Early diagnosis in chronic pancreatitis / how early can we make the diagnosis in chronic pancreatitis?

Mariana Jinga (București)
Definition of chronic pancreatitis in adults

• Chronic pancreatitis is characterized by:
  • pancreatic infiltration of inflammatory cells → progressive inflammatory changes
  • progressive fibrosis,
  • loss of exocrine & endocrine tissue.

• 3 criteria for the diagnosis of CP are:
  • chronic inflammation,
  • fibrosis,
  • atrophy

• Except in cases of suspicion of malignancy, pancreatic biopsy is not required
• Chronic pancreatitis may be:
  – asymptomatic over long periods of time,
  – can present with a fibrotic mass,
  – or there may be symptoms of pancreatic insufficiency without pain.

• The serum amylase and lipase concentrations tend to be normal in patients with chronic pancreatitis

• Morphologically, chronic pancreatitis is a patchy focal disease characterized by a mononuclear infiltrate and fibrosis

• H and E stained pancreas with chronic pancreatitis: Pancreatic biopsy showing extensive fibrosis, chronic inflammation, residual ductal structures, and a residual islet. There is no acinar tissue remaining.
Clinical manifestation of CP

1. Abdominal pain
   - is a dominant feature of chronic pancreatitis
   - epigastric, often radiates to the back
   - is often worse 15 to 30 minutes after eating
   - early in the course of chronic pancreatitis, the pain may occur in discrete attacks; as the condition progresses, the pain tends to become more continuous.
Clinical manifestation of CP

1. Abdominal pain
   • two typical pain patterns were observed
     • episodes of pain (usually lasting less than 10 days) with pain free intervals lasting from months to more than a year
     • prolonged periods of daily pain or clusters of severe pain exacerbations
   • it may be absent in some cases
Clinical manifestation of CP

2. Pancreatic insufficiency
   - clinically significant protein and fat deficiencies do not occur until > 90% of pancreatic function is lost

- Fat malabsorption:
  - Steatorrhea usually occurs prior to protein deficiencies since lipolytic activity decreases faster than proteolysis

- Pancreatic diabetes:
  - diabetes mellitus usually occurs late in the course of CP
  - is usually insulin requiring
  - diabetic ketoacidosis and nephropathy are rare
  - neuropathy and retinopathy occur more frequently

Freedman Steven, Clinical manifestations and diagnosis of chronic pancreatitis in adults Up To Date 2013
Clinical manifestation of CP

The classic triad of:

- pancreatic calcifications,
- steatorrhea,
- and diabetes mellitus

strongly suggests the diagnosis,

This are usually seen together only in very advanced disease.
Pancreatic function tests

<table>
<thead>
<tr>
<th>Direct tests</th>
<th>Indirect tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretin–pancreozymin test</td>
<td>Fecal fat quantification</td>
</tr>
<tr>
<td>Endoscopic test</td>
<td>Fecal levels of pancreatic enzymes</td>
</tr>
<tr>
<td>Lundh test</td>
<td>NBT-PABA test</td>
</tr>
<tr>
<td>S-MRP$^a$</td>
<td>Pancreolauryl test</td>
</tr>
<tr>
<td></td>
<td>Amino acid consumption test</td>
</tr>
<tr>
<td></td>
<td>Breath tests ($^{13}$C-labelled substrates)</td>
</tr>
</tbody>
</table>

$^a$ S-MRP, secretin-enhanced magnetic resonance pancreatography.
Pancreatic function tests

Severity degree of exocrine pancreatic dysfunction based on the secretin–pancreozymin test.

