1130-0108/2008/100/12/746-751
REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS

REV ESP ENFERM DIG (Madrid)
Vol. 100. N.° 12, pp. 746-751, 2008

ORIGINAL PAPERS

Relapsing acute pancreatitis associated with gluten enteropathy. Clinical, laboratory, and evolutionary characteristics in thirty-four patients

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ABSTRACT

Objectives: to describe the frequency and the clinical and laboratory characteristics of relapsing acute pancreatitis (AP) associated with gluten enteropathy (GE).

Patients and methods: we prospectively examined all acute pancreatitis cases admitted to our Department in 2006. We recorded a total of 185 patients. With recurring forms, 40 (22%) in all, we used a clinical-lab protocol including serologic and genetic markers, and duodenal biopsy to rule out GE.

Results: a total of 34 patients (18%) met clinical-biological criteria for GE (group 1), and were compared to the remaining non-GE AP cases (n = 161) (group 2). Mean age in the GE group was 54 ± 25 years, slightly younger than group 2 (61 ± 14) (NS). There was a mild predominance of women (50%) in group 1 *versus* group 2 (38.5%) (NS). Seven patients in group 1 (20%) had severe AP, as compared to 27 (17%) in group 2 (NS). The presence of cholelithiasis in group 1 involved 6 cases (18%), which was significantly lower than in group 2 – 72 cases (45%) ($p < 0.05$). Four patients with GE developed pseudocysts (12%) *versus* 13 (8%) in group 2 (NS).

Tissue transglutaminase (tTG) was elevated only in 3 patients (9%). Nine patients (34%) were DQ2 (+) and 4 (12%) DQ8 (+); the rest (54%) were all negative for both markers. From an endoscopic perspective there was diffuse duodenitis in 32 patients (95%). Duodenal biopsies revealed villous atrophy (Marsh 3) in 2 patients (6%); submucosal inflammatory infiltration (Marsh 2) in 10 (29.4%); increased intraepithelial lymphocytes (Marsh 1) in 8 cases (23.5%), and normal mucosa (Marsh 0) in 14 patients (41.2%). Response to GFD after 1 year was excellent in 30 patients (88%).

Conclusions: relapsing AP with GE represents a relatively common association that is indistinguishable from other APs from a clinical-evolutive standpoint, except for a lower presence of cholelithiasis ($p < 0.05$).

RESUMEN

Objetivos: describir la frecuencia y características clínico-analíticas de la pancreatitis aguda (PA) recidivante con enteropatía por gluten (EG) asociada.

Pacientes y métodos: estudiamos de forma prospectiva los casos de pancreatitis agudas ingresados en nuestro Servicio durante el año 2006. Registramos un total de 185 pacientes. A las formas recurrentes que fueron 40 en total (22%), les aplicamos un protocolo clínico-analítico consistente en la determinación de marcadores serológicos, genéticos y biopsias duodenales, para descartar una EG asociada.

Resultados: un total de 34 pacientes (18%) cumplían criterios clínico-biológicos de EG asociada (grupo 1) y se compararon con el resto de las PA no-EG (n = 161) (grupo 2). La edad media en la EG fue de 54 ± 25 años, ligeramente inferior al grupo 2, (61 ± 14) (NS). Existía un ligero predominio de mujeres (50%) en el grupo 1, respecto al grupo 2 (38,5%) (NS). Siete pacientes del grupo 1 (20%) presentaron una PA grave, frente a 27 (17%) en el grupo 2 (NS). La presencia de colelitiasis en el grupo 1, fue de 6 casos (18%), significativamente inferior a la del grupo 2, de 72 casos (45%) ($p < 0,05$). Cuatro pacientes con EG desarrollaron seudoquistes (12%) frente a 13 (8%) en el grupo 2 (NS).

La transglutaminasa tisular (TGt) estaba elevada únicamente en 3 casos (9%). Nueve pacientes (34%) fueron DQ2 (+) y 4 (12%) DQ8 (+), siendo el resto (54%), negativos para ambos marcadores. Existía una duodenitis difusa desde el punto de vista endoscópico en 32 pacientes (95%). Las biopsias duodenales, mostraron atrofia vellositaria (Marsh 3) en 2 casos (6%); infiltración inflamatoria de la submucosa (Marsh 2) en 10 casos (29,4%); aumento de los linfocitos intraepiteliales (Marsh 1) en 8 casos (23,5%) y mucosa normal (Marsh 0) en 14 casos (41,2%). La respuesta a la DSG al año, fue excelente en 30 pacientes (88%).

