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***Case Control Study***

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

## Rashidi M et al. Drug induced pancreatitis

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# Abstract

**Aim**: to investigate the cause of acute pancreatitis (AP) by conducting a more thorough investigation of drugs and their possible etiological role.

 **Methods:** We conducted a study investigating the cause of AP in a large retrospective cohort of 613 adult patients admitted with AP at Akershus University Hospital, Norway from 2000 until 2009 evaluated with standard ward investigations. This group was compared with a prospectively evaluated group (*n =* 57) admitted from January 2010 until September 2010 investigated more extensively by means of 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 had more alcohol and medication use in addition to radiological investigations during inpatient hospital stay and in the follow up period. 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 to 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 actual etiology.

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

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

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# 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 cause accounting for about 70% of the cases[1]. The etiology is reported as unknown in 10%-20%, which is unfortunate as patients with AP are at risk of new attacks[2]. Diagnosis of bile stone may be missed if only first line imaging has been 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 radiologic 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-induces pancreatitis is unknown and a time-effect and dose-effect relation is also unknown. By meticulous medical history and radiological examinations several risk factors may often be revealed. Many studies have aimed at finding the causative action stating both under-reporting as well as inaccuracies[4,5].

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

**MATERIALS AND METHODS**

The study consists of two cohorts: (1) a retrospective analyses of clinical records of all patients (*n =* 613) admitted to Akershus University Hospital with AP during a ten years period from January 2000 to December 2009; and (2) a prospective evaluation of 57 consecutive patients admitted with AP in the time period January until 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 co-morbidities was also documented in order 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 given 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. Due to the sporadic nature of registration of non-prescribed medications in the retrospective cohort, this was not registered. Almost all medications in Norway must be prescribed by a doctor and are registered in a national 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 hold 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 specifically[8].

## Statistics analysis

Students two-tailed *t*-test and Pearson`s **2 test were used to test differences between groups as appropriate and Fisher exact test in cross-tables with numbers < 7.

# Results

Patient characteristics are given in Table 1 and demonstrate that the retrospective and prospective groups were comparable with regards to gender, age, American Society of Anesthesiologists (ASA) severity, CRP and CT-scores. As expected, the use of radiological investigations was more extensive in the prospective group as compared to the retrospective group, as shown in table 2. In the prospective group, all patients were investigated with some radiological examination, and many (40%) with three radiological tools: US, CT and magnetic resonance imaging (MRI). Biliary and alcoholic pancreatitis was the most frequent etiology in both the retrospective and prospective group, 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. 58% (*n =* 33) of patients used these drugs with 26 patients using one of these medications and 12 patients using more than 2 medicines associated with AP as a side-effect (Table 5). Between 31 and 310 users of these medicines are expected to develop AP due to these medicines. In our prospective group, detailed description of medication use was noted and Table 5 summarizes 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 as compared to the retrospective group (26% *vs* 6%. respectively). This may be due to more thorough questioning of the patient at time of admission and further stresses the importance of finding the causative factor as this may increase the likelihood of optimizing treatment, improving prognosis and reducing risk of recurrence.

# Discussion

The most common cause of AP in Europa 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-Balter et al found the etiology to be bile stone in 17.1%, alcohol in 14.6% and others/unknown in 67.8% of the patients[10]. The discrepancy of these findings as compared to our cohort may be due to the degree of investigations being less in out-patient cases with assumed lower severity and thereby less extensively 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 was performed. However, in a significant minority, uncertainty will exist when several possible causes such as bile stones, alcohol and medicines are identified. It is not possible to be certain which then 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 ultrasonography (USG), 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 with magnetic resonance cholangiopancreaticography (MRCP), endoscopic ultrasonography (EUS) and possibly endoscopic retrograde cholangiopancreaticography (ERCP) as indicated. Repetition of endoscopic ultrasonography is also indicated as this increases the sensitivity of diagnosing bile stones[12]. If no cause is found, some authors suggest empirical treatment of possible biliary cause with either cholecystectomy or ERCP and papillotomy[3]. However, these procedures are surgical with possible complications as well as death[13].

## bile stone and alcohol

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

Alcohol is a known independent risk factor in the development of both acute and chronic pancreatitis and patients in the prospective group were specifically questioned with regards to type, amount and timing of consumption prior to admission. However, it is also well-known that many of these patients have consumed alcohol many times prior to 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 quite variable volumes and types of alcohol in single or multiple occasions without any direct correlation to 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 discharge, the general practitioner was also notified of the complete course of the hospital admission in order to provide a suitable follow-up.

