Changing of the Etiology of Acute Pancreatitis after Using a Systematic Search

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Background: *Alcohol and gallstone are the 2 most common etiologies of acute pancreatitis (AP). In Thailand, alcohol has been believed to be the leading etiology of AP. However, a thorough and systematic search may discover real etiology of AP.*
Material and Method: *During 2006 to 2007, seventy-eight patients with AP were prospectively searched for the etiology by: 1. Performing liver chemistry tests and transabdominal ultrasonography (US) for gallstone in every case; 2. Measuring serum triglyceride and calcium in every case; 3. Investigating definite drugs use or other identified etiology; 4. Asking about the amount of alcohol ingestion (amount > 80 g/day for > 5 years was required for alcoholic AP; 5. Performing CT scan (if age > 40 years) and EUS if no etiology was identified. Results were compared with the retrospective data from medical records of 66 AP patients during 2003-2005.*
Results: *Of the 78 patients, the etiologies were alcohol in 32 (41%), gallstones in 29 (37%), miscellaneous in 13 (17%) and idiopathic AP in 4 patients (5%). When compared with the retrospective data of the 66 patients over the past 3 years, the etiologies were alcohol 53%, gallstone 22%, miscellaneous 11% and idiopathic 14%. Among the 45 patients of the study period (58%) who consumed alcohol more than the defined threshold for alcoholic AP, 13 (29%) were found to have other explainable causes of AP, i.e gallstones in 10, hypertriglyceridemia in 2 and AIDS cholangiopathy in 1 patient.*
Conclusion: *Alcohol was probably over-diagnosed as a leading etiology of AP in the past. A systematic search of the etiologies lowered the frequency of alcoholic and idiopathic AP but discovered more patients with gallstone pancreatitis. One-fourth of AP patients who were heavy drinkers had other explainable etiologies of AP.*

Keywords: *Acute disease, Alcohol drinking, Causality, Etiology, Pancreatitis, Alcoholic*

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Acute pancreatitis (AP) is an inflammatory condition of the pancreas with varying local and systemic involvements. Alcohol and gallstone are the two leading etiologies of AP worldwide, accounting for approximately 80% of the patients, although the leading etiology may differ among countries[1,2]. However, most published data from Western or Asian countries[1-4] now showed an increasing trend for gallstone pancreatitis to be the leading etiology of AP. In Thailand, alcohol has been believed to be the leading etiology of AP[5]. Although a recent retrospective study of surgical patients with severe AP showed an increasing rate of gallstone pancreatitis, the most common etiology, however, remained alcohol[6].

It is now clear that it is essential to diagnose gallstone pancreatitis because of its impact on patient management, such as endoscopic sphincterotomy and cholecystectomy to prevent recurrence. Thus, most guidelines recommend testing liver chemistries and performing transabdominal ultrasonography (US) in every patient with AP[7-10]. Testing of serum triglyceride and calcium in every patient is also advocated by a recent consensus[11,12]. However, now the more difficult issue becomes: how to diagnose alcoholic AP; so because, so far, there are no clear-cut guidelines about

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how to diagnose alcoholic AP[7-10] with no definite threshold amount of alcohol consumption exists to diagnose alcohol as an etiology of AP[11,13]. Currently, most criteria in the literature for diagnosing alcoholic AP in the literatures are based on arbitrary thresholds rather than evidence. Thus, regarding patients who were diagnosed with alcoholic AP through the surveyed history of alcohol consumption alone, the real culprits of AP may be something else. A thorough and systematic search before diagnosing alcoholic AP may discover other explainable etiologies of AP.

The objective of this study is to determine the etiology of AP prospectively using a systematic search approach and to compare the results with the retrospective data of the etiology of AP before the study period.

Material and Method

During January 2006 to December 2007, all consecutive patients who were diagnosed as AP in our institute were included in the study. AP was diagnosed by at least 2 of the 3 criteria of the followings; acute abdominal pain, elevated serum amylase or lipase of more than 3 folds of normal upper limits and an imaging study (CT scan or MRI) consistent with AP. All patients' etiologies were investigated for the etiology using a systematic search, which included the following:

1) Performing liver function testing and transabdominal US in every patient. The presence of elevated ALT more than 3 folds of normal upper limit[14] or detection of gallstones by US or bile duct stone by CT scan or endoscopic retrograde cholangiography (ERCP) in a patient was diagnosed as gallstone pancreatitis.

