Pancreatology 13 (2013) 8–17

Contents lists available at SciVerse ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

The Spanish Pancreatic Club recommendations for the diagnosis and treatment of chronic pancreatitis: Part 1 (diagnosis)

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ARTICLE INFO

Article history:
Received 14 July 2012
Received in revised form
13 November 2012
Accepted 18 November 2012

Keywords:
Chronic pancreatitis
Therapy
Diagnosis
Exocrine pancreatic insufficiency
Guidelines

ABSTRACT

Chronic pancreatitis (CP) is a relatively uncommon, complex and heterogeneous disease. The absence of a gold standard applicable to the initial phases of CP makes its early diagnosis difficult. Some of its complications, particularly chronic pain, can be difficult to manage. There is much variability in the diagnosis and treatment of CP and its complications amongst centers and professionals. The Spanish Pancreatic Club has developed a consensus on the management of CP. Two coordinators chose a multidisciplinary panel of 24 experts on this disease. A list of questions was drafted, and two experts reviewed each question. Then, a draft was produced and shared with the entire panel of experts and discussed in a face-to-face meeting. This first part of the consensus addresses the diagnosis of CP and its complications.

1. Justification

CP is characterized by the development of deficiencies in both exocrine and endocrine function, with morphologic alterations affecting the parenchyma and the ducts of the pancreatic glands. This causes a great variation in the clinical manifestations of the disease. Its main symptom is pain that usually occurs in early stages when detectable functional and structural manifestations have not developed [1]. Recently, the advent of endoscopic ultrasound has allowed for the detection of minimal structural changes in early stages that suggest the existence of CP [2]. However, the absence of a gold standard at the present time makes it impossible to know the true diagnostic accuracy of ultrasound-detected changes. Logically, the initial management of patients with CP includes pain treatment and assessment and treatment of pancreatic insufficiency. Treatment may be primarily pharmacological, endoscopic and surgical; therefore, the approach should always be multidisciplinary [3]. The

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1424-3903/$ – see front matter
http://dx.doi.org/10.1016/j.pan.2012.11.309

complexity of this pancreatic disease, the difficulty of accurate diagnosis and the diversity of treatments probably justify the lack of consensus guidelines for its management [4–6].

2. Objective

For the above reasons, the Spanish Pancreatic Club held a consensus conference to guide the diagnostic and therapeutic approach of professionals who attend patients with CP.

3. Methodology

As in the previous consensus [7–9], the methodology used is a modification of the Consensus Development Conferences [10]. The sections of the conference were the panel of experts, the questions raised and the agenda. The responsibility for planning and managing the logistics of the consensus conference fell to the Pancreatic Pathology Unit of the University General Hospital of Alicante, Spain. The members of the panel of experts were chosen from amongst the faculty of various medical and surgical specialties commonly involved in managing CP. These members were selected according to criteria of clinical and research experience related to this disease, experience in its methodology and statistics and a systematic review of the literature. The national and international reputation of each of the experts in the field of their specialty was also considered. The final panel was composed of 24 experts (13 gastroenterologists, 2 endoscopists, 3 surgeons, 4 endocrinologists and 2 anesthesiologists). To avoid bias, the identities of the panel members remained hidden until the final phase of the consensus conference so that each of the members was unaware of the identities of the rest.

The consensus conference agenda was defined according to the development of a number of key questions about different diagnostic and therapeutic aspects of CP. With this scheme of action on the agenda, 23 questions were finally included and distributed to the panelists. Each panelist was required to answer two questions, and each answer had to be based on the available scientific evidence, i.e., on a systematic review of the existing medical literature. Thus, the panelists provided some recommendations based on a common scale. The degree of scientific evidence was based on the ratings given by the Oxford Centre for Evidence-Based Medicine [11]. The integration of the different answers of the panelists to the proposed questions constituted the first draft of the consensus text. During the consensus conference, attended by all the panelists, this first draft was distributed to each of the panelists for everyone to have the opportunity to participate in the final draft of each answer. With these new contributions, a second draft was produced and discussed at a joint meeting of the panelists and coordinators. It was at that time that the identities of the panelists and the allocation of questions were revealed. The current consensus text was finalized at that meeting. A summary of all the questions and the recommendations is depicted in Table 1.

4. What is chronic pancreatitis?

Despite extensive efforts over the past 50 years, there is no widely accepted clinical definition of CP. There have been several meetings of experts [12–14] with the aim of achieving a consensus. Each report that they have issued has based the definition of CP on the diagnostic methods available at that time, from histology to modern imaging techniques such as magnetic resonance imaging (MRI) [14].

From a general point of view, CP is defined as an inflammatory disease of the pancreas characterized by irreversible morphologic changes that typically cause pain and/or permanent loss of exocrine and endocrine function [15]. Morphological changes include irregular dilation of the main duct and secondary ducts, calcification of ducts and parenchyma, irregularly shaped parenchyma, pseudocysts and glandular atrophy. There may be stenosis of the distal common bile duct and, more rarely, of the duodenum and transverse colon. Vascular involvement is not uncommon in the form of venous thrombosis (splenic) and arterial pseudoaneurysms. The typical microscopic examination detects the presence of fibrosis and acinar atrophy, which are accompanied by a variable component of chronic inflammatory infiltrate. Involvement is often patchy. The presence of acinar atrophy alone is not considered CP. In addition, one must distinguish between CP and fibrosis without inflammation, which can be observed in normal subjects [14].

