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Clinical and laboratory diagnosis of chronic pancreatitis

J.-Matthias Löhr

Gastrocentrum, Karolinska Institutet & Karolinska University Hospital, Stockholm, Sweden

e-mail: matthias.lohr@ki.se

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1. Introduction

Chronic pancreatitis (CP) is still far to rarely diagnosed as symptoms are non-specific and training of physicians in clinical pancreatology is dire (26). With an incidence of 3-4/100,000 inhabitants and a prevalence of 10-40/100,000 inhabitants, CP is a relatively common disease in industrialized countries (16). CP represents the farther end of a disease continuum between acute and chronic pancreatitis (14). This chapter aims to cover the essentials of diagnosing chronic pancreatitis and, at the same time, points to open issues for clinical research.

2. Clinical diagnosis

The clinical picture of CP can vary, depending on the underlying etiology, the stage of disease and the age of the patient (5). The typical clinical picture of CP is that of a patient who, after years of alcohol abuse and smoking and a history of recurrent abdominal pain develops steatorrhea and general malnutrition. Together with weight loss and bloating, these are the four cardinal symptoms of chronic pancreatitis and pancreatic exocrine insufficiency (**Table 1**). In the late phase, a diagnosis is easy to establish as morphological changes can be readily seen with any kind of imaging.

The description of the clinical picture and the clinical diagnosis has not changed since the inaugural descriptions of Gülzow (9) and later Amman (1, 2). Of the four cardinal symptoms, abdominal pain is the most prevalent one, however, representing a symptom common to a broad variety of diseases of the abdomen and beyond (5, 22). At later stages, pancreatic pain can become independent of the inflammatory process in the pancreas (4).

The most important issue for the clinician is to think of the pancreas as a source of these symptoms. Once this connection is made and appropriate laboratory tests (below) and imaging are done, the diagnosis of CP can be easily established – or disregarded.

Table 1: Cardinal symptoms of chronic pancreatitis

Abdominal pain
Loose stools/steatorrhea
Weight loss
Bloating

In summary, there is no single symptom pathognomonic to chronic pancreatitis, i.e. the diagnosis cannot be established solely on the basis of clinical symptoms. However, in the said enigmatic patient, the clinical diagnosis is still very likely.

Upon physical exam, signs may be subtle. Patients not reporting pain may have a tenderness of the abdomen to palpation. The head/body region can be easily palpated against the vertebra. A special procedure is the deep

palpation of the pancreas with the patient turned to the right side, more towards the spleen (Mallet-Guy maneuver) that may be the only positive finding (15). Palpable resistance stemming from pancreatic pseudocysts can be a typical finding (after an acute episode). In the case of (isolated) splenic vein thrombosis, an enlarged spleen (splenomegaly) can be palpated (also best in a position to the right). A rare but typical sign in patients with longstanding CP and pain can be a marmorized skin on the abdomen, then called *Erythema ab igne*: this is the result of repetitive application of hot water bottles to the stomach in an effort to alleviate pain (21). Other nonspecific indicators supporting the diagnosis can be signs of nicotine abuse (coloring of fingers and sometimes the beard) or alcohol abuse (poor oral hygiene, *foetor ex ore*) as well as any sign of malnourishment pointing to malnutrition (low BMI, thin skinfold, broken skin/nails, perioral rhagadae etc.).

3. Serum markers

Generic markers

The conventional markers of inflammation, i.e. elevated erythrocyte sedimentation rate (ESR) and elevated leucocytes (WBC) are of no use in establishing the diagnosis of CP. Depending of the character of the respective disease form, stage, and time point, these may or may not be elevated. As chronic pancreatitis is a smoldering disease with subclinical inflammation progressing in the pancreas, ordinary serum markers of inflammation will not be elevated.