2) Measuring serum triglyceride and calcium in every patient[12].

3) Considering other well-established explainable causes of AP e.g definite drugs causing AP, active connective tissue diseases, abdominal trauma, etc[12].

4) Asking patients about the amount of their alcohol consumption. The amount of more than 80 g/day of ethanol for more than 5 years was arbitrarily considered as an etiology[13].

5) Performing abdominal CT scan if all the above etiologies were negative and the patient's age was more than 40 years[15].

6) Performing EUS if all of the above etiologies were negative[16].

7) Diagnosing idiopathic AP if all of the above work-ups were negative.

The diagnostic etiologies obtained from this systematic search were compared with the retrospective data from medical records of all patients with AP diagnosed during the 3 years preceding to this study (2003 to 2005). Data were presented in per cent of each etiologic group.

The present study was approved by the Siriraj Ethics Committee.

Results

Over the 2-year-period, there were 78 patients diagnosed as AP in our institute. Sixty patients (77%) were male and the mean age at diagnosis was 46 $\pm$ 16 years (range 15-87 years). The etiologies of AP after using a prospective systematic search were alcohol in 32 (41%), gallstones in 29 (37%), miscellaneous in 13 (17%), and 4 (5%) idiopathic AP. Details of the etiologies were shown in Table 1.

Comparison of the etiology of AP with those during 2003-2005 is shown in Table 2. Overall, there were 66 patients over the 3-year period. The etiologies were alcohol in 35 (53%), gallstones in 15 (22%), miscellaneous in 7 (11%) and idiopathic in 9 (14%). Fig. 1 demonstrates the changes of the etiologies of AP before and after using the systematic search. The frequency of alcoholic AP and idiopathic AP declined, frequency of gallstone pancreatitis rose and the miscellaneous causes remained stable after using a systematic search approach.

Table 1. Etiologies of AP in 78 patients after using a systemic search

Etiology	Number of patients (%)
Alcohol	32 (41)
Gallstone	29 (37)
Miscellaneous	13 (17)
Hypertriglyceridemia	5
Hypercalcemia	1
Drugs	2
SLE	1
HIV	1
Intraductal papillary mucinous neoplasm (IPMN)	1
Sphincter of Oddi dysfunction (SOD) type 1	1
Ascariasis	1
Idiopathic	4 (5)
Total	78 (100)

Table 2. Comparison of the etiologies of AP before and after using a systemic search

Etiologies	No. of patients, n (%)				
	2003	2004	2005	Total from 2003-2005	After systemic search 2006-2007
Alcohol	9 (50)	14 (54)	12 (55)	35 (53)	32 (41)
Gallstone	4 (22)	6 (23)	5 (23)	15 (22)	29 (37)
Miscellaneous	2 (11)	2 (8)	3 (13)	7 (11)	13 (17)
Hypertriglyceridemia		1	2	3	5
Hypercalcemia	1			1	1
Drugs			1	1	2
SLE		1		1	1
HIV					1
IPMN					1
Ischemic	1			1	
SOD type 1					1
Parasites					1
Idiopathic	3 (17)	4 (15)	2 (9)	9 (14)	4 (5)
Total	18 (100)	26 (100)	22 (100)	66 (100)	78 (100)

Of the 78 patients in the study period, 45 (58%) had a history of alcohol consumption that exceeded the defined threshold for the diagnosis of alcoholic AP in this study. However, 13 patients (29%) had other explainable etiologies of AP, which were gallstones in 10 patients (22%), hypertriglyceridemia in 2 patients (4%) and 1 patient (2%) associated with AIDS cholangiopathy.

Discussion

Diagnosis of the etiology of AP is important in guiding the management plan and the prevention of recurrence for the patients. Thus, most guidelines and consensuses suggested searching for gallstone[8-11,17], hypertriglyceridemia[11,12] and hypercalcemia[11,12] in every patient. In contrast, diagnosis of alcohol as an etiology of AP is more difficult and not straightforward. Although the probability of developing alcoholic AP is increased with the amount and duration of alcohol consumption[13], it becomes clear that there is no definite threshold for the amount of alcohol consumption that will cause AP[13]. This is attributed to the complex relationship between the amount of alcohol consumption and the development of AP, including the inaccuracy of history taking in alcoholic patients, the role of genetic predisposition[18] and finally, because alcoholic patients are also at risk for pigment gallstones[19] and hypertriglyceridemia, which can themselves cause AP. Therefore, in the authors' opinion, alcoholic AP should be diagnosed after exclusion of the other etiologies. Although there have been a lot of epidemiologic studies on the etiology of AP from different centers, countries and continents[1], many of them were retrospective or did not clearly define their criteria for diagnosing alcoholic AP. A prospective systematic search would be more accurate in discovering the etiology of AP.