4.1. Recommendation

CP is an inflammatory disease of the pancreas characterized by irreversible morphological changes that typically cause pain and/or permanent loss of exocrine and endocrine function. The diagnosis must be reached by the combination of clinical data, imaging techniques and/or functional tests (Level of evidence 5. Grade of recommendation D).

5. Which non-endoscopic imaging techniques allow the diagnosis of chronic pancreatitis?

CP diagnosis by imaging techniques is based on the morphological changes of the gland that can be very evident in its advanced stages but difficult to detect in early stages [16,17].

In plain abdominal radiography, the presence of calcifications in the pancreatic area with compatible clinical manifestations can be diagnostic of CP.

Transabdominal ultrasound only detects advanced stages of CP [18].

Computerized tomography (CT) is the best non-endoscopic imaging technique to diagnose and localize pancreatic calcifications. Similar to ultrasound, CT is only useful for the diagnosis of CP in advanced stages. Dilation of the pancreatic duct and its secondary branches correlates well with endoscopic retrograde cholangiopancreatography (ERCP). It also detects parenchymal atrophy and focal lesions.

MRI is more sensitive for detecting early stages of CP by observing signal changes prior to morphological changes. These changes include loss of the normal high-intensity signal in T1-weighted sequences. In the arterial phase, after gadolinium administration, the signal strength decreases, giving the pancreas a heterogeneous appearance; uptake progressively increases in the later stages [19]. Magnetic resonance cholangiopancreatography (MRCP) allows for excellent visualization of the bile and pancreatic ducts. Pancreatic duct abnormalities include irregular dilation and a beaded appearance, frequently containing intraductal calculi. The collateral branches are also dilated in advanced stages [20]. MRCP after secretin administration may provide a better visualization of the pancreatic duct and its branches and simultaneously permit an assessment of exocrine pancreatic function based on the quantification of duodenal filling and diffusion coefficient [21].

5.1. Recommendation

The diagnosis of CP by imaging techniques—radiography, abdominal ultrasound, CT and MRI/MRCP—is relatively easy in advanced stages of the disease. MRI/MRCP and secretin MRCP are the non-endoscopic techniques that can detect less advanced stages of disease with greater reliability. (Level of evidence 2c. Grade of recommendation B.)

Table 1
Summary of Spanish Pancreatic Club recommendations for the diagnosis and treatment of chronic pancreatitis: part 1 (diagnosis).

1. What is chronic pancreatitis?
   - CP is an inflammatory disease of the pancreas characterized by irreversible morphological changes.
   - The diagnosis must be reached by the combination of clinical data, imaging techniques and/or functional tests.
2. Which non-endoscopic imaging techniques allow the diagnosis of chronic pancreatitis?
   - The diagnosis of CP by imaging techniques is relatively easy in advanced stages of the disease.
   - MRCP is the non-endoscopic technique that can detect less advanced stages of CP.
3. Which endoscopic imaging techniques allow the diagnosis of CP?
   - EUS is the most sensitive imaging technique for the diagnosis of CP, and its specificity increases with greater numbers of diagnostic criteria.
4. How is exocrine pancreatic insufficiency defined and diagnosed?
   - The gold standard for this diagnosis is CFA, determined by quantifying fat excretion in faeces collected for 72 consecutive hours.
   - The ^{13}C-mixed triglyceride breath test is a suitable alternative to CFA for the diagnosis of EPI in the context of CP.
5. How is endocrine pancreatic insufficiency defined and diagnosed?
   - Criteria for the diagnosis of DM secondary to CP are FPG $\geq$126 mg/dL and/or HbA1c $\geq$ 6.5%.
6. What is the etiology of chronic pancreatitis? What should be the initial etiologic study?
   - Alcohol and tobacco use show a clear relationship with CP development.
   - Other demonstrated causes, although less frequent, are obstructive, autoimmune pancreatitis and hereditary pancreatitis.
   - The initial etiologic study should be a medical history, a general blood analysis and a genetic study if the patient meets the criteria for hereditary pancreatitis. A sweat test and imaging techniques may also be useful.
7. Are there different types of CP?
   - CP may be classified into the following types: chronic calcifying pancreatitis, obstructive CP, autoimmune pancreatitis and groove pancreatitis.
8. When to request a genetic study of CP and how to interpret the results?
   - Patients with pancreatitis of unknown cause, with a family history or with children with unexplained episodes of this condition should be tested for mutations in PRSS1, CFTR, SPINK1 and CTRC.
9. Autoimmune pancreatitis: how to diagnose it and how to treat it?
   - The diagnosis of autoimmune pancreatitis is established by combining radiological findings, histological changes, serological alterations, systemic manifestations and therapeutic response to systemic corticosteroids.
   - It is based on the Japanese school and the HISORt criteria, which have been combined in the International Consensus on Diagnostic Criteria of autoimmune pancreatitis.
   - Treatment consists of the administration of corticosteroids.
   - There is no consensus about the option of maintenance treatment with low doses of corticosteroids.
   - Corticosteroid or azathioprine is recommended for the treatment of relapses.
   - In case of repeated recurrence, immunomodulatory therapy has good preliminary results.
10. What prognostic and developmental stage classification should be used?
    - The M-ANNHEIM and Büchler classifications provide the most prognostic information.
11. What clinical and laboratory parameters should be used for the follow-up of patients with chronic pancreatitis?
    - In patients with stable CP, clinical and laboratory follow-up is recommended every 6 months. In patients with complications, follow-up must be performed as necessary for each case.
    - The presence of endocrine and exocrine pancreatic insufficiency should be evaluated annually.
12. In which CP patients, how and when should a pancreas cancer screening be performed?
    - Hereditary pancreatitis is the only form of pancreatitis in which screening is recommended for identifying pancreatic cancer at an early stage.
    - The recommended technique is EUS.
    - Screening should begin at age 45 or 15 years before the age at diagnosis of the youngest familial case.

