World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i6.2104

World J Gastroenterol 2016 February 14; 22(6): 2104-2110
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Case Control Study

Prospective evaluation of the cause of acute pancreatitis, with special attention to medicines

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Author contributions: Rashidi M and Røkke O designed the study, collected the data, conducted the statistical analysis and wrote the manuscript.

Institutional review board statement: The local ethics committee was contacted and permission was not required as no intervention outside the normal hospital protocol was planned.

Conflict-of-interest statement: The authors of this manuscript declare no conflicts of interest.

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Received: June 17, 2015
Peer-review started: June 19, 2015
First decision: July 10, 2015
Revised: July 24, 2015
Accepted: September 13, 2015

Article in press: September 14, 2015
Published online: February 14, 2016

Abstract

AIM: To investigate the cause of acute pancreatitis (AP) by conducting a thorough investigation of drugs and their possible etiological role.

METHODS: We investigated the cause of AP in a large retrospective cohort of 613 adult patients admitted with AP at the Akershus University Hospital, Norway, from 2000 until 2009, who were evaluated with standard ward investigations. This group was compared with a prospectively evaluated group (n = 57) admitted from January 2010 until September 2010 who investigated more extensively using medical history and radiological assessment.

RESULTS: The groups were comparable with regards to gender, age, comorbidity and severity. The most common etiology was bile stones and alcohol, occurring in 60% in both groups. The prospective group was examined more thoroughly with regards to the use of alcohol and medicines. An increased number of radiological investigations during hospital stay and at follow-up were also performed. A more extensive use of radiological evaluation did not increase the detection frequency of bile stones. In the prospective group, more than half of the patients had two or more possible causes of pancreatitis, being mostly a combination of bile stones and drugs. No possible cause was found in only 3.5% of these patients, compared with 29.7% in the retrospective group.

CONCLUSION: A detailed medical history and extensive radiological evaluation may determine a possible etiology in almost all cases of AP. Many patients

have several possible risk factors, and uncertainty remains in establishing the definitive etiology.

Key words: Acute pancreatitis; Etiology; Medicines; Drugs; Bile stones; Alcohol

Core tip: We conducted a study investigating a large cohort of patients admitted with acute pancreatitis to gain knowledge of the possible causes.

Rashidi M, Røkke O. Prospective evaluation of the cause of acute pancreatitis, with special attention to medicines. *World J Gastroenterol* 2016; 22(6): 2104-2110 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i6/2104.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i6.2104

INTRODUCTION

Acute pancreatitis (AP) is the most common disease of the pancreas, and is a significant cause of morbidity and mortality in patients admitted with abdominal pain. The etiology varies among countries. Bile stones and alcohol remain the main causes, accounting for about 70% of cases[1]. The etiology is reported as unknown in 10%-20%, which is unfortunate, because patients with AP are at risk of new attacks[2]. Diagnosis of bile stones might be missed if only first line imaging is conducted during the first acute admission[3]. The aim of this study was to determine whether a more thorough medical history combined with more extensive radiological evaluation could increase the chance of finding the etiology of AP, thereby improving treatment and further prognosis. In Norway, there are 286 registered drugs with AP as a possible side effect, and their use is increasing[4]. A causative relation between drugs and AP is difficult to establish in most cases. The pathophysiological pathways causing drug-induced pancreatitis are unknown and possible time-effect and dose-effect relations are also unknown. Using meticulous medical history and radiological examinations, several risk factors are often revealed. Many studies have attempted to find the causative action, stating both under-reporting as well as inaccuracies[4,5].

In the present study, we compared a retrospective cohort of patients assessed with standard investigations with a cohort that was studied prospectively with a more extensive medical history, with special attention to the use of pharmacological agents, as well as broad radiological assessment. We presented circumstantial evidence for the possible role of drugs as causative factors in a defined geographical area.