Smoking in combination with alcohol has also been suggested to further increase the risk of pancreatitis[15]. We therefore aim to inform 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]. The causative link to the development of AP is difficult to document[16]. Several case reports as well as larger studies have given 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 due to 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 may be due to 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 epidemiologic 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 to non-users, and increasing doses of Simvastatin being 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 (Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Atorvastatin, Rosorvastatin)[7]. Simvastatin and other statins (*n =* 14) were the most commonly used pancreatogenic drugs found in our prospective cohort. Statins are also commonly used 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 may possibly be due to the more common presence of gallstones and hypertriglyceridemia[21]. These confounding variables must therefore be considered and a causative link is difficult to establish in the individual patient due to 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 accurately determine 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 introduction of any new medication, the patient should be informed to contact their physician if they experience any side-effects. If on detailed medical history a drug is the most likely etiology, the necessity of drug continuation must outweigh the risk of recurrence of acute pancreatic. The possibility of re-challenge and possibly 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

Hyper-triglyceridemia is a cause of AP secondary to fatty acid-induced acinar cell damage[23], and may also be associated with a more severe course of 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 definition of the true cause difficult.

Tumor in the pancreas was also considered a cause of pancreatitis on about 1.5 and 1.9% in our cohorts, as in 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 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 suggesting that genetic traits may be a disposition for development of AP. In one study the authors suggested that about 1/3 of patients with acute recurrent pancreatitis carried mutations for hereditary pancreatitis including trypsinogen (PRSS1), cystic fibrosis transmembrane conductor regulator (CFTR), achymotrypsiogen 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 development of AP. One might speculate that such genetic traits may in some way 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 specter of etiological factors such as drugs, infections, trauma, anatomic abnormalities and secondary to Ascaris in the pancreatic duct[1].

## Limitation of study

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

Knowledge of etiology is of crucial importance in order to optimize treatment and thereby improve prognosis. Our data shows that we in many cases of AP can find several possible etiologies. Bile stone and alcohol remain the main causes of AP in about 60% of Norwegian patients and these frequencies are mainly unchanged despite more detailed medical history and radiological investigations conducted in the prospective sample as compared to the retrospective group. Drugs associated with AP are in widespread use but a definite causality is difficult to prove in most cases. We therefore recommend meticulous assessment of the patient by means of detailed medical history and radiological investigation in order to broaden our understanding in establishing 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 specter of drugs as a possible cause of acute onset pancreatitis.

***Innovations and breakthroughs***

In this article, the authors report a large cohort of retrospectively reviewed patients with AP comparing them to a prospectively included group investigated more broadly in order to identify the cause of disease onset.

***Applications***

A more detailed history and radiological evaluation may determine at least one possible etiology in almost all cases of AP. The clinician should therefore ensure that detailed investigation of possible etiology has been done in order 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 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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## Table 1 Patient characteristics n (%)

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Prospective group** | **Retrospective group** | ***p*-value** |
|   | (*n =* 57) | (*n =* 613) |   |
| 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 (0-592) |   |
| Severe pancreatitis |   |   |   |
|  CRP | 31 (54) | 276 (45) | < 0.975 |
|  CT  | 3/30 (10) | 33/327 (10) | < 0.945 |
| Complications |   |   | < 0.66 |
|  None | 45 (79) | 497 (81) |   |
|  Systemic | 8 (14) | 89/598 (14.9) |   |
|  Local | 4 (7) | 43/599 (7.2) |   |
| Mortality | 1 (2) | 36 (6) | < 0.356 |
| Severity of pancreatitis |   |   | > 0.713 |
|  Mild | 50 | 521 |   |
|  Moderate severe | 2 | 54 |   |
|  Severe | 5 | 38 |   |

CT: computed tomography.

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

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Prospective group** | **Retrospective group** | ***p*-value** |
|  | (*n =* 57) | (*n =* 585 evaluable) |  |
| 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) | 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.

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Prospective group** | **Retrospective group** | ***p*-value** |
| **(*n =* 57)** | **(*n =* 613)** |
|   | Patients | Patients using medicines1 | Patients | Patients using medicines1 |   |
| 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) |   |   |
| Medicines1 | 11 (19.3) | 11 (100) | 15 (2.4) | 15 (100) |   |
| Unknown2 | 4 (7.0) | 0 | 182 (29.7) | 0 |   |
| All | 57 (100) | 33 (58) | 613 (100) |   |   |

1Medicines associated with pancreatitis as a side-effect; 2Two 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 |

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

|  |  |
| --- | --- |
| **Use of possible pancreatogenic medication in 33 patients with AP** |  |
| **Use of a singe drug** | **Use of two drugs** | **Use of three drugs** |
| Name | *n* |   | *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 |

AP: acute pancreatitis.