6. Which endoscopic imaging techniques allow the diagnosis of CP?

Although ERCP has traditionally been considered the gold standard for morphological diagnosis, the emergence of new imaging methods, such as endoscopic ultrasound (EUS) and MRCP, along with the complications associated with ERCP, have relegated it to the background [22].

EUS is the most sensitive imaging method for CP diagnosis and allows for the targeted collection of samples [23]. Some criteria that characterize the disease have been defined and are divided amongst parenchymal and ductal criteria [24,25]. So far, there is no

optimal cut-off to establish the diagnosis of CP. In clinical practice, a cut-off of four criteria is often used. With the assumption that not all criteria are equally important, the Rosemont classification [26] has been proposed, in which the endoscopic ultrasound criteria of CP and its specific validity are strictly defined. However, this classification does not improve the diagnostic value of the above-mentioned criteria [27]. Another problem for the validation of EUS has been the gold standard. When comparing EUS with ERCP and the secretin test, the agreement is 100% in severe forms (>5 criteria), 50% in moderate forms (3–5 criteria) and 13% in mild forms (0–2 criteria). In fact, up to 25% of patients with normal secretin–cerulein tests show EUS abnormalities suggestive of CP. When the applied gold standard is the sum of findings of ERCP, the secretin test and the clinical characteristics of the patient, EUS shows a diagnostic sensitivity greater than 84% and a specificity approaching 100% [28]. When compared with histology as the gold standard, the sensitivity of EUS for the diagnosis of CP exceeds 80%, with a specificity of 100% [29]. Moreover, there is an excellent correlation between the number of EUS criteria present and CP severity on histology [30].

6.1. Recommendation

ERCP allows diagnosis of CP. However, its role is currently limited in favor of other, less invasive imaging methods. (Level of evidence 3. Grade of recommendation C.) EUS is the most sensitive imaging technique for the diagnosis of CP, and its specificity increases with greater numbers of diagnostic criteria. (Level of evidence 1b. Grade of recommendation A.)

7. How is exocrine pancreatic insufficiency defined and diagnosed?

Based on the concept of insufficiency as the inability of an organ to perform its physiological function and taking into account the known functional reserve of the pancreas, exocrine pancreatic insufficiency (EPI) must refer exclusively to the situation in which the disturbance of pancreatic function is associated with an inability of the pancreas to facilitate normal digestion.

Currently, the gold standard for the diagnosis of EPI is the determination of the coefficient of fat absorption (CFA) by measuring fat excretion in faeces collected for 72 consecutive hours However, this technique has several disadvantages: it is troublesome both for patient and laboratory staff, so it is not wide available and the studies validating this method are old [31,32]. In CP, a pancreatic secretion below 10% of the lower limit of normality as measured by the secretin–cholecystokinin test correlates with the presence of steatorrhea [33]. Thus, it could be used as a test for the diagnosis of EPI. However, this test is not recommended due to the invasiveness, complexity, cost and lack of protocols. A variant of this test has been described that uses an endoscope to obtain a duodenal aspirate [34], but no studies have correlated the endoscopic pancreatic function test with the CFA. Classically, it is thought that a concentration of elastase in faeces below 50 mcg/g is consistent with the presence of EPI. However, there are no reports on the correlation between faecal elastase and CFA in patients with CP, and in patients with cystic fibrosis, this correlation is poor, with a sensitivity of only 40% and a specificity of 81% for the diagnosis of EPI [35]. Amongst the substrates used for the breath test, the ^{13}C-mixed triglyceride, which is the only one that has been appropriately compared to the CFA, stands out for showing a high correlation, a sensitivity of 91% and a specificity of 91% for the diagnosis of EPI [36]. Unfortunately, this test is not widely available. The level of duodenal filling during secretin-stimulated MRCP has a sensitivity of 69% and a specificity of 90% in the diagnosis of EPI measured by CFA [37].

