LR+ of <2 and LR– of >0.5 and no effect for LR = 1.
US, ultrasonography; ERCP, endoscopic retrograde cholangio-pancreatography; CT, computed tomography; EUS. endoscopic ultrasonography.

younger. Patients with pancreatitis complained significantly more of pain as first presenting symptom. Ultrasound was less likely to find a discrete mass in the patients with pancreatitis. If a mass was found it was significantly larger than in patients with PCA. An ERCP with brush cytology was performed selectively as part of a study in the early years and found that brush cytology was significantly more suspicious for adenocarcinoma in the PCA group. In 28% of the patients with PCA there was no discrete mass seen on CT. This was 46% in the pancreatitis group and was significantly higher. In contrast, a diffusely enlarged pathological pancreatic head was seen in 67% of the patients with pancreatic cancer compared with 43% of the patients with pancreatitis. A EUS found a discrete pancreatic mass in approximately three-quarters of both groups but was able to detect signs of pancreatitis significantly more often in patients with pancreatitis compared with PCA (19% vs. 4%). Agreement concerning vascular involvement between CT and EUS was 53 out of 68 patient (78%). Using CT, seven patients who were resectable on EUS were found to be unresectable while EUS found eight patients with vascular ingrowth with no signs of ingrowth on CT. Agreement concerning pathological lymph nodes was seen in 53 out of 59 patients (89%). There were five patients with pathological nodes not found on EUS and one patient had pathological nodes not seen on CT. Tumours were significantly smaller on CT compared with EUS (1 cm $\pm$ 1.5 vs. 2.3 cm $\pm$ 1.5, $P < 0.05$).

Several significant differences were seen with pre-operative work-up and the likelihood ratios were calculated for all significant variables and are shown in Table 3. Of all the variables only signs of pancreatitis on EUS without a discrete mass was considered clinically relevant with a moderate impact on the positive likelihood ratio and a large impact on the negative likelihood ratio.

A separate analyses was made of patients with or without a discrete mass on CT scan and the results are summarized in Table 4. Differences, including a focally enlarged pancreatic head were seen more often. A normal caliber of the ducts occurred in 49% of the patients with no mass on CT compared with 36% of the patients with a mass. The other patients had dilatated ducts. The EUS had similar outcome independent on the presence of a mass on CT.

The short-term outcome is summarized in Table 5 and comparable for both groups. The overall complication rate defined as the occurrence of one or more complications was seen in 133 patient (46%). Mortality was not seen in 290 pancreatoduodenectomies.

Discussion

In the present study, we found that the incidence of benign inflammatory disease of the pancreas was 63 out 639 patients (9.9%) who were scheduled to undergo pancreatoduodenectomy for suspected pancreatic cancer. There were 24 patients (38%) with LPSP, 8 patients (13%) with the intermediate form and 31 patients (49%) with focal chronic pancreatitis. A multitude of symptoms and diagnostic factors were significantly different between patients with pancreatitis and patients with pancreas adenocarcinoma but only pancreatitis seen on EUS without a discrete mass seemed to have any clinical relevance.

The incidence of pancreatitis in the present study is comparable with that of the literature which suggest that benign pathology

Table 4 Discrete mass vs. no mass on CT

	Discrete mass *n* = 155	No discrete mass *n* = 79	*P*
Head focally enlarged	133 (86%)	9 (11%)	<0.001
Diffusely enlarged	3 (2%)	4 (5%)	0.230
Both ducts normal caliber	55 (36%)	39 (49%)	0.041
Pancreatic duct dilatation	47 (30%)	7 (9%)	<0.001
CBD dilatation	12 (8%)	12 (15%)	0.076
Double duct sign	36 (23%)	19 (24%)	0.888
Gallbladder inflammation	4 (3%)	3 (4%)	0.691
ERCP performed	*n* = 142	*n* = 76	
Double duct sign	59 (42%)	27 (36%)	0.386
Suspicious brush	9 / 26 (35%)	7 / 22 (32%)	0.838
EUS performed	*n* = 37	*n* = 48	
Discrete mass	27 (73%)	37 (77%)	0.663
Signs of pancreatitis	4 (11%)	5 (10%)	1.000
Normal pancreas	6 (16%)	7 (15%)	0.836
Pancreatitis	26 (17%)	30 (38%)	<0.001
Pancreatic cancer	129 (83%)	49 (62%)	<0.001
Size of neoplasm	3.0 (1.5–11)	2.5 (1.0–5.0)	0.003