<table>
<thead>
<tr>
<th>Dysfunction Level</th>
<th>Normal Output of Enzymes and Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal output of enzymes and bicarbonate</td>
</tr>
<tr>
<td>Mild dysfunction</td>
<td>Secretion of enzymes and bicarbonate ≥ 75% the lower limit of normal</td>
</tr>
<tr>
<td>Moderate dysfunction</td>
<td>Secretion of enzymes and bicarbonate between 30 and 75% the lower limit of normal</td>
</tr>
<tr>
<td>Severe dysfunction</td>
<td>Secretion of enzymes and bicarbonate &lt; 30% the lower limit of normal</td>
</tr>
</tbody>
</table>

Mean accuracy of exocrine pancreatic function tests for the diagnosis of chronic pancreatitis (4).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretin–pancreozymin test</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>Fecal chymotrypsin</td>
<td>57</td>
<td>88</td>
</tr>
<tr>
<td>Fecal elastase</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>Optimised serum pancreolauryl test</td>
<td>82</td>
<td>90</td>
</tr>
</tbody>
</table>

• ERCP can be abnormal in a number of patients who end up with normal pancreas on autopsy

• CT scan cannot rule out early-stage chronic pancreatitis

• Histology - in early-stage CP the inflammatory changes could be patchy and conventional image-guided biopsy can miss pathology and is not used
• Hernandez et al. found complete concordance between ERCP and EUS for normal results and severe disease but only 17% agreement for mild disease.

• Combining the results of three studies on CP, EUS had a sensitivity of 87% and specificity of 75% where we defined early-stage CP as less than three EUS features using conventional criteria.
• EUS is the most sensitive method for the diagnosis of chronic pancreatitis.

• EUS allows the evaluation of pancreatic parenchymal and ductal changes with a high accuracy.

• EUS is operator dependent, and the diagnosis of CP is based on subjective criteria associated with variability.


Catalano MF, Kaul V, Pezanoski J, Guda N, Geenen N. Long-term outcome of endosonographically detected minimum criteria for chronic pancreatitis (MCCP) when conventional imaging and functional testing are normal. Gastrointestinal Endosc 2007 April;65(5):AB120
Conventional EUS Criteria for diagnosis of CP

Patients with five or more EUS criteria were diagnosed with chronic pancreatitis, whereas the disease was excluded in cases with 0–2 criteria.

<table>
<thead>
<tr>
<th>Ductal features</th>
<th>Wiersema et al</th>
<th>Catalano et al</th>
<th>Sahai et al</th>
<th>Wallace et al</th>
<th>DeWitt et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Irregularity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperechoic wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculi</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Side branch dilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narrowing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Parenchymal features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechoic foci</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypoechoic Foci (&gt;3 mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cysts (&gt;3 mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobularity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prominent interlobular septae</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Heterogenous</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperechoic strands</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shadowing calcifications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Total # of Features</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>
Parenchymal and ductal EUS features of chronic pancreatitis
‘Early-stage’ or ‘minimal-change’ CP

• CP is a progressive disease
• CP have not a diagnostic gold standard
• Evaluation of EUS in early-stage CP is difficult.
• The Rosemont Criteria is an important step towards improving objectivity and diagnostic precision of CP, and can be used independently of age and gender of the patient.
• ‘Early-stage’ CP = a patient with:
  • pancreatic-type pain,
  • normal CT, ERCP, and secretin test,
  • ‘indeterminate’ for CP using the EUS Rosemont Criteria.
• patients with early-stage CP have demonstrable progression of EUS features of CP
EUS image of the body of the pancreas with subtle findings of chronic pancreatitis: parenchymal lobularity with noncontiguous lobules. These aggregate findings are consistent with early-stage chronic pancreatitis.
Patients at highest risk to have early-stage CP whom we consider for EUS.

- Male gender,
- Age median age 65 years
- Smoking,
- Alcohol abuse
- Obscure pancreatic type pain
- Acute recurrent pancreatitis of unknown aetiology
  - Unexplained abdominal pain suspected to be of pancreatic origin, especially if there is a history of alcohol abuse
  - Acute pancreatitis of unclear etiology or idiopathic acute recurrent pancreatitis (IRAP)
  - Unexplained weight loss
  - Chronic diarrhoea, especially steatorrhea of unclear etiology
  - Equivocal findings of the pancreas on non-invasive imaging (for example, CT scan showing dilated pancreatic duct or subtle pancreatic calcifications)
  - New-onset diabetes in a patient without family history of diabetes
• Pancreatic duct (PD) abnormalities seen on ERCP have a poor sensitivity and specificity for diagnosing early, or mild, CP.