7.1. Recommendation

Exocrine pancreatic insufficiency should only be described as the situation in which the disturbance of pancreatic function is associated with the inability of the pancreas to perform normal digestion. (Level of evidence 5. Grade of recommendation D.) Although not wide available, CFA – determined by quantifying fat excretion in faeces collected for 72 consecutive hours – is considered the gold standard for this diagnosis. (Level of evidence 5. Grade of recommendation D.) Greatly reduced values of faecal elastase are cause to suspect the existence of EPI. (Level of evidence 5. Grade of recommendation D.) The ^{13}C-mixed triglyceride breath test could be a suitable alternative to CFA for the diagnosis of EPI in the context of CP. (Level of evidence 1b. Grade of recommendation A.) The presence of reduced duodenal filling after secretin administration during a study of MRCP may be an indicator of exocrine pancreatic insufficiency, although normal duodenal filling does not rule out its existence. (Level of evidence 1b. Grade of recommendation A.)

8. How is endocrine pancreatic insufficiency defined and diagnosed?

Diabetes mellitus secondary to CP (DM-CP), also classified as type 3c diabetes, is included in 'other specific forms' of diabetes in the etiological classification of DM of the American Diabetes Association and is defined as a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion and/or action secondary to processes that affect the pancreas diffusely [38].

For the diagnosis of DM-CP, it is recommended to determine fasting plasma glucose (FPG) and/or glycosylated hemoglobin (HbA1c). FPG $\geq$126 mg/dL and/or HbA1c $\geq$ 6.5% would be diagnostic of DM; in the absence of unequivocal hyperglycaemia, the result should be confirmed by repeating the test [38]. In cases of doubt or limiting values, the test must be repeated or the plasma glucose measured after 120 min of oral glucose overload (75 g) because consistent changes in blood glucose compatible with DM can be observed in the oral glucose tolerance test in 22% of patients with normal baseline glucose [39]. In this case, FPG $\geq$200 mg/dL confirm the diagnosis.

8.1. Recommendation

DM-CP is defined as a group of metabolic diseases characterized by hyperglycaemia due to defects in insulin secretion and/or action secondary to processes that affect the pancreas diffusely. (Level of evidence 5. Grade of recommendation D.) Criteria for the diagnosis of DM secondary to CP are FPG $\geq$126 mg/dL and/or HbA1c $\geq$6.5%. (Level of evidence 1a. Grade of recommendation B.)

9. What is the etiology of chronic pancreatitis? What should be the initial etiologic study?

In 2001 [15] the etiologic classification system called TIGAR-O was published and subsequently modified [40]. This classification is based on the fact that in most cases, CP is the result of the interaction of multiple risk factors, although sometimes its etiology is unknown.

Today excessive alcohol consumption is considered the main cause of CP in industrialized countries, but it is estimated that there must be individual susceptibility (genetic basis combined with

environmental co-factors) and that only a minority (5%) of heavy drinkers develop pancreatitis [15]. Based on cohort studies, alcohol is considered the dominant etiology in a patient with CP if the patient consumes at least 60 g per day [41,42].

The fact that drinkers often are also heavy smokers introduces a number of limitations to the studies that analyze the relationship between tobacco use and pancreatitis. However, although tobacco use is proposed to be an independent dose-dependent risk factor for developing CP, probably it could behave as a co-factor and accelerate disease progression in alcoholic pancreatitis [41,43–45].

The presence of a ductal obstruction may also cause CP, as further outlined below. Although a higher prevalence of pancreas divisum has been found in patients with CP than in the general population [46], it has been suggested that it may act as an etiologic co-factor linked to genetic factors [47]. Twenty per cent of patients with renal insufficiency have pancreatic morphological alterations, compared to only 5% of controls [48]. However, several studies on this topic are not sufficiently consistent.

Finally, some drugs, such as angiotensin inhibitors, statins, didanosine, azathioprine, steroids, lamivudine, hydrochlorothiazide, valproic acid, oral contraceptives and interferon, have been described as inducers of CP [49]. Other recognized causes of CP, such as autoimmune pancreatitis and hereditary pancreatitis, will be discussed below.

The first step to start an etiological study is a correct full medical history with interrogations about medications taken and a history of chronic renal failure, alcohol use and tobacco use. In case of suspected high alcohol consumption that is denied by the patient, it may help to talk with relatives or assess laboratory abnormalities associated with excessive alcohol consumption, such as elevated carbohydrate-deficient transferrin, gamma-glutamyltransferase, ferritin, mean corpuscular value or elevated glutamic-oxaloacetic transaminase/glutamic-pyruvic transaminase ratio. Additionally, it may be useful for the diagnosis of autoimmune pancreatitis to identify high levels of IgG4 and autoantibodies. Imaging techniques such as CT and secretin stimulated MRCP can help identify pancreatic morphological alterations. It is also useful to perform a sweat test (or CFTR gene sequencing – see below) to detect cystic fibrosis. In situations of doubt, performing an EUS can assist in the diagnosis and staging of CP [50]. Moreover, EUS allows histological material to be obtained that confirms the presence of IgG4-positive lymphoplasmacytes, which are characteristic of autoimmune pancreatitis, or that will reasonably rule out the presence of atypias.