Pancreatic enzymes

Seventy-seven years ago, it was stated that “elevated amylase has become a cornerstone in the diagnosis of pancreatitis” (7). Although the specificity of both serum amylase and lipase for chronic pancreatitis is acceptable, in the range of 90%–95%, their sensitivity is extremely low, oscillating around 10%. As a consequence, serum markers can not be used for establishing the diagnosis of chronic pancreatitis. There are many possible reasons for elevated serum amylase and lipase levels and thus, elevated levels in patients with abdominal pain have a low specificity for chronic pancreatitis (8). Serum elastase-1 is useful in acute pancreatitis (29) but has no better performance in chronic pancreatitis (10).

Plasma trypsin-like activity has been claimed to be a sensitive and specific marker for early (mild) chronic pancreatitis; however, the only study in this patient population comprised 16 patients and had some methodological ambiguities (13). Trypsinogen concentrations have also been suggested to be a good indicator for chronic pancreatitis (24). While plasma trypsin-like activity and trypsinogen concentrations are elevated in a quarter of patients with established chronic pancreatitis, they seem to remain normal in early chronic pancreatitis. While we could not demonstrate significant differences for absolute values of cationic (PRSS1) and anionic trypsinogen (PRSS2) (18) in AIP, CP and healthy controls, we found a change in the PRSS1-PRSS2 ratio: In healthy individuals (ratio 1:3) and in AIP (ratio 1:2) PRSS2 dominates (18). In non-AIP CP (24) the ratio is shifted towards PRSS1 (ratio 2:1).

If one reflects on how amylase, like any other digestive enzyme, reaches the circulation (serum) (25), its low specificity and sensitivity are not surprising. After massive damage of exocrine pancreatic tissue, that is, leakage through dead cells, serum levels rise significantly; however, this condition is not indicative of chronic pancreatitis, but rather acute pancreatitis.

Pancreatic enzymes below the lower level of normal (LLN) are routinely detected in patients with CP. If such LLN amylase is detected, advanced chronic pancreatitis with significant, if not severe pancreatic exocrine insufficiency can be expected (20). However, newer studies comparing pancreatic enzyme serum levels with fecal elastase-1 (see below) and other pancreatic function tests are lacking.

Other promising markers such as pancreatic

stone protein (27) and procarboxypeptidase B (23) have also not fulfilled their promise as sensitive markers for chronic pancreatitis.
Taken together, neither a generic marker nor serum levels of pancreatic enzymes can be used to establish the diagnosis of CP.

Markers of malnutrition

As chronic pancreatitis cannot be diagnosed with blood tests, the resulting malnutrition could be diagnosed in cases where the patient with CP has already developed pancreatic exocrine insufficiency (PEI). In the field of malnutrition, a series of serum parameters are established as markers indicating malnutrition (**Table 2**). They have proven useful in chronic pancreatitis to predict pancreatic exocrine insufficiency (17) and are correlated with further symptoms of malnutrition such as osteoporosis (11).

Table 2: Decreased serum components which can serve as markers of malnutrition

Prealbumin
Hemoglobulin
Retinol binding protein
Vitamin D (25-OH cholecalciferol)
Vitamin E (alpha-tocopherol)
Magnesium
Zinc

4. Other markers

For the diagnosis of (chronic) pancreatitis, some other body fluids could be used. One would be pancreatic juice collected during ERCP or in the duodenum stimulated after secretin injection. In an attempt to describe markers from pancreatic juice samples, we could not detect any differences with high-resolution 2D-PAGE (28). The cytological analysis does not reveal anything diagnostically relevant for establishing the diagnosis of CP, however, it may help identifying individuals at risk to develop pancreatic cancer (19).

Fecal elastase-1 (FE-1), a marker of pancreatic exocrine insufficiency (PEI) can also be measured. In itself, however, FE-1 is not specific, i.e. it cannot be used to establish the diagnosis of chronic pancreatitis but represents a screening test (6). It is a rather crude marker that if positive (below 200 ug/g) constitutes the diagnosis of PEI and in so doing would confirm the diagnosis of any sort of chronic pancreatitis. The threshold is under debate (3), especially in patient not undergoing pancrestic surgery, however, a result of < 100 ug/g can safely be considered indicative of a significant if not severe pancreatic exocrine insufficiency according to the latest European guidelines (12).

