Painless form of chronic pancreatitis – multicentre study

This manuscript is dedicated to long term Editor in chief of this journal – Prof. Vilim Simanek.

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Background. The painless form of chronic pancreatitis is one of the rarer forms of the disease. While 80% to 90% of all chronic pancreatitis cases have abdominal pain as their clinical symptom, a smaller proportion of persons with chronic pancreatitis do not report typical pain. This form of the disease is often associated with exocrine and endocrine pancreatic insufficiency and weight loss, but the absence of pain symptoms may initially lead to misdiagnosis.
Methods. In a cohort of 257 people with chronic pancreatitis, the painless form was diagnosed in 30 individuals (11.6%), with an average age of 56 years and a predominance of men (71.4%). Thirty-eight percent were non-smokers and 47.6% of patients smoked up to 10 cigarettes per day. Alcohol intake of less than 40 g per day was reported by 61.9% of subjects. A quarter were moderately overweight, with a mean BMI of 26.5. Newly diagnosed diabetes mellitus had 25.7% of the subjects.
Results. A frequent finding was the demonstration of morphological changes, with calcifications found in 85,7% and dilatation of the pancreatic duct greater than 6.0 mm in 66%. A surprising finding was the presence of metabolic syndrome in 42.8% and the most frequent finding was the demonstration of decreased external pancreatic secretion (90%).
Conclusion. Painless chronic pancreatitis is usually treated conservatively. We demonstrate a subset of 28 patients with painless chronic pancreatitis treated surgically. Most frequent indications were benign stenosis of the intrapancreatic bile duct and stenosis of the pancreatic duct. Although approximately 1 in 10 people with chronic pancreatitis present with a painless form of it, so that the form of the disease is described as rare, this does not change the fact that management of these people is still not optimal.

Key words: pancreatic pain, painless form of pancreatitis, diabetes mellitus, pancreatic calcifications, exocrine insufficiency

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INTRODUCTION

According to the new definition of 2016, chronic pancreatitis is defined as a fibro-inflammatory syndrome caused by a combination of environmental, genetic, immunological, metabolic and other risk factors[1]. With the definition, a conceptual model of chronic pancreatitis was developed, which divides the development of the disease into five phases, marked by capital letters A to E.

Stage A is characterized by the presence of risk factors involved in the development of chronic pancreatitis and progresses to stage B when acute relapsing pancreatitis is present. In this stage, the first, mostly clinically unaffected changes occur, which are referred to as the early stage of the disease – C. Stage D is the fully developed phase of the disease and possible complications. Clinically, the onset of the disease is usually characterized by abdominal discomfort, abdominal pain or episodes of pancreatitis, mostly in the first years of the disease. This corresponds to the early stage of the disease, whereas the presence of exocrine or endocrine pancreatic insufficiency refers to stage E, the end stage of chronic pancreatitis[2]. Chronic pancreatitis, which is also referred to as inflammatory, progressive involvement of the exocrine part of the pancreas, is clinically associated most often with the presence of diabetes mellitus, digestive insufficiency and, above all, in about 70% to 90% with abdominal pain[3].

The first descriptions of chronic painless pancreatitis date back to the 1950s and 1960s, when Gambill et al. published the first observations of a painless course of chronic pancreatitis in 1948 (ref.[4]), and 10 years later further observations were published that confirmed Gambill's findings[5-7]. Goulston and Galagher found significant steatorrhea, a positive finding of diabetes mellitus, or a finding of pancreatic calcifications in 16 persons with a painless form of chronic pancreatitis[7]. Amodio et al. in a representative cohort of 74 persons with the painless form of chronic pancreatitis evaluated the presence of symptoms and signs of the painless form of chronic pancreatitis found steatorrhea in 20%, steatorrhea in 19%,

and weight loss in 16% of persons without symptoms and signs for the diagnosis of chronic pancreatitis[2]. A meta-analytic study of the prevalence of the painless form of chronic pancreatitis, evaluating a cohort of 5057 people, found a clinical diagnosis of painless chronic pancreatitis in 1569 of those evaluated – the prevalence of the disease was thus 12% (ref.[8]).

METHODS OF OBSERVATION

A total of 257 individuals with chronic pancreatitis diagnosed according to the criteria published in 2017 as UEG evidence-based guidelines[9] were evaluated, with emphasis on imaging evaluation (CT, MRI, MRCP, endosonography, and rarely ERCP). A subset of the study population was a group of 28 individuals with painless disease, from the set of 148 patients with chronic pancreatitis, collected during last 5 years and treated surgically, who were indicated for surgical treatment after diagnosis of painless chronic pancreatitis.

