Classification of pancreatitis

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An international group of doctors* interested in pancreatic disease met in Cambridge in March 1983, under the auspices of the Pancreatic Society of Great Britain and Ireland, to discuss the classification of pancreatitis in the light of developments that have taken place in the 20 years since the crucial conference in Marseille.¹

The Marseille delegates had separated pancreatitis into four main groups: (1) acute, (2) relapsing acute (with clinical and biological restitution of the gland), (3) chronic relapsing (chronic pancreatitis with acute exacerbations), (4) chronic (with anatomical and/or functional residual damage to the gland).

This classification has had a profound influence on the study of pancreatitis but some problems have persisted. Clinicians can recognise acute first onset pancreatitis and define advanced chronic pancreatitis, but difficulties of definition have arisen between these extremes. The distinction between relapsing acute and chronic relapsing pancreatitis is usually made on grounds of function, as pathological specimens are rarely available – but most patients with pancreatic disease are managed without function tests. The fact that the official Marseille publication is not easily available has led to misquotation and some misunderstanding. One implication that has been taken is that alcohol abuse leads only to chronic pancreatitis; it is now appreciated that alcohol induced pancreatitis may present acutely and that alcohol induced disease is not inevitably progressive.

Clinicians not familiar with the details of the Marseille classification have often used 'acute' and 'chronic' in a temporal sense, analogous to their usage in liver disease. Chronic hepatitis means a persisting problem – but does not necessarily imply irreversible damage. Chronic pancreatitis, strictly speaking, means irreversible change.

New pancreatic imaging methods have become popular during the last decade, and these, in conjunction with function data, provide some measure of organ damage. Disease activity is less easy to define, unless the tests are repeated. As yet, no subgroup markers are fully validated.

Specialist views

Many different scientific disciplines are interested in pancreatitis, and their specialists look at the disease from different points of view. The Workshop therefore split initially into five speciality groups, these being: demography and aetiology, exocrine function, imaging, histopathology, and surgery.

Each group reviewed progress within its particular field of interest and attempted to define types of pancreatitis which they could recognise.

Aetiology

Aetiology has crucial prognostic value, as pancreatitis may be halted once the cause is removed. Thus it is recognised that pancreatitis caused by gall stones almost never leads to chronic disease. The importance of alcohol has also been fully substantiated. There is no threshold of alcohol consumption above which pancreatitis seems inevitable; most alcoholics do not have clinically evident pancreatic disease and those factors which determine disease in an individual are yet to be


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defined. Sensitivity markers would have a central
place in such an aetiological classification but are not
yet available; further studies on proteins such as
lactoferrin and stone protein or tissue characterisers
such as HLA antigens are important. The cause of
the types of chronic calcifying pancreatitis found in
Africa and India remain obscure; more detailed
nutritional studies are required. Drug induced acute
pancreatitis has become better recognised and is
perhaps more common than hitherto. The
hypothesis that the congenital anomaly of pancreas
division is able to cause obstructive pancreatitis has
been proposed.

Exocrine function

Biochemical tests have an important role in the
diagnosis and classification of pancreatitis. Serum
amylase (or iso-amylase) and lipase remain the most
reliable tests for acute pancreatitis; values greater
than 10 SD above the laboratory mean (5 × upper
normal limit) are diagnostic. Levels may return
to normal within 48–72 hours of the acute episode after
which more information may be obtained by
imaging. It is recognised that high concentrations of
serum amylase may occur without acute inflam-
mation – for example, in patients with ‘cysts’ – and
that normal concentrations may be found in acute
inflammation when the pancreas is chronically
diseased. Impairment of exocrine function may
persist for some long time after a single acute attack.

Pancreatic exocrine reserve is best measured by
duodenal aspiration after direct stimulation of the
gland, with assay of bicarbonate and enzyme protein
output. Duodenal drainage tests detect pancreatic
insufficiency when damage is marked or moderate,
but do not predict progress of the disease or help to
define aetiology. Markers in duodenal aspirate or
pancreatic juice – for example, lactoferrin, stone
protein, and trypsin inhibitor – may be more
informative.

Indirect tests of pancreatic function – for
example, pancreatic polypeptide release, radio-
immunoassay of trypsin, pancreatic iso-amylase
inhibitor, and tubeless tests such as the pancreo-
lauryl test, can define severe pancreatic insuf-
iciency, but are insensitive at earlier stages of the
disease.

Sequential tests of pancreatic function are
necessary to define whether the disease is recover-
ing, static, or progressive.

Imaging

Endoscopic pancreatography (ERP) has been
widely used in patients with known or suspected
chronic pancreatitis; its role in patients with acute
pancreatitis has yet to be defined. The imaging
group emphasised the importance of high quality
radiographs, and proposed new definitions and
gradings of pancreatogram changes in pancreatitis:
normal, equivocal (normal except for fewer than
three abnormal side branches), mild (more than
three abnormal side branches but normal main
duct), moderate (abnormal main duct with or
without branch changes), and marked (as moderate
pancreatitis but also at least one of the following –
duct obstruction, severe irregularity or dilatation,
ductal filling defects, or a cavity).

The sensitivity and specificity of ultrasound and
computed tomography scanning are also dependent
upon quality: observer variation has restricted the
general acceptance of ultrasound scanning. Agreed
criteria for grading are shown in the Table.

The group emphasised that imaging abnormalities
did not always correlate with the state of the gland as
judged by other methods (histopathology and
function testing) and that pancreatograms and scans
can be normal in patients with histologically proven
disease.

Histopathology

The histopathology group distinguished only acute
and chronic varieties of pancreatitis: some
specimens contain features of both.