Table 1 Patient characteristics *n* (%)

	Prospective group (*n* = 57)	Retrospective group (*n* = 613)	*P* value
Age (yr)	52.4 (17-94)	58.9 (5-96)	0.062
Gender (M:F)	35 (61): 22 (39)	320 (52): 293 (48)	0.179
Comorbidity			
None	14 (25)	219 (36)	
Heart disease	13 (23)	127 (21)	
Hypertension	19 (33)	170 (28)	
Pulmonary disease	5 (9)	69 (11)	
Diabetes mellitus	4 (7)	57 (9)	
Previous pancreatitis	15 (26)	38 (6)	< 0.001
Duration of pain (h)	24 (0-504)	20 (0-0.592)	
Severe pancreatitis			
CRP	31 (54)	276 (45)	0.975
CT	3 (10)	33 (10)	0.945
Complications			0.660
None	45 (79)	497 (81)	
Systemic	8 (14)	89 (14.9)	
Local	4 (7)	43 (7.2)	
Mortality	1 (2)	36 (6)	0.356
Severity of pancreatitis			0.713
Mild	50 (88)	521 (85)	
Moderate severe	2 (4)	54 (9)	
Severe	5 (8)	38 (6)	

CT: Computed tomography.

PATIENTS AND METHODS

The study comprised two cohorts: (1) a retrospective analyses of clinical records of all patients (*n* = 613) admitted to the Akershus University Hospital with AP during a ten year period from January 2000 to December 2009; and (2) a prospective evaluation of 57 consecutive patients admitted with AP from January to September 2010. AP was defined as the acute onset of persistent epigastric pain in the presence of serum amylase level above three times the upper limit of normal (amylase > 200 IU/mL) or a computed tomography (CT) scan showing peripancreatic inflammation, with or without pancreatic necrosis. Organ failure and comorbidities were also documented to classify disease severity into mild, moderate or acute, according to the revised Atlanta classification system[6]. In these patients, a thorough clinical history was taken, with special attention to alcohol and regular and/or new medication(s). Patient characteristics are shown in Table 1. When no cause was defined in the prospective group during first level radiological or laboratory investigation, further radiological evaluation was performed, either during the hospital stay, or at follow-up after 2-3 mo. Current and past regular and occasional medication use was registered. The sporadic nature of registration of non-prescribed medications in the retrospective cohort meant that this was not registered. Almost all medications in Norway must be prescribed by a doctor and are registered in a national

Table 2 Investigations during hospital stay and/or follow-up, *n* (%)

	Prospective group (*n* = 57)	Retrospective group (*n* = 585 evaluable)	*P* value
All patients with ultrasonography	51 (89.5)	420 (71.8)	0.007
All patients with CT	45 (78.9)	311 (53.1)	
All patients with MRI	32 (56.1)	196 (33.5)	0.001
US	5 (8.8)	142 (24.3)	
US + CT	16 (28.1)	143 (24.4)	
US + MRI	7 (12.3)	86 (14.7)	
US + CT+ MRI	23 (40.3)	49 (8.4)	
CT alone	4 (7.0)	88 (15.4)	
CT + MRI	2 (3.5)	31 (5.3)	
MRI alone	0	30 (5.1)	
No imaging	0	16 (2.7)	

CT: Computed tomography; MRI: Magnetic resonance imaging; US: Ultrasonography.

pharmacological database[7]. Akershus University Hospital Emergency Department serves around 500000 inhabitants, accounting for 10% of the Norwegian population, with a precise definition of geographical areas of responsibility and number of inhabitants in that area. This allows us to obtain precise figures of the number of users of different prescribed medications in our catchment area. Furthermore, there is a precise national publication describing all pharmacological agents and their side effects, such as AP[8]. The frequency of side-effects are given as: frequent (≥ 1/100-< 1/10), less frequent (≥ 1/1000-< 1/100), seldom (≥ 1/10.000-< 1/1000), very seldom (< 10.000) and case reports. We can therefore calculate the minimal and maximal expected cases of AP induced by medicines in our area, which is minimum 31 and maximum 310 cases of AP due to medicines in our catchment-area.