Conclusiones: la PA recidivante con EG, constituye una asociación relativamente frecuente, indistinguible desde el punto de vista clínico y evolutivo del resto de PA, excepto por una menor presencia de colelitiasis ($p < 0,05$).

Received: 22-09-08.
Accepted: 29-09-08.

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A specific diagnostic protocol is much needed in the identification of these patients since GFD is the only effective therapy to prevent new AP events from developing.

Key words: Celiac disease. Acute pancreatitis.

En estos pacientes es muy conveniente la realización de un protocolo diagnóstico específico para su identificación, ya que la DSG constituye la única medida eficaz, para prevenir la aparición de nuevos episodios de PA.

Palabras clave: Enfermedad celiaca. Pancreatitis aguda.

Rodrigo L, Álvarez N, Riestra S, de Francisco R, González Bernardo O, García Isidro L, López Vázquez A, López Larrea C. Relapsing acute pancreatitis associated with gluten enteropathy. Clinical, laboratory, and evolutionary characteristics in thirty-four patients. Rev Esp Enferm Dig 2008; 100: 746-751.

INTRODUCTION

Acute pancreatitis (AP) is a relatively common disease that affects approximately 300,000 patients per year in the United States, with a mortality rate around 5% (1). Its mean incidence in Spain is closely similar, and is estimated in some 35-40 cases/100,000 population/year (2).

It may clinically manifest in several ways, and most commonly involves a single isolated episode; however, its presentation as recurrent events -- the variant designated "acute relapsing pancreatitis or ARP" -- is not uncommon, and it also may more rarely manifest in the form of chronic abdominal pain. Causes are diverse and most commonly include the presence of cholelithiasis and/or choledocholithiasis followed by excessive alcohol use, these two causes representing around 75% of cases.

Many other potential etiologies exist, including abdominal trauma, some drugs, hypertriglyceridemia, mesenteric ischemia, autoimmune pancreatitis, pancreatic ductal abnormalities, either congenital as pancreas divisum or acquired, and pancreatic flow obstruction from pancreas cancer or associated inflammatory disorders. Taken together, all these causes approximately represent 10% of cases (3). However, in around 15% of cases the etiology of AP remains unknown despite imaging and laboratory studies.

Some relapsing AP cases result from pancreatic duct drainage obstruction secondary to papillary stenosis or sphincter of Oddi dysfunction (SOD) (4). Pancreatic insufficiency and relapsing pancreatitis have been related to the presence of associated gluten enteropathy (GE). It was traditionally thought that both conditions were perhaps interrelated as a consequence of nutritional deficiency in association with gluten intolerance, since both the endocrine and exocrine functions are usually decreased in children and adults with malnutrition. It is currently posited that both pancreatic and biliary disorders seemingly associated with GE may rather be secondary to duodenal inflammation and associated secondary papillary stenosis (5-10).

PATIENTS AND METHODS

A prospective study of AP patients admitted to our Gastroenterology Unit in 2006 was carried out, for a total of 185 cases. Of these we separately grouped together all ARP cases, defined as those with 2 or more acute episodes, which totaled 40 patients.

A diagnosis with AP was established according to widely accepted clinical and biological criteria based on the presence of persistent abdominal pain radiating in a belt-like manner to the back, together with elevated serum pancreatic enzymes (amylase and/or lipase) at least above three times the upper limit of the normal range.

Imaging techniques to morphologically assess pancreatic gland status first include abdominal ultrasounds to ascertain the presence or absence of cholelithiasis, followed as needed by dynamic CT to evaluate the presence and extent of pancreatic necrosis and/or associated local complications. When cholangitis, choledocholithiasis, jaundice and/or papillary obstruction were suspected, we performed an ERCP procedure with sphincterotomy as needed.