Analysis comprised Mann–Whitney, χ^2 test and Fisher's exact test were applicable.
CT, computed tomography; EUS. endoscopic ultrasonography.

Table 5 Intra-operative and post-operative characteristics

	Pancreatitis *n* = 63	PCA *n* = 227	*P*
Median operative time	295 (180–552)	285 (140–62)	0.312
Vascular wedge resection	3 (5%)	38 (17%)	0.016
Estimated blood loss	1000 (200–3600)	1100 (50–8500)	0.731
Transfusion (no. of packed cells)	0 (0–29)	0 (0–14)	0.972
Overall post-operative complications	26 (41%)	107 (47%)	0.408
Pancreaticojejunostomy leakage	8 (13%)	14 (6%)	0.105
Hepaticojejunostomy leakage	1 (2%)	4 (2%)	1.000
Bleeding	6 (10%)	11 (5%)	0.220
Abscess	6 (10%)	19 (8%)	0.773
Wound infection	7 (11%)	14 (6%)	0.179
Delayed gastric emptying	12 (19%)	39 (17%)	0.731
Systemic	13 (21%)	59 (26%)	0.384
Relaparotomy	9 (14%)	19 (8%)	0.160
Post-operative hospital stay in days	14 (6–94)	14 (6–222)	0.840
Mortality	0	0	–

Analysis comprised Mann–Whitney, χ^2 test and Fisher's exact test were applicable. PCA, pancreatic adenocarcinoma.

will be encountered in 3–12% of the pancreatoduodenectomies done for a presumed malignancy.[4,5,7,8,23,24] In a large study from the Hopkins group and Mayo clinic the incidence was (176 out of 1574 scheduled pancreatoduodenectomies) 11.2%.[12] However, the proportion of patients with LPSP was lower (37 out of 176 patients), 21% compared with 38%, in the present study using the same criteria.

In the present study, the mean age of patients with pancreatitis was significantly lower compared with findings in the literature.[12,25] The present study did find a female-to-male ratio consistent with the literature.[12,25] The clinical presentation of patients with pancreatitis and pancreatic adenocarcinoma was very similar. However, patients with pancreatitis presented more often with pain and less often with jaundice. Patients with LPSP had the

highest rate of jaundice comparable to that of the Hopkins and Mayo experience. Intermittent jaundice which disappears spontaneously has been reported in patients with LPSP although not noted in the patients from the present study.[11]

Significantly fewer patients with pancreatitis had a discrete mass on CT scan. This was also seen in the Hopkins and Mayo study.[12] A CT scan generally describes diffuse enlargement of the gland with loss of parenchymal markings.[16,26] The entire pancreatic gland was described as diffusely enlarged in 11% of the patients with delayed and prolonged enhancement of the affected area.[16,26] Diffuse enlargement was noted in 68% of the patients in a Japanese study[25] and in less than half in a Belgium study.[27]

The CT data in the present study has to be interpreted with caution because the methodology of the CT scan has evolved throughout the years. Slide thickness, the use of intravenous contrast and timing varied throughout the study period. The other studies concerning this subject were subject to similar limitations.