9.1. Recommendation

Alcohol and tobacco use show a clear relationship with CP development. (Level of evidence 2a. Grade of recommendation B.) Other demonstrated causes, although less frequent, are obstructive, autoimmune pancreatitis and hereditary pancreatitis, which will be addressed in other sections. The initial etiologic study that should be performed on a patient is a medical history including family history and harmful habits, previous and current related diseases, a general blood analysis with gamma-globulins and a genetic study if the patient meets the criteria for hereditary pancreatitis (see question 8). A sweat test and imaging techniques such as CT, MRI and EUS may also be useful. (Level of evidence 5. Grade of recommendation D.)

10. Are there different types of CP?

In general, the clinical, functional and morphological characteristics of patients with CP are similar [15]. However, certain etiological factors of the disease have well-differentiated behavior and histological features [51]. Therefore, CP can be classified according to clinical features, histology and response to treatment:

- *Calcifying CP*: characterized by abdominal pain, recurrent bouts of acute pancreatitis, development of calcification and the development of endocrine and exocrine pancreatic insufficiency. Histologically, it is associated with perilobular fibrosis and acinar destruction with infiltration of acute and chronic inflammatory cells. The causes are alcohol and tobacco abuse and hereditary and idiopathic factors [15].
- *Obstructive CP*: develops secondary to an area of ductal obstruction. Dilation of the pancreatic duct proximal to the obstruction, acinar cell atrophy and diffuse and uniform fibrosis appear [51]. It is usually the result of the presence of a tumor or is secondary to post-inflammatory ductal stenosis, trauma, dysfunction of the sphincter of Oddi or pancreas divisum. It is often painless but may appear with symptoms of acute pancreatitis. Sometimes calcifications may occur. Histological and functional changes of this type of CP can be fully or partially reversible if the process responsible for it is treated at an early stage.
- *Autoimmune CP*: its characteristics are detailed in a later section.
- *Groove pancreatitis*: affects the groove formed between the head of the pancreas, duodenum and the bile duct. Two types have been described: the pure form (located in the groove, preserves pancreatic tissue without causing stenosis of the main pancreatic duct) and the segmentary form (fibrous scar tissue that fills the duodenal groove and that extends to the pancreatic parenchyma, with Santorini and bile duct stenosis and without affecting the main pancreatic duct) [52].

10.1. Recommendation

According to the clinical, morphological and histological features and response to treatment, CP may be classified into the following types: chronic calcifying pancreatitis, obstructive CP, autoimmune pancreatitis and groove pancreatitis. (Level of evidence 5. Grade of recommendation D.)

11. When to request a genetic study of CP and how to interpret the results?

Hereditary CP is an autosomal dominant inherited disease with a penetrance of 80%. In 70% of hereditary CP patients, mutations of the protease, serine, 1 (trypsin 1) *PRSS1* gene have been reported [53,54]. Variants of the serine protease inhibitor Kazal type 1 (*SPINK1*) gene have also been associated with CP; SPINK1 blocks intrapancreatic trypsin activity to prevent additional activation of trypsinogen and limits further tissue damage [55]. The chymotrypsin C (*CTRC*) gene has low penetrance. Mutations in *CTRC* have been associated with CP [56,57]. Another gene whose mutations may be associated with CP is cystic fibrosis transmembrane conductance regulator (*CFTR*) [58–62]. Patients with mutations in multiple susceptibility genes have been reported, e.g., patients with mutations in both *CFTR* and *SPINK1* have a very high risk of pancreatitis [63]. *PRRS1* mutations are considered to cause hereditary CP, while mutations in *SPINK1*, *CFTR* and *CTRC* predispose to alcoholic, idiopathic and tropical pancreatitis.

It is now proposed that patients with recurrent pancreatitis, with family history of pancreatitis or children with unexplained episodes of this disease should be tested for *PRSS1* mutations [64]. The diagnosis of hereditary pancreatitis is important not only for the risk of CP but for the high risk (nearly 40%) of pancreatic cancer [65]. It is recommended that the identification of other genes

associated with pancreatitis be performed only within protocols approved by research ethics committees [66]. However, this position should be revised according to new findings that emerge in this field and the possibility that the elimination of co-factors, such as tobacco or alcohol use, will change its natural history. When a patient with *PRSS1* mutations is identified, lifestyle changes should be recommended, such as cessation of alcohol intake (because of its pancreatic toxicity) and tobacco use (a risk factor for the development of pancreatic cancer). We also need to assess all direct family members and provide genetic counseling.

11.1. Recommendation

Patients with chronic pancreatitis of unknown cause, with a family history or with children with unexplained episodes of this condition should be tested for mutations in *PRSS1*, *CFTR*, *SPINK1* and *CTRC*. (Level of evidence 5. Grade of recommendation D.)