Severity criteria were assessed using the Apache II classification with obesity included as an independent poor-prognosis factor, its assessment above six being suggestive of severity risk and hence conducive to intensive patient monitoring and pertinent specific therapeutic measures. All patients received standard therapy based on routine analgesia, adequate water and electrolyte replacement, early nutritional support, and complication management.

To study associated gluten intolerance serum tissue transglutaminase (tTG) antibodies were measured with a commercial ELISA test (Orgentec, Diagnostica, Mainz, Germany), and positive values were considered (> 1 U/ml) (11).

Similarly, genetic studies were undertaken to determine HLA-II-related GE susceptibility markers (DQ2 and DQ8) using standard PCR-SSP techniques (12). Multiple duodenal biopsies were obtained through duo-

denoscopy from the second duodenal portion using a Fujinon EC-250WR endoscope, and classified according to Marsh stages (13).

All patients with consistent clinical and/or laboratory features, together with the presence of genetic susceptibility markers and/or positive serologic markers –(high transglutaminase (tTG)– and/or compatible duodenal histology and/or sustained response to gluten-free diet for more than six months were diagnosed with gluten-sensitive enteropathy (GE). So-called latent and potential celiac disease (CD) forms are included therein.

Patients thus diagnosed with GE were started on a gluten-free diet (GFD), and their clinical-laboratory response was monitored every six months with follow-up on an outpatient basis, their outcome being assessed at one year.

Statistical analysis

Continuous variables were expressed as mean plus standard deviation values. Percentages were used for categorical variables. The former were analyzed using Student's t-test; the latter were analyzed using the chi-squared test with Yates' correction, or Fisher's exact test as needed. Differences between groups were considered significant at a p-value below 0.05.

RESULTS

Of all 185 acute pancreatitis cases admitted to our hospital's gastrointestinal unit during 2006, 40 cases (21.6%) met relapsing pancreatitis criteria. All these patients underwent a clinical-biological protocol to rule out associated GE, and we found 34 such patients, which represents 18.3% of all patients with AP and 85% (34/40) of relapsing forms.

Patients with associated GE (n = 34) (group 1) were compared to those with AP but no GE (n = 161) (group 2). The mean age of patients in group 1 was 54 ± 25 years (24-82), and gender distribution was similar in 17 cases (50%). Forty-four percent were older than 60 at the time of diagnosis. Mean age for patients in group 2 was slightly higher, with a lower percentage of women (NS).

Regarding clinical forms 7 (20%) patients had severe illness, and required admission to intensive care, in group 1 *versus* 27 (17%) in group 2, with no significant differences. Six patients (18%) had cholelithiasis in group 1 *versus* 72 (45%) in group 2, and this was the only significant difference found between groups ($p < 0.05$).

Four patients in group 1 underwent cholecyistectomy for associated cholelithiasis, and all AP relapsed in all of them despite gallbladder excision and with no accompanying choledocholithiasis.

ERCP was performed in 4 patients (12%) within group 1 as compared to 24 (15%) within group 2 (NS).

Four patients (12%) received endoscopic sphincterotomy (ES) during ERCP, and 2 of them (6%) suffered from iatrogenic duodenal perforation, which was resolved in both cases with conservative therapy.

The presence of local complications should also be highlighted since 4 patients (12%) had pseudocysts in group 1 *versus* 13 (8%) in group 2 (NS).

The general and clinical characteristics and incidence of complications for both groups are listed in table I. A female patient in group 1 (3%) underwent pancreas head resection using Whipple's procedure for persistent pain. Another patient (3%) was operated upon to clean and drain a pancreatic abscess that had not responded to intensive antibiotic therapy. No case of mortality was recorded in this series. Upper digestive endoscopy, which was performed for all 34 patients in the study, revealed macroscopic diffuse duodenitis signs in most subjects, namely in 32 (95%).