Rather than relying on a single imaging modality, the diagnosis of benign inflammatory disease of the pancreas is probably best made by a panel of diagnostic studies. Other diagnostic modalities such as ERCP with brush cytology, EUS and MRCP could aid in making a correct diagnosis. For instance, a pancreaticogram generally shows fairly distinctive irregular narrowing of the small ducts.[16,28] Brush cytology was regularly performed in our centre and very useful but lacked specificity.

A EUS seemed useful in the present study and should be performed when in doubt. The absence or presence of signs of pancreatitis was discriminatory. A EUS can display small pancreatic lesions undetectable by CT and MRI. In addition, EUS can also localize lymph node metastases and/or vascular tumour infiltration with high sensitivity.[29] The major limitations of the technique are operator dependence and a limited field of visualization for detecting metastatic spread to the liver and peritoneum. Also, the positive predictive value of EUS for pancreatic cancer declines to 60% in patients with concurrent chronic pancreatitis.[30] Histological confirmation may be of additional value, but EUS-fine needle aspiration (FNA) also showed some limitations in the presence of chronic pancreatitis, in particular, a lower sensitivity in comparison to patients without chronic inflammation (73.8% vs. 91.3%, $P < 0.02$).[31]

Finally, one might suggest that the addition of fluorodeoxyglucose positron emission tomography (FDG-PET) might be useful in distinguishing these entities.[32] This novel tool was not readily available during the study period.

Preoperative biopsies were rarely performed in the present study and thus not analysed. An adequate sample is needed in order to evaluate the tissue for all the pathological characteristics of benign inflammatory disease. Even core biopsies will not provide enough tissue to distinguish between these features. Furthermore, there is a high rate of false-negative results from FNA and biopsies as seen in a previous study, especially in patients who have the smallest lesions and the best prognosis after resection.[33]

Many studies have observed a marked clinical improvement of patients with LPSP after steroid therapy.[10,22,25,28,34–36] Considering the fact that up to 10% of the patients undergo unnecessary laparotomy, it is interesting to note a relatively straightforward trial with steroids can prevent a laparotomy. This approach is only warranted after accurate preoperative diagnosis which may be possible with accurate imaging combined with the recently described association of elevated IgG4 levels and LPSP.[22,37] A non-operative management strategy carries the risk of delaying the treatment of pancreatic adenocarcinoma and strict criteria which are diagnostic of LPSP are currently lacking. Steroids as a diagnostic tool are not useful in differentiating between LPSP from PCA as a malignant pancreatic mass may also react to this treatment and thus also decrease in size.

In the present study, morbidity was 46% and the mortality rate was zero and this influenced the decision to perform a pancreatoduodenectomy. This combined with the fact that resection is an excellent treatment for unmanageable pain in these patients. In the present study, 71% of the patients had symptoms of pain. Long-term follow-up suggests that patients who undergo a pancreatoduodenectomy for pancreatitis with unmanageable pain have a successful outcome including a durable relief of symptoms and an improved quality of life. This would in fact mean that potentially only 18 patients (3%) out of 639 scheduled for a pancreatoduodenectomy undergo unnecessary surgery.

The Memorial Sloan-Kettering group proposed an algorithm in which IgG4 levels are obtained in patients with a suspected LPSP.[24] If elevated, the patient is placed on a short trial with steroids followed by a repeat CT scan in 4–6 weeks. If there is a decrease in the size of the mass, steroids should be discontinued. If there is an increase in size or no change the patient should undergo resection. This algorithm does not take into account the fact that patients with pancreatic cancer could possible also react to steroids as many neoplasms are surrounded by a zone carcinoma induced pancreatitis. However, IgG4 levels are not always elevated in Caucasian patients compared with oriental patients.[22,37]

The incidence of pancreatitis is 9.9% of all scheduled pancreatoduodenectomies. The differentiation is very challenging. An EUS has some potential to discriminate but the results are still not optimal. A clear-cut diagnostic tool is not readily available but instead the combined result of many tests has to guide the clinician in the decision-making process.

Conflicts of interest

None declared.

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