12. Autoimmune pancreatitis: how to diagnose it and how to treat it?

Autoimmune pancreatitis lacks specific symptomatology. The main differential diagnosis is pancreatic cancer, and autoimmune pancreatitis must be suspected when there is a pancreatopathy of unclear origin combined with autoimmune diseases or when confirmed after histological analysis [67]. Because clinical manifestations are not very sensitive or specific, diagnosis of autoimmune pancreatitis is based on radiological manifestations, laboratory test alterations and histological findings, although there is no uniform consensus [68,69]. Increased serum IgG4 is the analytical parameter with the most diagnostic value [70,71]. In fact, it has been considered as an IgG4 related systemic disease and not as a true form of CP; however, this increase has also been found in some patients with pancreatic cancer and in normal subjects [72]. Characteristic image features are an enlarged pancreas (focal or diffuse) with delayed enhancement, sometimes associated with rim-like enhancement [halo at the edge ('capsule-like rim')] and an irregular narrowing of the pancreatic duct (segmentary or diffuse) often combined with a narrowing of the bile ducts [73]. The histopathological changes are considered the reference standard: abundant lymphoplasmacytic infiltrate, predominantly periductal, intense fibrosis with more or less acinar mass replacement (relative to the initial or advanced stage of autoimmune pancreatitis) and obliterative phlebitis [67,74]. Abundant IgG4-positive plasma cells are often observed in the pancreas and other organs when affected [67,75,76]. Pancreatic cytology obtained by fine-needle aspiration is not accepted to establish the histologic diagnosis of autoimmune pancreatitis and a core biopsy or surgical resection is required [73,76]. The existence of IgG4-positive plasma cells after endoscopic biopsy of the duodenal papilla has high specificity and moderate sensitivity for the diagnosis of autoimmune pancreatitis type 1 [75]. The effectiveness of corticosteroid treatment for the resolution of its symptoms and morphological alterations is a specific feature of this condition [68,69,77].

At present, there are two main, clearly defined diagnostic criteria for autoimmune pancreatitis: those of the Japanese school [78] and those of the Mayo Clinic in the U.S. (HISORt criteria) [79]. The International Association of Pancreatology developed in 2010 the International Consensus on Diagnostic Criteria (ICDC) for autoimmune pancreatitis [80] in an attempt to unify the diagnostic criteria established by various societies, including the two mentioned. The ICDC classifies the disease as type 1 or type 2. The terms lymphoplasmacytic sclerosing pancreatitis (LPSP; without granulocytic epithelial lesions) and idiopathic duct-centric pancreatitis (IDCP; with granulocytic lesions) refer only to histological patterns. However, because the histological data are not always available, the terms type 1 and type 2 have been introduced to describe the clinical profiles associated with LPSP and IDCP, respectively. Type 2 is not an IgG4 related disease. To establish the diagnosis of autoimmune pancreatitis, the ICDC uses a combination of cardinal features of the disease, such as imaging findings, serology, involvement of other organs, histology and response to treatment. Each of these features is categorized as level 1 or level 2 according to its diagnostic reliability (Tables 2 and 3).

Treatment with steroids is a standard therapy [81,82]. There is no standardized treatment regimen, but steroid treatment is based on the data of multiple retrospective studies and expert opinions. The treatment is clearly effective during the first weeks, and the absence of a response casts doubt upon the diagnosis [77]. Initially, 0.6 mg/kg/day of prednisone is usually administered orally for 2–4 weeks, at which time the response is considered to be positive if there is a clear improvement of clinical signs, serum IgG4 and/or imaging tests. In this case, the dose is progressively tapered by 5 mg/week for a total treatment duration of 11 weeks, at which time the treatment is discontinued or reduced to 2.5–5 mg/day for at least 6–12 months. The relapse rate is much higher with short-term treatment than with prolonged treatments, and the reintroduction of steroid therapy has a positive response. Some groups recommend maintenance treatment with low doses of corticosteroids (2.5–5 mg/day) for a period of up to 3 years because the recurrence rate is lower [81]. In these cases, treatment with immunomodulators (azathioprine, mycophenolate mofetil) has been tested, with encouraging preliminary results. In subtype 2 of autoimmune pancreatitis relapses are rare [83]. In case of relapse, it is recommended to restart treatment with high doses of corticosteroids or azathioprine [84].

12.1. Recommendation

The diagnosis of autoimmune pancreatitis is established by combining radiological findings, histological changes, serological alterations, systemic manifestations and therapeutic response to systemic corticosteroids and is based on rankings such as those of the Japanese school and the HISORt criteria, which have been combined in the International Consensus on Diagnostic Criteria of autoimmune pancreatitis. (Level of evidence 5. Grade of recommendation D.) Treatment consists of the administration of corticosteroids for 3–6 months. There is no consensus about the option of maintenance treatment with low doses of corticosteroids. Corticosteroid or azathioprine is recommended for the treatment of relapses. (Level of evidence 2A. Grade of recommendation B.) In relapses, which are more frequent with the short-term treatment, the initial doses of steroids should be introduced, which normally elicits a good response. (Level of evidence 2b. Grade of recommendation B.) In case of repeated recurrence, immunomodulatory therapy has good preliminary results. (Level of evidence 4. Grade of recommendation C.)