• MRCP with secretin stimulation may eventually replace ERCP but has similar limitations.

• CT is fairly specific for severe disease but not sensitive for mild or moderate disease and can even miss calcifications.
The EUS Rosemont Criteria of Cr.P
Parenchymal and ductal features of chronic pancreatitis by Rosemont criteria

<table>
<thead>
<tr>
<th>Rank</th>
<th>Feature</th>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenchymal features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Hyperechoic foci with shadowing</td>
<td>Major A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Lobularity</td>
<td>Major B</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>A. With honeycombing</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>B. Without honeycombing</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Hyperchoic foci without shadowing</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Cysts</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Stranding</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Ductal features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>MPD calculi</td>
<td>Major A</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Irregular MPD contour</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Dilated side branches</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>MPD dilation</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Hyperechoic MPD margin</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>TABLE 4. EUS diagnosis of CP on the basis of consensus criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Consistent with CP</td>
</tr>
<tr>
<td>A. 1 major A feature (+) ≥ 3 minor features</td>
</tr>
<tr>
<td>B. 1 major A feature (+) major B feature</td>
</tr>
<tr>
<td>C. 2 major A features</td>
</tr>
<tr>
<td>II. Suggestive of CP†</td>
</tr>
<tr>
<td>A. 1 major A feature (+) &lt; 3 minor features</td>
</tr>
<tr>
<td>B. 1 major B feature (+) ≥ 3 minor features</td>
</tr>
<tr>
<td>C. ≥ 5 minor features (any)</td>
</tr>
<tr>
<td>III. Indeterminate for CP†</td>
</tr>
<tr>
<td>A. 3 to 4 minor features, no major features</td>
</tr>
<tr>
<td>B. major B feature alone or with &lt; 3 minor features</td>
</tr>
<tr>
<td>IV. Normal</td>
</tr>
<tr>
<td>≤ 2 minor‡ features, no major features</td>
</tr>
</tbody>
</table>

*EUS diagnosis of CP should be made in the appropriate clinical setting.
†Diagnosis requires confirmation by additional imaging study (ERCP, CT, MRI, or PFT).
‡Excludes cysts, dilated MPD, hyperechoic nonshadowing foci, dilated side branch.
• EUS is currently considered to be the most accurate method for the diagnosis of chronic pancreatitis
• The number of EUS criteria increases as the disease progresses.
• Presence of 0 to 2 EUS criteria, chronic pancreatitis is possible but unlikely,
• in the presence ≥ 5 or more EUS criteria chronic pancreatitis is highly likely
• Patients with 3 or 4 EUS criteria of chronic pancreatitis are in a gray zone, where the disease may be present but should be confirmed by another functional or imaging method such as endoscopic pancreatic function test or s-MRCP and MRI.

EUS Elastography

Normal Pancreas

- Elastographic imaging of the normal pancreas is characterized by a uniform, homogenous green color distribution (representing intermediate stiffness) throughout the organ and the reproducibility of the signal is comparatively good.

- On qualitative analysis, a healthy pancreas appears to be predominantly green in color with a homogenous (41.7%) or heterogeneous (58.3%) pattern. On quantitative analysis, a healthy pancreas showed a mean elasticity value of 0.55% (95% CI 0.42-0.68%).

Pancreatic masses appearing mostly blue were considered to be malignant, whereas other patterns were considered as benign.
EUS quantitative elastography

- Quantitative elastography shows diagnostic sensitivity and specificity of 91%.
- Specific strain ratio obtained during EUS showed an excellent accuracy for the diagnosis of chronic pancreatitis.
- EUS–elastography could allow quantification of the degree of pancreatic fibrosis and thus evaluation of the severity of the disease.
- Nevertheless, the strain ratio cut-off point of 2.25 used in Iglesias’s study for the diagnosis of chronic pancreatitis should be validated in future studies.
- Continuous increase of the strain ratio as the number of EUS criteria of chronic pancreatitis increases.
• EUS elastography of normal pancreas
  EUS: uniform, homogenous green color distribution (representing intermediate stiffness).
• **EUS elastography of pancreatic cancer**: heterogeneous blue color distribution (representing hard stiffness).