Statistical analysis

Student's two-tailed *t*-test and Pearson's χ^2 test were used to test differences between groups as appropriate, and Fisher exact test was used in cross-tables with numbers < 7.

RESULTS

Patient characteristics are shown in Table 1 and demonstrate that the retrospective and prospective groups were comparable with regards to gender, age, American Society of Anesthesiologists severity, CRP and CT-scores. As expected, the use of radiological investigations was more extensive in the prospective group compared with the retrospective group, as shown in Table 2. In the prospective group, all patients were investigated using some form of radiological examination, and many (40%) with three radiological tools: ultrasonography (US), CT and magnetic resonance imaging. Biliary and alcoholic pancreatitis was the most frequent etiology in the retrospective and prospective group, at 61% and 58% respectively (Table 3). Table 4 summarizes details of the prospective group with regards to the use of medications with AP registered as a possible side effect. Fifty-eight percent (*n* = 33) of patients used these drugs, with 21 patients using one of these medications and 12 patients using more than two medicines associated with AP as a side effect (Table 5). In our prospective group, detailed description of medication use was noted and Table 5 summarizes the drugs used, showing statins and anti-hypertensive drugs to be the most commonly used medicines.

Our data shows a significantly higher number of patients reporting previous episodes of pancreatitis in the prospective groups compared with the retrospective group (26% *vs* 6%. respectively). This may be caused by a more thorough questioning of the patient at time of admission, and further stresses the importance of finding the causative factor, because this might increase the likelihood of optimizing treatment, improving prognosis and reducing risk of recurrence.

DISCUSSION

The most common cause of AP in Europe and North America is gallstones (50%) and alcohol (25%), whereas idiopathic pancreatitis is seen in around 10% of cases[9]. The present study showed a lower frequency of bile-stones or alcohol (60%), whereas idiopathic pancreatitis was diagnosed in almost 30% in the retrospective group. In a large population-based analysis of 1224121 patient visits diagnosed with AP with a 75% admission rate, McNabb-Baltar *et al*[10] found the etiology to be bile stones in 17.1%, alcohol in 14.6% and others/unknown in 67.8% of the patients. The discrepancy of these findings compared with our cohort might reflect the lower degree of investigations in outpatient cases with assumed lower severity and, therefore, less extensive radiological evaluation.

The present study revealed that a possible cause of AP can be defined in almost all cases if a meticulous history and radiological evaluation are performed. However, in a significant minority, uncertainty exists when several possible causes, such as bile stones, alcohol and medicines, are identified. In these cases, it is not possible to be certain which is the true cause.

In most patients, the etiology is determined during the first admission to hospital. First line evaluation consists of medical history and abdominal US, and often contrast-enhanced CT. In about 20% of patients where no definitive causative agent is found, a repeat meticulous history is also recommended[11] and a secondary line of investigation is necessary, using magnetic resonance cholangiopancreaticography (MRCP), endoscopic ultrasonography (EUS) and possibly endoscopic retrograde cholangiopancreaticography (ERCP), as indicated. Repetition of EUS is also indicated, because this increases the sensitivity of

Table 3 Cause of acute pancreatitis in the prospective and retrospective group *n* (%)

	Prospective group (n = 57)		Retrospective group (n = 613)		*P* value
	Patients	Patients using medicines[1]	Patients	Patients using medicines[1]	
Bile stone	23 (40.4)	13 (57)	271 (44.2)	4 (0.1)	< 0.001
Bile stone or alcohol	4 (7.0)	4 (100)	14 (2.3)		
Alcohol	6 (10.5)	1 (17)	87 (14.2)	1 (0.1)	
Hypertriglyceridemia	3 (5.2)	3 (100)	8 (1.3)		
ERCP	1 (1.8)	0	19 (3.1)		
PTC	1 (1.8)	0	0		
Tumor/cancer pancreas	1 (1.8)	0	9 (1.5)		
Pancreas divisum	2 (3.5)	1 (50)	1 (0.2)		
Stone in pancreatic duct	1 (1.8)	0	1 (0.2)		
Postoperative pancreatitis	0	0	3 (0.5)		
Trauma	0	0	1 (0.2)		
Viral infection	0	0	2 (0.3)		
Medicines[1]	11 (19.3)	11 (100)	15 (2.4)	15 (100)	
Unknown[2]	4 (7.0)	0	182 (29.7)	0	
All	57 (100)	33 (58)	613 (100)		