The initial phase of acute pancreatitis is
c conveniently called oedematous although this lesion
is difficult to identify in human material. The earliest
experimental changes (three to six hours after a
defined insult) include separation of duct epithelial
cells, with swelling and disruption of cytoplasmic
organelles in the acinar cells. Later there is fat
necrosis and/or necrosis of pancreatic tissue (some
of which is because of vascular occlusion); either of
these features may be dominant, and both can be
associated with haemorrhage.

Two types of acute damage can be recognised:
necrosis of duct epithelia with periductal acute
inflammation – and perilobular necrosis probably
owing to hypoperfusion. Chronic inflammatory
changes include fibrosis, duct abnormalities, calcifi-
cation, and inflammatory infiltrate. Fibrosis
(particularly perilobular and panlobular) indicates a
previous inflammatory process. Segmental duct
dilatation and alternating dilatation and stenosis are
more specific than general dilatation. Pancreatic
islets are normally unaffected but may show
compensatory hypertrophy.

Pathological definitions of pancreatitis are
confused by the fact that similar changes are seen in
elderly patients without known pancreatic disease.
Table  Chronic pancreatitis – Image grading

<table>
<thead>
<tr>
<th>ERP</th>
<th>US and CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Normal</td>
<td>Quality study visualising whole gland without abnormal features</td>
</tr>
<tr>
<td>2 Equivocal</td>
<td>Less than three abnormal branches One sign only Main duct enlarged (&lt;4 mm) Gland enlarged (up to 2×N) Cavities (&lt;10 mm) Irregular ducts Focal acute pancreatitis Parenchymal heterogeneity Duct wall echoes increased Irregular head/body contour</td>
</tr>
<tr>
<td>3 Mild</td>
<td>More than three abnormal branches Two or more signs</td>
</tr>
<tr>
<td>4 Moderate</td>
<td>Abnormal main duct and branches</td>
</tr>
<tr>
<td>5 Marked</td>
<td>As above with one or more of: Large cavities (&gt;10 mm) Gross gland enlargement (&gt;2×N) Intraduct filling defects or calculi Duct obstruction, structure or gross irregularity Contiguous organ invasion</td>
</tr>
</tbody>
</table>

The ducts may be dilated and associated with fibrosis: microscopic foci of calcification, duct hyperplasia, metaplasia, and protein plugs are not uncommon.

Surgery

The surgeons were particularly concerned with defining severity in acute pancreatitis, in order to provide prognostic guidelines. The group separated mild acute pancreatitis (no multisystem failure with uncomplicated recovery), and severe acute pancreatitis (multisystem failure with early or late local or systemic complications), and defined certain local complications: phlegmon – an inflammatory mass in and around the pancreas; pseudocyst – a localised collection of fluid containing high concentrations of pancreatic enzymes within, adjacent or remote from the pancreas; abscess – pus in and around the pancreas.

Surgeons favour a classification which includes statements on aetiology, clinical status, functional, and morphological changes.

Classification – consensus and problems

Deliberations of the specialist groups led to broader discussion on classification. It was agreed to recommend retention of the terms ‘acute pancreatitis’ and ‘chronic pancreatitis’, despite the confusion which has arisen from their use.

Acute pancreatitis

This is defined as an acute condition typically presenting with abdominal pain, and usually associated with raised pancreatic enzymes in blood or urine, due to inflammatory disease of the pancreas.

Chronic pancreatitis

This is defined as a continuing inflammatory disease of the pancreas, characterised by irreversible morphological change, and typically causing pain and/or permanent loss of function.

Acute pancreatitis may recur. Many patients with chronic pancreatitis may have acute exacerbations but the condition may be completely painless.

Two main problems became apparent during the discussion. The first was to define acceptable criteria for ‘irreversible morphological change’ and ‘loss of function’. Scans, pancreatograms and function studies are sensitive tests of severe disease, but less accurate in the early stages; comparative studies are difficult to interpret because techniques vary and an independent endpoint is often missing. The Workshop supported the idea of grading test results as proposed by the imaging group. Similar gradations should be defined for function tests. It would then be possible to agree criteria for diagnosis, which could depend upon a combination of tests (or a score) – for example, marked abnormalities in any one test, or moderate abnormalities in two, or mild changes in three (assuming a compatible clinical picture and exclusion of carcinoma).

The second main problem concerns the definition of patients who suffer repeated attacks of pancreatic pain, but in whom unequivocal morphological or functional abnormalities have not yet been shown. The Workshop discussed the need for a grouping
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intermediate between acute and chronic pancreatitis, perhaps only as a ‘holding grade’ before final classification. This concept was eventually rejected, it being assumed that most clinicians would naturally use the term ‘probable chronic pancreatitis’ where necessary.

Conclusion

The Marseille classification has been of great value in categorising pancreatic inflammatory disease, in particular the single acute event (acute pancreatitis) or the persisting disease state with residual damage (chronic pancreatitis). In practice the intermediate categories of ‘relapsing acute’ and ‘chronic relapsing’ are less easy to use. A single attack of acute pancreatitis may leave function and/or anatomy altered for some time. On the other hand, a patient with silent underlying disease may first present with an acute attack.

Only two clinical types of pancreatitis need be recognised – acute, or chronic with residual damage. Definitions should be expanded to include aetiology which predicts prognosis, and statements of function and morphological damage which can now be made more precisely. Markers in blood or pancreatic juice may eventually define important subgroups. An agreed terminology is an essential basis for further understanding and study.

Reference

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M Sarner and P B Cotton

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