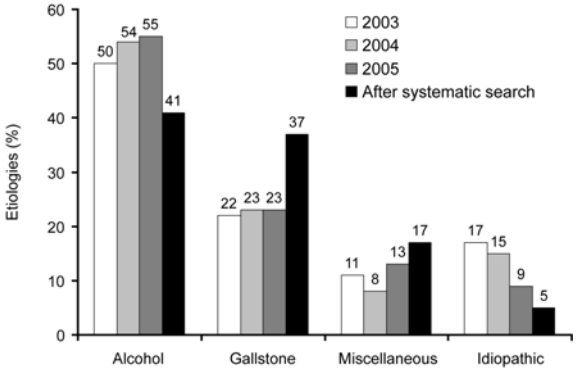

Fig. 1 Comparison of the etiologies of AP before and after using a systemic search

Results of the present study showed that after using a systematic search of the etiology of AP and, particularly, by exclusion of other potential etiologies before diagnosing alcoholic AP, the frequency of alcoholic AP declined and that of gallstone pancreatitis rose when they were compared with the retrospective

data 3 years prior to the study. Moreover, idiopathic AP became uncommon and accounted for only 5% of AP.

Although the present study is relatively small, one may argue that the differences in etiologies between the study period and the preceding 3 years are primarily because of the incomplete case collection in the past as reflected by the numbers of patients in the study period (78 patients in 2 years) which is higher than the 18-22 cases per year during the 3 preceding years. However, data of each preceding year prior to the present study showed a quite constant rate of alcoholic AP (50-55%) and gallstone pancreatitis (20-22%), which are difficult to explain simply by reason of incomplete case recordings. Furthermore, the etiology was clearly and abruptly changed during the study period after using a systematic search; the quite constant rates of the miscellaneous causes (8-17%) and the slight decline of idiopathic AP from 9-17% to 5% also supported the view that the main change was between alcohol and gallstone pancreatitis and the reduction of idiopathic AP.

Another interesting finding in the present study is that 58% of the 78 patients in the study period would have been diagnosed as alcoholic AP if the diagnosis was based solely on the amount of alcohol intake without taking into account of other etiologies. This number (58%) is close to the 50-55% rates of alcoholic AP diagnosed during 2003-2005. However, the systemic search discovered gallstones and hypertriglyceridemic pancreatitis in over one-fourth of these alcoholic patients, hence lowering the frequency of alcoholic AP to 41%. These results likely indicated that the high rates of alcoholic AP found in the past might be due to the over-diagnosis of alcoholic AP.

Adding a CT scan (in patients older than 40 years)[15] and EUS before diagnosing patients as idiopathic AP in the present study have been advocated by some investigators to search for small ampullary tumor, pancreatic tumor and microlithiasis[16]. In the present study, the authors discovered 1 patient with sphincter of Oddi dysfunction type 1 through using EUS followed by ERCP, and another with IPMN discovered by CT scan and EUS.

In conclusion, alcohol might previously have been over-diagnosed as a leading etiology of AP in Thailand. A systematic search lowered the frequency of alcoholic AP and discovered more patients with gallstone pancreatitis, which would definitely impact patients' management. Approximately one-fourth of AP patients with history of heavy alcoholic drinking had other explainable causes of AP, mainly gallstones and hypertriglyceridemia.