[1]Medicines associated with pancreatitis as a side effect; [2]Two of these had a previous cholecystectomy due to bile stones, suggesting small bile-stones as a possible cause. ERCP: Endoscopic retrograde cholangiopancreaticography.

Table 4 Details of drugs used in patients with possible etiologies in the prospective group

Etiology	Generic name	*n*
Bile stone (n = 23)	Azathioprine	1
of which medicine users (n = 13)	Simvastatin	1
	Diclofenac	1
	Amipril	1
	Enalapril	1
	Drospirenin/etinylostradiol	1
	Simvastatin, Amipril	1
	Atorvastatin, Ezetimib	1
	Amipril	1
	Simvastatin, Amipril, Diclofenac	1
	Methotrexate	1
	Atorvastatin	1
	Simvastatin,	1
	Candesartan hydrochlorothiazide	1
	Simvastatin, Losartan hydrochlorothiazide	1
Bile stone or alcohol (n = 4)	Estradiol	1
of which medicine users (n = 4)	Ramipril, Prednisolone	1
	Estradiol	1
	Diclofenac	1
Alcohol (n = 6)	Prednisolone	1
of which medicine users (n = 1)		
Hypertriglyceridemia (n = 3)	Gabapentin	1
of which medicine users (n = 3)	Simvastatin	1
	Venlafaxine	1
Medication (n = 11)	Azathioprine	2
of which medicine users (n = 11)	Simvastatin	1
	Atorvastatin	1
	Venlafaxine, Ramipril, Asparginase	1
	Atorvastatin	1
	Methotrexate, Prednisolone, Etanercept	1
	Mycofenolic acid, Tacrolimus, Prednisolone	1
	Cyclosporine, Pravastatin, Simvastatin, Ramipril	1
	Diclofenac	1
	Simvastatin, Losartan hydrochlorothiazide	1
Pancreas divisum (n = 2)	Simvastatin	1
of which medicine users (n = 1)		
Total number		34

diagnosing bile stones[12]. If no cause is found, some authors suggest empirical treatment of the possible biliary cause using either cholecystectomy or ERCP and papillotomy[3]. However, these procedures are surgical, with possible complications, including death[13].

Bile stones and alcohol

In a Norwegian population study, ultrasound testing revealed gallbladder stones in 21.9% of the participants and the lifetime risk of biliary pancreatitis in the presence of gallstones has been reported to be around 2%[14]. Therefore, with a much higher prevalence of bile stones in our study population, we assumed that bile stones were a definite risk factor and all patients admitted with biliary pancreatitis underwent cholecystectomy at our center.

Alcohol is a known independent risk factor in the development of both acute and chronic pancreatitis. Patients in the prospective group were specifically questioned with regards to type, amount and timing of consumption before admission. However, it is also well known that many of these patients have consumed alcohol many times before the attack of AP, without harmful effect on the pancreas. In our data, a dose-response curve could not be demonstrated, as patients with AP had ingested variable volumes and types of alcohol, on single or multiple occasions, without any direct correlation with disease severity. When alcohol was the suspected etiology, the patient was informed of its dangerous effect on the pancreas and recommended complete cessation of its intake. On