13. What prognostic and developmental stage classification should be used?

Multiple classification systems of CP have been proposed; however, none of them has been extended to clinical practice or used as a standard for comparative studies.

The ABC system [85] divides patients according to the absence of abdominal pain (A), pain without complications (B) and pain with complications (C). The Japan Pancreas Society has proposed a classification that reflects the quality of life and can be used for assessments of clinical course and treatment effects [86]. The Manchester classification [87] divides CP into three stages: mild,

Table 2
Level 1 and level 2 criteria for type 1 autoimmune pancreatitis.

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical[a]): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (endoscopic retrograde pancreatography)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2 × upper limit of normal value	IgG4, 1-2 × upper limit of normal value
OOI	Other organ involvement	a or b a. Histology of extrapancreatic organs Any three of the following: (1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration (2) Storiform fibrosis (3) Obliterative phlebitis (4) Abundant (>10 cells/HPF) IgG4-positive cells b. Typical radiological evidence At least one of the following: (1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture (2) Retroperitoneal fibrosis	a or b a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct: Both of the following: (1) Marked lymphoplasmacytic infiltration without granulocytic infiltration (2) Abundant (>10 cells/HPF) IgG4-positive cells b. Physical or radiological evidence At least one of the following: (1) Symmetrically enlarged salivary/lachrymal glands (2) Radiological evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection) At least 3 of the following: (1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration (2) Obliterative phlebitis (3) Storiform fibrosis (4) Abundant (>10 cells/HPF) IgG4-positive cells	LPSP (core biopsy) Any 2 of the following: (1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration (2) Obliterative phlebitis (3) Storiform fibrosis(4) Abundant (>10 cells/HPF) IgG4-positive cells
Response to steroid		Diagnostic steroid trial Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

[a] Atypical low density mass, ductal dilation or distal pancreatic atrophy. These atypical features in a patient with obstructive jaundice highly suggest pancreatic carcinoma. These cases must be considered as pancreatic cancer if there is not collateral evidence of autoimmune pancreatitis and an exhaustive study to rule out malignancy has been done. HPF: high power field. From the International Consensus Diagnostic Criteria for Autoimmune Pancreatitis, Shimosegawa et al., Pancreas 2011 (80).

moderate and final. Finally, two new classifications have been proposed: the M-ANNHEIM classification [40] offers the opportunity to categorize patients according to etiology and compare the different clinical courses depending on the developmental stage and disease severity and incorporates a scale to determine the index of disease severity. The classification of Büchler [88] establishes three degrees of disease based on a combination of clinical, morphological and pancreatic function criteria. While the latter system is much less extensive and elaborated than M-ANNHEIM, it has some advantages due to its simplicity and easy reproducibility in clinical practice.

13.1. Recommendation

No prospective studies have validated the different classifications of the prognosis and developmental stage of CP. Of the proposed systems, the M-ANNHEIM and Büchler classifications provide the most prognostic information. (Level of evidence 5. Grade of recommendation D.)

14. What clinical and laboratory parameters should be used for the follow-up of patients with chronic pancreatitis?

The objective of monitoring CP is the early detection of endocrine and exocrine insufficiency and the presence of complications that can occur at any stage of the disease. These complications are pseudocysts, biliary obstruction, duodenal obstruction, bacterial overgrowth, pancreatic ascites, intraductal, retroperitoneal or intracystic hemorrhage, splenic and/or mesenteric thrombosis and pancreatic cancer. For monitoring CP, it is not well established how often follow-up should be performed and which parameters should be controlled. It seems reasonable in patients with stable CP to

Table 3
Level 1 and level 2 criteria for type 2 autoimmune pancreatitis.

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (atypical[a]): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (endoscopic retrograde pancreatography)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, $z < 5$ mm)
OOI	Other organ involvement		Clinically diagnosed inflammatory bowel disease
H	Histology of the pancreas (core biopsy/resection)	IDCP: Both of the following: (1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation (2) Absent or scant (0–10 cells/HPF) IgG4-positive cells	Both of the following: (1) Granulocytic and lymphoplasmacytic acinar infiltrate (2) Absent or scant (0–10 cells/HPF) IgG4-positive cells
Response to steroid		Diagnostic steroid trial Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in manifestations	

[a] Atypical low density mass, ductal dilation or distal pancreatic atrophy. These atypical features in a patient with obstructive jaundice highly suggest pancreatic carcinoma. These cases must be considered as pancreatic cancer if there is not collateral evidence of autoimmune pancreatitis and an exhaustive study to rule out malignancy has been done. HPF: high power field. From the International Consensus Diagnostic Criteria for Autoimmune Pancreatitis, Shimosegawa et al., Pancreas 2011 (80).

perform a clinical and laboratory follow-up every 6 months. In patients with complications, the follow-up must be performed as necessary in each case.

The course of abdominal pain can be unpredictable but tends to improve over time; conversely, EPI and DM-CP tend to get worse. It is important to establish a differential diagnosis with other processes that can cause abdominal pain episodes with similar characteristics. Jaundice is due to obstruction of the intrapancreatic common bile duct by inflammation and fibrosis of the pancreas, and in some cases by compression of a pseudocyst.