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ความเปลี่ยนแปลงของสาเหตุของโรคตับอ่อนอักเสบเฉียบพลัน หลังการใช้แนวทางการสืบค้นสาเหตุอย่างเป็นระบบ

สุพจน์ พงศ์ประสบชัย, รุจิเรข ธรรมเจริญ, สถาพร มานัสสถิตย์

ภูมิหลัง: *แอลกอฮอล์และนิ่วทางเดินน้ำดีเป็น 2 สาเหตุที่พบบ่อยที่สุดของตับอ่อนอักเสบเฉียบพลัน ในประเทศไทยเชื่อกันว่าแอลกอฮอล์เป็นสาเหตุที่พบมากที่สุด แต่หากมีการหาสาเหตุอย่างถูกต้องและเป็นระบบน่าจะพบสาเหตุที่แท้จริง*

วัสดุและวิธีการ: *ผู้ป่วยทุกรายที่ได้รับการวินิจฉัยเป็นตับอ่อนอักเสบเฉียบพลันระหว่างปี พ.ศ. 2549-2550 จะได้รับการสืบค้นหาสาเหตุอย่างเป็นระบบโดย 1. ตรวจเลือดการทำงานของตับและอัลตราซาวด์ทางเดินน้ำดีทุกราย 2. ตรวจระดับไตรกลีเซอไรด์และแคลเซียมในเลือดทุกราย 3. ตรวจหายาหรือสาเหตุอื่น ๆ ที่เป็นไปได้ 4. ถามปริมาณการดื่มแอลกอฮอล์ (ปริมาณเอธานอลมากกว่า 80 กรัมต่อวัน เป็นเวลามากกว่า 5 ปีจึงจะถือว่าเป็นสาเหตุ) 5. ตรวจเอกซเรย์คอมพิวเตอร์ช่องท้อง หากยังไม่พบสาเหตุและผู้ป่วยอายุมากกว่า 40 ปี 6. ตรวจส่องกล้องอัลตราซาวด์หากยังไม่พบสาเหตุ จึงให้การวินิจฉัยเป็นตับอ่อนอักเสบเฉียบพลันที่ไม่ทราบสาเหตุ สาเหตุที่ได้จะนำไปเปรียบเทียบกับข้อมูลสรุปจากเวชระเบียนของผู้ป่วยตับอ่อนอักเสบเฉียบพลันในปี พ.ศ. 2546-2548*

ผลการศึกษา: *มีผู้ป่วยทั้งสิ้น 78 ราย ในช่วง 2 ปีของการศึกษา สาเหตุเป็น แอลกอฮอล์ 32 ราย (ร้อยละ 41) นิ่วทางเดินน้ำดี 29 ราย (ร้อยละ 37) สาเหตุอื่นๆ 13 ราย (ร้อยละ 17) และไม่ทราบสาเหตุ 4 ราย (ร้อยละ 5) เมื่อเปรียบเทียบกับข้อมูลจากเวชระเบียนของผู้ป่วย 66 รายในช่วง 3 ปีก่อนการวิจัยพบว่าสาเหตุเป็นแอลกอฮอล์ร้อยละ 53 นิ่วทางเดินน้ำดีร้อยละ 22 สาเหตุอื่น ๆ ร้อยละ 11 และไม่ทราบสาเหตุร้อยละ 14 ผู้ป่วย 45 รายในช่วงการวิจัย (ร้อยละ 58) มีประวัติแอลกอฮอล์มากถึงเกณฑ์การวินิจฉัยตับอ่อนอักเสบจากแอลกอฮอล์ได้ แต่ 13 ราย (ร้อยละ 29) พบสาเหตุอื่น ๆ ที่สามารถเป็นสาเหตุของตับอ่อนอักเสบเฉียบพลันได้ ได้แก่ นิ่วทางเดินน้ำดี 10 ราย ภาวะไตรกลีเซอไรด์ในเลือดสูง 2 ราย และโรคทางเดินน้ำดีในผู้ป่วยเอดส์ 1 ราย*

สรุป: *ในอดีตแอลกอฮอล์อาจได้รับการวินิจฉัยเป็นสาเหตุของตับอ่อนอักเสบเฉียบพลันมากเกินจริง การสืบค้นหาสาเหตุอย่างเป็นระบบพบแอลกอฮอล์เป็นสาเหตุลดลง แต่เพิ่มสาเหตุที่เกิดจากนิ่วทางเดินน้ำดี และสาเหตุอื่น ๆ มากขึ้น หนึ่งในสี่ของผู้ป่วยที่ดื่มแอลกอฮอล์สามารถพบสาเหตุอื่นๆ ของตับอ่อนอักเสบเฉียบพลันได้โดยเฉพาะนิ่วทางเดินน้ำดี*