Table I. General and clinical characteristics, and complications of patients with AP with and without associated GE

Characteristics	*AP with GE (n = 34)*	*AP without GE (n = 161)*	*p-value*
Mean age, years	54 ± 25	61 ± 18	NS
Women, n (%)	17 (50)	62 (38.5)	NS
Severe forms	7 (20)	27 (17)	NS
Cholelithiasis, n (%)	6 (18)	72 (45)	< 0.05
ERCP, n (%)	4 (12)	24 (15)	NS
Cholecystectomy, n (%)	6 (17)	30 (19)	NS
Pseudocysts, n (%)	4 (12)	13 (8)	NS

AP: acute pancreatitis; GE: gluten enteropathy; ERCP: endoscopic retrograde cholangio-pancreatography; NS: non-significant.

Serum tGT levels were clearly elevated in 3 cases (9%); the remaining 31 cases (91%) had minimally elevated or normal levels.

Regarding genetic markers for gluten susceptibility 9 (34%) patients were DQ2-positive; 4 cases (12%) were DQ8-positive, and the remaining 21 patients (44%) were considered DQ2- and DQ8-negative, with some positive allele for one or both heterodimers (Table II).

Table II. Genetic and serum markers in patients with AP and GE associated (n = 34)

Positive transglutaminase	3 (9%)
HLA-DQ2 (+)	9 (34%)
HLA-DQ8 (+)	4 (12%)

AP: acute pancreatitis; GE: gluten enteropathy.

As for histological findings in duodenal biopsies intestinal mucosal and submucosal inflammation or minimal changes were predominant (Marsh 0-2 stage), and only 2 patients had clear villous atrophy (6%) (Table III). The response to gluten-free diet (GFD) was excellent at one year of follow-up, and 31 (88%) patients remained symptom- and relapse-free.

Table III. Classification of duodenal biopsies (Marsh) in patients with AP and GE (n = 34)

Stage 0	14 (41%)
Stage 1	8 (23%)
Stage 2	10 (30%)
Stage 3	2 (6%)

AP: acute pancreatitis; GE: gluten enteropathy.

DISCUSSION

The association between acute pancreatitis and CD or gluten intolerance is well established, with cases and isolated series reported for several years now (14,15). Similarly, cases of calcified chronic pancreatitis have been described in association with CD and congenital abnormalities such as pancreas divisum (16) or malnutrition, including the so-called "tropical pancreatitis" mainly in India (17).

Recent epidemiological studies suggest that this association is much more common than previously thought. Thus, a study reported in 2007 that was carried out in a general population included in a Swedish National Registry followed up for 40 years (1964-2003) identified a total of 14,239 individuals with celiac disease, as compared to 69,381 control subjects matched for age, sex, and place of residence who were followed for longer than one year with no previous diagnosis of pancreatitis. During follow-up celiac patients were seen to have a relative risk of 3.3 (95% CI: 2.6-4.4) ($p < 0.001$) regarding the development of acute pancreatitis, and even higher for chronic pancreatitis, with an OR of 19.8 (95% CI: 9.2-42.8) ($p < 0.001$). Increased risk for pancreatitis was found only in patients diagnosed with CD during adulthood. Therefore, this study conclusively demonstrates that celiac patients have a significantly greater lifetime risk of pancreatitis, both acute and chronic, when compared to the general population (18).

Mechanisms postulated for a relationship between CD and pancreatic-biliary inflammation include slow gallbladder voiding from decreased cholecystokinin release and even hypothetical malnutrition. However, it is currently posited that the primary cause is related to the presence of diffuse duodenal inflammation, which would secondarily condition the presence of papillary stenosis.

Thus, Patel et al. (19) performed a study in 169 patients tested for potential sphincter of Oddi dysfunction, who underwent pancreatic-biliary manometry, anti-gliadin and anti-endomysium antibody measurements, and duodenal and papillary biopsies in case of CD-positive serology. They found 12 patients with CD (7.1%) with a mean age of 61 years, far above that of subjects without CD (37 years). All celiac patients had recurrent abdominal pain and/or idiopathic pancreatitis. Two of them had mildly elevated liver function tests, and 10 had high amylase and/or lipase levels. Only 3 of 12 patients had been previously diagnosed with celiac disease. All patients had manometric evidence for stenosis, and there was histologically confirmed periampullary inflammation. Patients were treated with GFD and developed a sustained clinical response (19).