Table 5 Number of drugs used in patients with medicines as a possible etiology

Use of a single drug		Use of two drugs		Use of three drugs	
Name	*n*	Name	*n*	Name	*n*
Azathioprine	3	Simvastatin, Amlodipine	1	Simvastatin, Ramipril.	2
Simvastatin	4	Simvastatin, Candesartan hydrochlorothiazide	1	Diclofenac	
Gabapentin	1	Simvastatin, Losartan hydrochlorothiazide	2	Atorvastatin, Ezetimib, Ramipril	1
Methotrexate	1	Simvastatin, Pravastatin	1		
Estradiol	1	Ramipril, Prednisolone	1	Atorvastatin, Venlafaxine, Ramipril	1
Asparginase	1			Methotrexate, Etanercept, Prednisolone	1
Diclofenac	2			Mycofenolic acid, Tacrolimus, Prednisolone	1
Atorvastatin	2				
Venlafaxine	1				
Furosemide	1				
Enalapril	1				
Drospirenin etinylostradiol	1				
Estradiol	1				
Prednisolone	1				
Sum	21		6		6

discharge, the general practitioner was also notified of the complete course of the hospital admission to provide a suitable follow-up.

Smoking in combination with alcohol has also been suggested to further increase the risk of pancreatitis[15]. Therefore, we recommend informing patients of this both on a general health basis and specifically related to pancreatitis.

Drugs

The importance of drugs as a causative agent of AP is currently under discussion. Some authors question their relevance[5], while others suggest that it is underreported[4]. A causative link to the development of AP is difficult to document[16]. Several case reports, as well as larger studies, have provided comprehensive data on these drugs and the limitation of published data[5,17,18]. The most common drugs indicated include L-asparginase, which may not be associated with elevated levels of amylase because inhibition of protein synthesis, as well as steroids, Valproic acid, Azathioprine and Mesalazine. AP caused by ciprofloxacin has also been reported in 3.1% of patient treated for infectious colitis, with cessation of disease on ciprofloxacin termination[19]. This convincing drug-link to pancreatitis might reflect a possible amplifying drug side effect when combined with an acute inflammatory condition. In the present study, 33 (58%) of 57 patients used medication associated with AP. In a recent epidemiological report from the United States, statin use was as high as 50% for men and 36% for women between the ages of 65 and 74 years[20]. The authors suggested that Simvastatin was associated with a reduced risk of AP in the cohort of users compared with non-users, and increasing doses of Simvastatin were associated with further risk reduction. According to the Norwegian Electronic Pharmacy Data, the corresponding numbers in Norway were 39% for men and 36% for women (for Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Atorvastatin, Rosorvastatin)[7]. Simvastatin and other statins (n = 14) were the most commonly used pancreatitogenic drugs in our prospective cohort. Statins are also used commonly as a treatment for hypertriglyceridemia, which is also an independent risk factor for pancreatitis. Similarly, many patients with diabetes mellitus (DM) use statins to reduce cardiovascular risk. Patients with DM also have a higher risk of pancreatitis, which might be caused by the more common presence of gallstones and hypertriglyceridemia[21]. Thus, these confounding variables must be considered, and a causative link is difficult to establish in individual patients because of the lack of studies investigating re-challenge and lifetime risk analysis. Many patients use the drugs intermittently and in combination with other drugs, which makes it difficult to determine accurately the causative role of the drug, which may have a direct toxic effect on the pancreas or an indirect effect on pancreas physiology[22]. As with the introduction of any new medication, the patient should asked to contact their physician if they experience any side effects. If the detailed medical history suggests that a drug is the most likely etiology, the necessity of drug continuation must outweigh the risk of recurrence of AP. The possibility of re-challenge and drug substitution must also be reviewed. These factors must be tailored according to the individual patient, and general recommendations are difficult to give.

Other causes of pancreatitis

Hypertriglyceridemia is a cause of AP secondary to fatty acid-induced acinar cell damage[23], and might also be associated with a more severe course of the disease[24]. Zeng *et al*[25] showed that a high level

of triglycerides was associated with a more severe disease in patients with bile stone pancreatitis. In the present study, three patients in the prospective cohort had hypertriglyceridemia as a possible cause of pancreatitis. All three patients used Simvastatin, which makes a certain determination of the true cause difficult.