In all 257 subjects with chronic pancreatitis, treated conservatively, some anamnestic data were purposefully monitored, especially the history of acute pancreatitis, presence of pain at the time of examination, history of biliary disease, habitus according to BMI, alcohol intake, smoking, course of the disease after the diagnosis of chronic pancreatitis, presence of diabetes mellitus, fecal elastase value, stool pattern and morphological changes in the pancreas using non-invasive imaging methods.

Persons with a history of acute necrotizing pancreatitis, acute relapsing chronic pancreatitis, autoimmune pancreatitis, and patients with suspected malignant lesions where the diagnostic markers were not definite for chronic pancreatitis were excluded from the study.

The exocrine capacity of the pancreas was investigated by determining elastase-1 in the stool of the subjects included in the study, and a value of less than 100 ug/g stool was considered a definite pathological finding. In addition, the presence of newly diagnosed diabetes mellitus and weight loss (weight loss of 2 kg or more was considered significant) were monitored. Using imaging methods, pancreatic duct enlargement of more than 5 mm, dilatation of the secondary branches of the pancreatic duct, an image of pancreatic atrophy and the presence of pancreatic calcifications were evaluated as pathological findings.

RESULTS

In the group of 257 people with chronic pancreatitis, treated only conservatively, 30 individuals (11.6%) were diagnosed with a painless form of chronic pancreatitis. In the rest of the subjects, the painless form of the disease was not present, as they initially reported episodes of pancreatic pain or had an attack of acute pancreatitis. A diagnosis of autoimmune pancreatitis, IgG4 positive, was made in 17 patients with chronic pancreatitis (2.6%). In the people with the painless form of chronic pancreatitis, men predominated (19 men – 63.3% and 11 women – 36.3%). The average age of the group with painless form of chronic pancreatitis was 56.6 years (41–80 years).

Alcohol consumption was reported by 15 persons (50.0%), occasional drinking was reported by 2 persons. Ten persons were non-smokers (30.0%), 16 persons smoked up to 10 cigarettes per day (48.0%) and only 4 persons (7.5%) smoked more than 10 cigarettes per day.

The BMI of the cohort was raised to the obesity value and was 30.6 (20.7–34.3). Three persons underwent cholecystectomy (10.0%), two patients for cholelithiasis and one for acalculous cholecystitis.

A very common symptom at the time of the diagnosis of the painless form of chronic pancreatitis was weight loss of more than 2 kg in 18 patients (60.0%) and newly diagnosed diabetes mellitus in 16 patients (55.3%). Similarly, the presence of fat in the stool was found in 45.7%. Three patients reported unformed and more frequent stools, and five patients subjectively complained of occasional feelings of vomiting. No one was found to have manifest sarcopenia.

Imaging evaluation (CT or MRI, MRCP) showed irregular pancreatic duct translucency and/or enlargement of the main pancreatic duct above 5.0 mm in 14 persons (46.6%). Pancreatic duct obstruction with isolated presteatotic dilatation was not detected anywhere. The presence of pancreatic calcifications was found in 18 subjects, i.e. in 60%; the finding of dilatation of secondary pancreatic ducts was similarly frequent in 17 subjects (56.6%). We evaluated the findings as pancreatic atrophy in 11 patients (36.6%).

In our group of subjects, we diagnosed the simultaneous presence of metabolic syndrome in nine subjects (30.0%). In subjects with painless form of chronic pancreatitis, exocrine pancreatic insufficiency /fecal elastase-2 below 100 microgram/g stool/ was found in a high percentage of 63.3%, i.e. in 19 patients. Newly diagnosed diabetes mellitus was detected in 10 persons (30.0%). No genetic mutation was found, in contrast to an Italian study[2], where the authors found SPINK-1 mutation positivity in one patient (3.6%) and PRSS-1 mutation in the same case (4.0%).

In the group of 28 surgically treated persons with painless form of chronic pancreatitis, the most frequent operations were performed in 10 and 5 persons as a biliodigestive and pancreaticodigestive anastomosis. Men predominated (24 vs. 4), average age 55 years (41–71 years). 35.7% of the patients were regular drinkers of more than 40 g of alcohol per day, and 42.8% were regular smokers of more than 10 cigarettes per day. The number of newly diagnosed diabetic patients was lower than in the group with chronic pancreatitis without surgical indication (17.8%), on the contrary, changes in gland morphology were frequent – dilatation of the pancreatic duct in 50% and pancreatic calcification in 46.4% of those treated. Pancreatic atrophy was described in 17.8%. Pathological changes of the biliary tree were found in 35.7% of people with a painless form of chronic pancreatitis and surgical treatment. The mean BMI was 24.6, with only one patient having a BMI above 30.