Celiac disease is characterized by a systemic process that is autoimmune in nature -- the one of known etiology -- and primarily, though not exclusively, involves the gut, most frequently the most proximal portion of the small bowel, particularly the duodenum. In view of such grounds some authors have considered that it may be also related with autoimmune pancreatitis, which also exhibits biliary-pancreatic involvement and is characterized by increased serum IgG-4 and positive antibodies against carbonic anhydrase (20).

While this condition has well established genetic grounds, it may arise at any age, and up to 20% of cases are diagnosed in subjects older than 60 years, as was the case with this series, where up to 44% of patients remained undiagnosed and were beyond the sixth decade of life.

CD was considered a rare illness until recently, but it is now clear that this disease is very common, with a fairly homogeneous worldwide distribution and a mean prevalence of 1% among the general population; it also remains clearly subestimated and infradiagnosed (21-23).

CD clinical presentation forms in the adult are highly variable and overall less typical than in children (classic forms), and are consequently called "atypical forms". Diarrhea develops in fewer than 50% of cases, and many patients display marked constipation. Weight loss is absent or mild, and up to 30% of patients have overweight at diagnosis (24).

CD has been graphically described as an iceberg whose visible, clinically manifest portion is made up with classic forms, those that predominantly develop during childhood, whereas atypical adult forms represent the submerged, hidden portion and include so-called silent, latent, and potential forms, as well as gluten enteropathy (GE).

Other manifestations commonly associated with CD include ferropenic anemia, osteoporosis, thyroid changes, abnormal liver function tests, headache, asthenia, and skin disorders such as dermatitis herpetiformis, which oc-

curs in 25% of celiac patients as highly characteristic skin lesions – vesicular-crusty aspect, symetrical presentation in friction areas, and severe pruritus; this helps in the diagnosis since its presence implies the existence of associated CD, usually with scarce or intermittent digestive complaints due to non-atrophic, at times patchy duodenal lesions, in 100% of cases (25).

As regards currently available serum markers for CD diagnosis guidance, tTG is most commonly used, as it may be measured with commercial ELISA kits, and has high sensitivity and specificity (approaching 90%) in the presence of villous atrophy. However, in the absence of said villous atrophy, sensitivity is much lower and results are negative as occurred in the present study, where it only yielded positive results in 3 (9%) cases as only 2 patients had mild to moderate villous atrophy. Therefore, this test has very low diagnostic sensitivity in the adult, as it parallels the presence of intestinal villous atrophy, which in turn clearly predominates in classic childhood presentations and is usually absent in adults; this accounts for the fact that tTG is commonly negative. Diagnostic sensitivity in the adult is much lower than in children, around 15-30% of cases (26).

The range of histological changes in the duodenal mucosa is wide and not restricted -- as traditionally believed -- to intestinal villous atrophy; in contrast, this finding is rare in adults, where minimal changes predominate, ranging from a morphologically normal bowel mucosa (Marsh 0) to elevated intraepithelial lymphocytes, usually above 30% (Marsh 1), to crypt hyperplasia associated to submucosal diffuse inflammatory infiltration; most cases exhibit an excellent clinical response to sustained GFD administration, which confirms that these subjects are true celiac patients (27-29).

Hence, it is no wonder that no general consensus has been currently established regarding CD diagnostic criteria, primarily concerning the usefulness of available serum markers and histological parameters, which vary among the various guidelines published by a number of European and international expert committees (30-32).

Some groups are at risk for CD, including individuals with associated autoimmune conditions such as type-1 diabetes, thyroid disorders, and persistently abnormal liver function tests (33).

First-degree relatives of CD patients have an increased prevalence for this condition, which is estimated around 10-15% and also includes second-degree family members, which clearly suggests genetic predisposition and familial clustering (34,35).

To summarize, the need for GE screening in patients with acute relapsing pancreatitis cannot be overemphasized, as such association is relatively common and may accompany severe and complicated disease, with no differences as compared to AP with different etiologies (biliary or alcoholic). Diagnosis is challenging since serological markers commonly used for GE screening are usually negative, and endoscopy with multiple duodenal biopsy sampling, preferably in distal and periampullary areas, is to be recommended. Gluten-free diet is indicated for uncertain cases, as most often results in significant clinical improvement, and prevents new recurrent episodes of acute and/or chronic pancreatitis.

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