Tumors in the pancreas were also considered a cause of pancreatitis in about 1.5% and 1.9% in our cohorts, which was similar to other studies. AP may be the presenting complication in up to 25% of patients with head of pancreas cancer.

In two patients in the retrospective cohort, viral infection was considered a causative agent. This has also been suggested by others describing AP caused by a rotavirus[26]. The mechanism is thought to be either viral infection ascending to the pancreatic duct to cause infection, or edema of the Ampulla of Vater similar to the mechanism of bile stone-induced AP[27-29].

Some reports are also emerging that suggest that genetic traits might be a disposition for the development of AP. In one study, the authors suggested that about 1/3 of patients with acute recurrent pancreatitis carried mutations associated with hereditary pancreatitis, including those in genes encoding trypsinogen (PRSS1), cystic fibrosis transmembrane conductor regulator (CFTR), achymotrypsinogen C (CTRC) and serine protease inhibitor Kazal type 1 (SPINK1)[16,30]. Beger *et al*[2] found that the p.N34S mutation in the *SPINK1* gene was found more often in patients with AP (12%) than in the normal population (2.4%), regardless of etiology, suggesting that this mutation lowers the threshold for the development of AP. We speculated that such genetic traits might lower the threshold for AP caused by other factors, such as drugs.

Lastly, it is important to be aware of subgroups of patients, such as the elderly and children, who have a different spectrum of etiological factors, such as drugs, infections, trauma, anatomical abnormalities and secondary to Ascaris in the pancreatic duct[1].

Limitations of the study

In this study, we only reported drug-use in patients presenting with AP requiring hospital admission. Registration of drug dosage, duration of use and drug rechallange were not performed when drug-induced pancreatitis was suspected as a possible cause; therefore, we emphasized how drugs may be a possible, but not definite, contributing factor to the reported cases in this study. Large case control studies would have an important role in furthering our knowledge compared with case reports that may be prone to bias towards newer drugs and more severe cases of AP.

Knowledge of etiology is crucially important to optimize treatment and, thereby, improve prognosis. Our data showed that in many cases of AP, we could find several possible etiologies. Bile stones and alcohol remain the main causes of AP in about 60% of Norwegian patients, and these frequencies remained unchanged despite more detailed medical history and radiological investigations conducted in the prospective sample compared with the retrospective group. Drugs associated with AP used widely; however, a definite cause is difficult to prove in most cases. Therefore, we recommend meticulous assessment of the patient using detailed medical history and radiological investigation to establish the etiology.

COMMENTS

Background

Acute pancreatitis (AP) is a serious disease, resulting in considerable morbidity and mortality. Many causes have been identified; however, in many cases, the etiology is unknown.

Research frontiers

Several studies have been published showing a wide spectrum of drugs as possible causes of acute onset pancreatitis.

Innovations and breakthroughs

In this article, the authors compare a large cohort of retrospectively reviewed patients with AP with a prospective group investigated more broadly to identify the cause of disease onset.

Applications

A more detailed history and radiological evaluation might determine at least one possible etiology in almost all cases of AP. The clinician should therefore ensure that detailed investigation of the possible etiology has been performed to tailor treatment according to the patient´s need.

Terminology

The revised Atlanta classification system is an international consensus classifying AP severity, allowing standardized reporting in research as well as in clinical practice.

Peer-review

The authors investigated possible causes of AP in retrospective and prospective cohorts of patients with a special focus on drug-induced disease. The most common etiologies were bile stones and AD alcohol in about 60% of cases, which is somewhat lower than the 80% reported elsewhere. No possible cause was found in 3.5% of the prospective cohort, which is also lower than previously reported data.

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P- Reviewer: Rakonczay Z **S- Editor**: Ma YJ **L- Editor**: Stewart G **E- Editor**: Wang CH

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ISSN 1007-9327