5. Conclusion

There are clinical symptoms indicative of chronic pancreatitis, however, none of them are specific or even pathognomonic. They should make a physician think of the pancreas as a source of the patients symptoms. Laboratory tests are also indicative at best: there is no positive test proving the diagnosis of CP. Very low (LLN) pancreatic serum enzymes can be a sign of significant pancreatic exocrine insufficiency (PEI) with chronic pancreatitis (CP) as a major etiology. The same holds true for low fecal elastase as an indicator of PEI and CP being the most frequent cause.

6. References

1. **Ammann RW**. Zur Klinik und Differentialdiagnose der chronischen Pankreatitis. *Dtsch Med Wchnschr* 110: 1322-1327, 1980. PMID: 7003706.
2. **Ammann RW, Akovbiantz A, Largiader F and Schueler G**. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology* 86(5 Pt 1): 820-828, 1984. PMID: 6706066.

3. **Benini L, Amodio A, Campagnola P, Agugiaro F, Cristofori C, Micciolo R, et al.** Fecal elastase-1 is useful in the detection of steatorrhea in patients with pancreatic diseases but not after pancreatic resection. *Pancreatology* 13(1): 38-42, 2013. PMID: 23395568.
4. **Ceyhan GO, Michalski CW, Demir IE, Muller MW and Friess H**. Pancreatic pain. *Best Pract Res Clin Gastroenterol* 22(1): 31-44, 2008. PMID: 18206811.
5. **Di Lorenzo C, Colletti RB, Lehmann HP, Boyle JT, Gerson WT, Hyams JS, et al.** Chronic Abdominal Pain In Children: a Technical Report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 40(3): 249-261, 2005. PMID: 15735476.
6. **Domingues-Munoz JE, Frulloni L, Hardt P, Lerch MM, Levy P and Löhr JM**. Potential for screening for chronic pancreatitis and pancreatic exocrine insufficiency using the faecal elastase-1 test. *Pancreatology* in press, 2016.
7. **Elman R, Arneson N and Graham EA**. Value of blood amylase estimations in the diagnosis of pancreatic disease. *Arch Surg* 19: 943-967, 1929.
8. **Frulloni L, Patrizi F, Bernardoni L and Cavallini G**. Pancreatic hyperenzymemia: clinical significance and diagnostic approach. *Journal of the Pancreas* 6(6): 536-551, 2005. PMID: 16286704.
9. **Gülzow M**. Erkrankungen des exkretorischen Pankreas. Erkrankungen des exkretorischen Pankreas. Jena, VEB Gustav Fischer, 1975.
10. **Gunkel U, Bitterlich N and Keim V**. Value of combinations of pancreatic function tests to predict mild or moderate chronic pancreatitis. *Z Gastroenterol* 39(3): 207-211, 2001. PMID: 11324137.
11. **Haas SL, Krins S and Löhr JM**. Altered bone metabolism and bone density in patients with chronic pancreatitis and pancreatic exocrine insufficiency. *submitted*, 2014.
12. **HaPanEU**. The UEG Evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. *UEGJ* in press, 2016.
13. **Hernandez CA, Nicolas JC, Fernandez J and Pizarro P**. Determination of plasma trypsin-like activity in healthy subjects, patients with mild to moderate alcoholic chronic pancreatitis, and patients with nonjaundice pancreatic cancer. *Dig Dis Sci* 50(11): 2165-2169, 2005. PMID: 16240234.
14. **Klöppel G and Maillet B**. The morphological basis for the evolution of acute pancreatitis into chronic pancreatitis. *Virch Arch A* 420: 1-4, 1992. PMID: 1539444.