DISCUSSION

In recent years, the prevalence of painless chronic pancreatitis has been an area that needs more attention than before. This is evidenced by the fact that of the more than 5 000 studies published between 1900 and 2020, only 42 studies with 14 277 patients[8] and a prevalence of 12% were used to assess the prevalence of the primary painless form of chronic pancreatitis. A high frequency of patients with the painless form of chronic pancreatitis was found to have pancreatic calcifications (96%), 51% had diabetes mellitus, 47% had exocrine pancreatic insufficiency, and 57% had an etiologic genetically induced or idiopathic form of the disease.

The significance of the average age of people with painless chronic pancreatitisis not clear[10]. In the study by Amodio et al.[2], the mean age of the cohort was 61 years, and more than 50% had no clinical symptoms. Hirth et al.[11] found a prevalence of this form of pancreatitis in 21% of persons classified as old versus 12% of young persons. However, a Swedish study demonstrated the opposite, i.e., the painless form was identified statistically significantly more clearly in persons younger than 55 years of age compared with the algic form[12].

What is still not fully understood is why chronic pancreatitis is painless in some patients. It has been suggested that there is a defect in intrapancreatic nerve supply[13], or an association between the presence of genes that affect sodium channel function, which may account for the different perception of pain[14,15].

Another debated question is whether and which genetic mutations may be a risk factor for the development of a painless form of chronic pancreatitis.

Systemic lupus erythematosus[16] and vascular disease[17,18] are also risk factors for the disease.

Very limited data have been published on the relationship between painless chronic pancreatitis and pancreatic cancer. It is a fact that due to the painless course of the disease, the diagnosis of pancreatitis is made with some delay or only at a later age. Hao et al.[19] found pancreatic carcinoma in cases of the painless form of chronic pancreatitis in 4 persons (2.1%).

Layer et al. found a pain-free form of chronic pancreatitis in 24% of a group with late-onset chronic pancreatitis, compared to the early-onset form, where all individuals reported pancreatic pain or painful episodes at the beginning of the disease[20]. Therefore, screening studies aimed at diagnosing pancreatic cancer in the painless form of chronic pancreatitis are much needed.

In our study, in agreement with the literature, we found a prevalence of the painless form of chronic pancreatitis of 11.6% and the mean age of the patients was 56 years. The most frequent subjective symptom at the time of diagnosis was weight loss and in one quarter of the patients were initially diagnosed with diabetes mellitus, whose value was identical to that reported in the Amodio study[2]. Changes in the main pancreatic duct and secondary branches were found in more than half of the evaluated subjects (60.0%). Exocrine pancreatic insufficiency, as determined by fecal elastase-1 value, was identified in 63%. As in other studies, the percentage of findings of pancreatic calcifications was high in our study – more than 60% of those examined. The finding of 40% of metabolic syndrome is also surprising. In the group of subjects with painless form of chronic pancreatitis we found no case pancreatic carcinoma, which however, might be due small number of subjects.

From a practical point of view, it should be emphasized that the symptomatology of patients with painless pancreatitis is quite varied and often different from the so-called classical form of chronic pancreatitis. Patients who do not have abdominal pain have a positive finding of calcifications, all without dilatation of the main pancreatic duct, or with a normal finding of the extrasecretory capacity of the gland. Conversely, some individuals present with dilatation of the pancreatic duct with exocrine and endocrine pancreatic insufficiency, without calcifications. In this group of individuals, some may be carriers of CFTR or SPINK1 mutations[2]. In Amodio study, pancreatic cystoids were also found in 74 individuals, in 7 individuals (9.5%), as a possible consequence of pancreatic duct obstruction[2]. In our study, we found no pancreatic cystoid.

A debated question is why pain is not experienced in these persons with such manifest morphological changes. Thus, it is hypothesized that pain is not induced because of the absence of inflammatory parenchymatous changes or because the central conduction and processing of the pain signal is altered. However, the exact answer is not known.

Most patients with painless chronic pancreatitis have positive findings of pancreatic calcifications. Here, age and smoking seem to play an important role, as they are particularly important inducers of pancreatic lithogen-

Table 1. Characteristics of the group.