• Elastography is a method for the real-time evaluation of tissue stiffness.

• Elastographic images are an index of tissue elasticity, which may be related to histopathological features.

• Analysis of tissue stiffness by quantitative EUS–elastography may provide additional relevant information in this setting.

• The strain ratio is measured in the head, body, and tail of the pancreas, and the elastographic result was the mean of these three values.

• EUS criteria of chronic pancreatitis and the Rosemont classification are also evaluated.
Key aspects for early recognition of chronic pancreatitis

Dyspepsia

• Predominance of epigastric pain
• Early postprandial or unrelated to meals
• May disturb nocturnal rest
Key aspects for early recognition of chronic pancreatitis

Presence of risk factors:

- Toxic habits:
  - Alcohol
  - Smoking
- Previous acute alcoholic or idiopathic pancreatitis
- Family history of pancreatic diseases
- Associated autoimmune diseases
- Metabolic disorders
Key aspects for early recognition of chronic pancreatitis

Imaging methods:

• Magnetic resonance imaging (MRI) + MR cholangiopancreatography (CPRM)
• Endoscopic ultrasononography (EUS)
• Multimodal EUS–based approach
  • EUS – elastography
  • EUS – function test
  • Dynamic EUS
Multimodal EUS-based approach for the diagnosis of early CP

- EUS examination of the pancreas + EUS elastography
- Aspiration of gastric juice + Secretin i.v.
- Diameter of main pancreatic duct in the head, body and tail at 0, 2, 4, 6, 8 and 10 min
- Sampling of duodenal juice at 15, 30 and 45 min.

J Enrique Dominguez-Muñoz, Master class program on pancreatic diseases and pancreatic exocrine insufficiency, University Hospital of Santiago de Compostela, Spain, July, 2013
Complications of CP

• pseudocyst formation,
• bile duct or duodenal obstruction,
• pancreatic ascites
• pleural effusion,
• splenic vein thrombosis,
• pseudoaneurysms,
• pancreatic cancer,
• acute attacks of pancreatitis
Genetic factors in chronic pancreatitis

- There are 4 subtypes of CP:
  - Hereditary (HCP),
  - idiopathic,
  - alcoholic
  - tropical pancreatitis.
- Genetic factors can explain a significant proportion of CP cases.
- The PRSS1 gene, encoding cationic trypsinogen, was found to be correlated with hereditary CP. (80% of HCP cases). This signalled the extensive search for other candidate genes within the trypsin pathway.
- Genes like SPINK1 and CTRC are associated with CP and should be considered as important contributing factors rather than causative.
- The search for candidate genes not part of the trypsin pathway has been less successful and the only gene consistently associated with CP is the Cystic Fibrosis Transmembrane Regulator.
• In case of HCP, the risk for relatives about their risk of inheriting the PRSS1 gene and developing pancreatitis should be explained.
• It is after all an autosomal dominant disease with a high risk of developing pancreatitis.
• the presence of a mutation does not predict the course of the disease nor affects the clinical management.
• the presence of a PRSS1 gene mutation increase the lifetime risk of pancreatic cancer by 40%
• Advices about lifestyle are necessary, consuming alcohol and fat food can influence the expression of the disease. → Especially important is to quit smoking because it can increase the severity of the pancreatitis attacks and also the risk of developing pancreatic cancer in HCP.
Conclusions

- Endoscopic ultrasonography (EUS) has become the method of choice for the diagnosis of chronic pancreatitis in clinical practice.

- EUS-elastography allows evaluating the degree of pancreatic fibrosis and thus supporting the diagnosis of chronic pancreatitis in cases of inconclusive EUS findings.

- The pancreatic function endoscopy test associated with EUS allows detecting patients with inconclusive EUS findings who will most probably develop chronic pancreatitis.

- The dynamic EUS evaluation of the main pancreatic duct after i.v. secretin provides with additional information to the static EUS for the early diagnosis of chronic pancreatitis.