15. **Lankisch PG**. Klinik und Prognose der chronischen Pankreatitis. Erkrankungen des exkretorischen Pankreas. Mössner J, Adler G, Fölsch UR and Singer MV. Jena, Gustav Fischer**:** 334-339, 1995.
16. **Levy P, Dominguez-Munoz E, Imrie C, Löhr M and Maisonneuve P**. Epidemiology of chronic pancreatitis: burden of the disease and consequences. *United European Gastroenterol J* 2(5): 345-354, 2014. PMID: 25360312.
17. **Lindkvist B, Dominguez-Munoz JE, Luaces-Regueira M, Castineiras-Alvarino M, Nieto-Garcia L and Iglesias-Garcia J**. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology* 12(4): 305-310, 2012. PMID: 22898630.
18. **Löhr JM, Faissner R, Koczan D, Bewerunge P, Bassi C, Brors B, et al.** Autoantibodies against the exocrine pancreas in autoimmune pancreatitis: gene and protein expression profiling and immunoassays identify pancreatic enzymes as a major target of the inflammatory process. *The American Journal of Gastroenterology* 105(9): 2060-2071, 2010. PMID: 20407433.
19. **Löhr M, Müller P, Mora J, Brinkmann B, Ostwald C, Farre A, et al.** p53 and K-ras mutations in pancreatic juice samples from patients with chronic pancreatitis. *Gastrointest Endosc* 53(7): 734-743, 2001. PMID: 11375580.
20. **Malferteiner P and Glasbrenner B**. Exokrine Pankreasfunktionstests. Erkrankungen des exkretorischen Pankreas. Mössner J, Adler G, Fölsch R and Singer MV. Jena/Stuttgart, G. Fischer Verlag**:** 147-159, 1995.
21. **Mok DW and Blumgart LH**. Erythema ab igne in chronic pancreatic pain: a diagnostic sign. *J R Soc Med* 77(4): 299-301, 1984. PMID: 6232383.
22. **Natesan S, Lee J, Volkamer H and Thoureen T**. Evidence-Based Medicine Approach to Abdominal Pain. *Emerg Med Clin North Am* 34(2): 165-190, 2016. PMID: 27133239.
23. **Printz H, Siegmund H, Wojte C, Schafer C, Hesse H, Rothmund M, et al.** "Human pancreas-specific protein" (procarboxypeptidase B): a valuable marker in pancreatitis? *Pancreas* 10(3): 222-230, 1995. PMID: 7624299.
24. **Rinderknecht H, Stace NH and Renner IG**. Effects of chronic alcohol abuse on exocrine pancreatic secretion in man. *Dig Dis Sci* 30: 65-71, 1985. PMID: 3965275.
25. **Rohr G**. Entry of pancreatic enzymes into the circulation. Diagnostic procedures in pancreatic disease. Ditschuneit H. Berlin, Springer**:** 63-66, 1986.
26. **Schmid R**. Pancreatologists: an endangered species? *Gastroenterology* 138(4): 1236, 2010. PMID: 20175967.

27. **Schmiegel W, Burchert M, Kalthoff H, Roeder C, Butzow G, Grimm H, et al.** Immunochemical characterization and quantitative distribution of pancreatic stone protein in sera and pancreatic secretions in pancreatic disorders. *Gastroenterology* 99(5): 1421-1430, 1990. PMID: 1698685.
28. **Wandschneider S, Fehring V, Jacobs-Emeis S, Thiesen HJ and Löhr M**. Autoimmune pancreatic disease: preparation of pancreatic juice for proteome analysis. *Electrophoresis* 22(20): 4383-4390, 2001. PMID: 11824606.
29. **Wilson RB, Warusavitarne J, Crameri DM, Alvaro F, Davies DJ and Merrett N**. Serum elastase in the diagnosis of acute pancreatitis: a prospective study. *ANZ J Surg* 75(3): 152-156, 2005. PMID: 15777396.