Total number of people with chronic pancreatitis examined	257
Number of people with painless pancreatitis	30 (11.6%)
M/F	19/11 (70.4%/29.6%)
Age at the time of diagnosis	56.6 (41–80)
Alcohol regularly more than 30 g	15 (50%)
Smoking/daily number of cigarettes	
0 cigarettes	10 (30%)
up to 10 cigarettes	16 (48%)

esis[9,21,22]. Nevertheless, it is not entirely clear which pathogenetic mechanisms are initially involved in the formation of concretions. Similarly, the presence of gene mutations and the absence of pancreatic concretions are not fully elucidated in terms of the process of stenotic changes of the main pancreatic duct. Pancreatic exocrine insufficiency is a frequent finding in persons with a painless form of chronic pancreatitis. There is a correlation between EPI and the extent of the main pancreatic duct and the finding of pancreatic atrophy. However, the presence of pancreatic calcifications does not correlate with endocrine or exocrine pancreatic insufficiency. The painless form of chronic pancreatitis is referred to as a subset of idiopathic chronic pancreatitis, unrelated to alcohol abuse or smoking[23]. There are, however, a number of questions without clear answers, such as the role of vascular changes in the induction of disease, the distinction between the painless form of chronic pancreatitis and the physiological senescence with subsequent gland atrophy, or the actual risk of painless chronic pancreatitis and pancreatic cancer.

The treatment of the painless form of chronic pancreatitis is primarily a conservative treatment. Hypothetically, for example, endoscopic therapy of some morphological changes could lead to a favorable effect on the course of the disease, but there is not enough evidence for this hypothesis. Large multicenter prospective studies are needed to provide clear answers to the still many unclear questions.

In our subset, 28 persons with painless chronic pancreatitis underwent biliodigestive (10 persons) or pancreaticoduodenal (6 persons) anastomosis because of benign stenosis of the intrapancreatic bile duct or because of stenosis of the pancreatic duct. For stenosis of both ducts with duodenal stenosis or for inflammatory pseudotumor, hemipancreatoduodenectomy was performed in nine patients, Frey's operation in two cases and left-sided pancreatectomy with splenectomy in one case. At least half of the surgical interventions in the painless form of chronic pancreatitis were performed not because of pancreatitis itself, but because of pancreatitis-induced changes in another system (biliary tract – stenosis, duodenum – stenosis). It can be concluded that a significant difference between the group of non-operated and operated persons can be considered as a lower incidence of diabetes mellitus in persons with surgical intervention (17.8% vs. 55.3%) and fewer regular drinkers of alcohol (50.0% vs. 35.7%). Nevertheless, we believe that there is no significant difference in etiology or risk factors for the development of the painless form of chronic pancreatitis between persons who underwent surgical intervention and those who did not, with a diagnosis of painless chronic pancreatitis.

STRENGTH AND LIMITATIONS OF THE STUDY

Limitations of this study include the small number of patients evaluated. The absence of pain, the presence pancreatic calcification without dilatation of the main pancreatic duct and normal levels of fecal elastase-1 may be not sufficient for the diagnosis of chronic pancreatitis.

Table 2. Symptoms of people with a painless form of chronic pancreatitis.

Diabetes mellitus	16 (55.3%)
Loss of body weight of more than 2 kg	18 (60.0%)
Sarkopenia	0
Metabolic syndrome	9 (30%)

Table 3. Painless form of chronic pancreatitis – morphological signs.

Dilatation of pancreatic duct larger than 6.0 mm	14 (46.6%)
Pancreatic calcification	18 (60.0%)
Pancreatic atrophy	11 (36.6%)
Cystoids	0

Table 4. Procedures for the painless form of chronic pancreatitis.

Biliodigestive anastomosis	10
Pancreaticoduodenal anastomosis	6
Hemipancreatoduodenectomy	9
Surgery according to Frey	2
Left-sided pancreatectomy with splenectomy	1
Total	28

Table 5. Painless form of chronic pancreatitis.

	Without surgery (n=30)	Surgery (n=28)
Gender (M/F)	19/11	24/4

The key questions are also why these patients did not develop attacks of pancreatitis. Absence of pancreatic-type pain could be explained by absence of inflammation or by an alteration in central pain processing.

Another important limitation is the interval of observation of these patients. In most studies the term follow-up is no longer than 3 years. We cannot answer the question whether painless chronic pancreatitis is a risk factor for pancreatic cancer development. A longer follow-up is necessary for correct answer.

CONCLUSION

The painless form of chronic pancreatitis is a rare form of pancreatitis. Painless course is one of the reasons why in these persons we initially encounter mostly advanced morphological changes of the pancreas and, especially common is the finding of pancreatic calcifications and dilatation of the pancreatic duct. Due to the frequency of both exocrine and endocrine pancreatic insufficiency, the disease, although not very frequent, should be considered if there are “unexplained" clinical symptoms, diabetes mellitus, clinical signs of exocrine pancreatic insufficiency, unformed stools possibly with undigested food residues, or vague weight loss, all especially in the elderly population.

Author contributions: PD: supervised the study; MP, MB, ML: coordinating and extracted datas; RA, AM, JD: devised the study design. All authors critically assessed the study design, read and approved the final manuscript.

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