Duodenal obstruction caused by CP may be due to inflammation of the pancreatic head or a pseudocyst. Pancreatic ascites occurs as a result of anterior pancreatic duct rupture or, more commonly, a pseudocyst. Patients with a change in the pattern of pain, weight loss and/or jaundice should be evaluated for pancreatic cancer.

With regard to the laboratory tests required by a patient with CP, there are no evidence-based data to establish which parameters should be analyzed and how often. Therefore, a reasonable recommendation would include the analysis of blood parameters that will allow the consequences of the disease to be controlled, which would involve a general analysis that includes nutritional parameters and liver, pancreatic and glycemic profiles.

To detect the occurrence of EPI, it is necessary to perform functional tests. Although, as commented above, the gold standard is CFA, it is a laborious, uncomfortable and not widely available test and usually is replaced by other more available (although less accurate) test such as faecal elastase [89] or the labeled triglyceride breath test [36]. In patients with EPI, it is advisable to occasionally perform bone densitometry due to the increased risk of developing osteopenia and osteoporosis [90]. The assessment of pancreatic endocrine function is recommended in all patients with CP through annual determination of FPG and HbA1c [38].

14.1. Recommendation

In patients with stable CP, clinical and laboratory follow-up is recommended every 6 months. In patients with complications, follow-up must be performed as necessary for each case. (Level of evidence 5. Grade of recommendation D.) The presence of endocrine and exocrine pancreatic insufficiency should be evaluated annually during follow-up. (Level of evidence 5. Grade of recommendation D.) At the onset of pain or if there are changes in the pattern, it is important to establish a differential diagnosis with other processes that can cause abdominal pain episodes with similar characteristics. (Level of evidence 2b. Grade of recommendation C.)

15. In which CP patients, how and when should a pancreas cancer screening be performed?

The relationship between CP and pancreatic cancer has been confirmed in several epidemiological studies and cohort studies. However, these studies have obtained variable findings regarding risk quantification, depending on the methods and the type of CP. There should not be a temporal overlap between the diagnosis of CP and pancreatic cancer. Therefore, to be considered a true case of cancer in a patient with CP, there must be a minimum of 2 years of progression from the diagnosis of CP. A meta-analysis was recently published to clarify which types of CP are at risk of progressing to pancreatic cancer [91]; it was concluded that 5% of patients with CP will develop pancreatic cancer within 20 years after diagnosis of pancreatitis. However, hereditary pancreatitis has a much higher risk of developing pancreatic cancer. CP patients have a risk of pancreatic cancer between 5 and 10 times higher than the general population, and the risk is even greater in hereditary pancreatitis [92,93]. Specifically, according to the International Hereditary Pancreatitis Study, the risk of pancreatic cancer is 50 times higher for hereditary pancreatitis patients than the general population [94], and according to the European Registry of Hereditary Pancreatitis and Pancreatic Cancer, these patients have an increasingly high risk of developing pancreatic cancer after 50 years of age regardless of genotype [65].

Experts at the IV International Symposium of Inherited Diseases of the Pancreas recommend a screening program for patients in the >10 risk group, i.e., those with hereditary pancreatitis [92].

There is no clear consensus on how to conduct pancreas cancer screening. Many centers recommend the use of EUS, based on its ability to identify pancreatic masses smaller than 1 cm [95,96] and the possibility of performing fine-needle aspiration. However, this possibility is reduced when there is pancreatic inflammation, as in the case of hereditary pancreatitis [97]. CT and MRCP also present difficulties because they have limited sensitivity for detecting small lesions that are potentially curable.

The proper time to begin screening is also controversial and is based on expert recommendations [92]. It has been established that screening should start at age 45. If there is a family history of hereditary pancreatitis, screening should begin 15 years before the youngest age at which a case of pancreatic cancer has appeared in that family. In smokers, screening should begin early [98]. There is also no agreement on the frequency of monitoring; recommendations range from annually to every 3 years [92].

15.1. Recommendation

Hereditary pancreatitis is the only form of pancreatitis in which screening is recommended for identifying pancreatic cancer at an early stage. (Level of evidence 2b. Grade of recommendation B.) The recommended technique is EUS performed every 1–3 years, but this technique has limitations. (Level of evidence 5. Grade of recommendation D.) Screening should begin at age 45 or 15 years before the age at diagnosis of the youngest familial case. (Level of evidence 5. Grade of recommendation D.)

In loving memory of Luisa Guarner and Miguel Pérez-Mateo.

Funding

The consensus has not received funding.

Conflicts of interest

Enrique de-Madaria, Enrique Domínguez-Muñoz, Julio Iglesias-García and José Lariño-Noia have been paid speakers by Abbott Laboratories. Enrique Domínguez-Muñoz is a Consultant for Abbott Laboratories and Pentax. Julio Iglesias-García is a Consultant for Cook Medical Company. Luis Gómez and Yolanda Sastre have been paid speakers by Mundipharma, Zambon, Ferrer Pharma and Grunenthal Pharma. José Ramón Aparicio is a Consultant for Boston Scientific.

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