Incidence and Clinical Features of Hyperlipidemic Acute Pancreatitis From Guangdong, China

A Retrospective Multicenter Study

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Objective: This study aimed to investigate the clinical features and incidence trends of hyperlipidemic acute pancreatitis (HLAP) of multicenter studies in Guangdong, China, for 15 years.

Methods: The medical records of 1582 patients with acute pancreatitis who were admitted to 4 general hospitals of Guangdong from January 1990 to December 2005 were reviewed. The inpatient medical and radiologic records were reviewed to determine clinical features, severity, complications, mortality, and recurrence rate.

Results: A total of 7.8% (123/1582) patients met the HLAP criteria. Incidence of HLAP was approximately 2.6 times increased during 15 years (3.4% in 1990–1994, 5.9% in 1995–1999, and 8.9% in 2000–2005, respectively) and ranged from 3.3% to 15.5% in 4 hospitals across Guangdong. A history of diabetes was present in 31.7% and alcohol use in 18.7%. The mean (SD) triglyceride levels were 13.6 (7.2) mmol/L. Amylase was elevated higher than normal in 81.2% but only 2 times normal in 17.1% and 3 times normal in 37.6%. The frequency of severe acute pancreatitis, organ dysfunction, rate of recurrence, and mortality of HLAP was significantly higher than biliary-induced pancreatitis.

Conclusions: The incidence of HLAP had significantly increased during the past 15 years with a clear geographic variation and remarkable severity and recurrent trend.

Key Words: hyperlipidemia, hypertriglyceridemia, acute pancreatitis, incidence, clinical features

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Because Speck1 first described the association between hyperlipidemia and acute pancreatitis (AP) in 1865, many studies have found that hyperlipidemia, especially severe hypertriglyceridemia (HTG), can cause AP, in addition to gallstone disease and alcohol-induced disease. Hyperlipidemia can be a primary cause, which occurs in 1.3% to 12.3% of patients with AP.2–5 The ratio of this etiology has a wide geographic variation, and the evidence for time trends of hyperlipidemic AP (HLAP) is less clear. In China, with the rapid economic development, Chinese lifestyle changed gradually in latest 3 decades. Studies show that the prevalence of HTG had risen from 13.3% to 30.2% between 1992 and 2002 in Beijing.6 However, the relationship between the increasing number of HTG and AP incidence remains unclear.

The evidence for severity and prognosis of HLAP is still controversial. It is generally believed that the outcome of HLAP is no different from AP of other causes, whereas a few studies indicated that patients with HTG seemed to have more severe acute pancreatitis (SAP) and higher complication rates.7–9 In this study, we choose 4 representative regions (Guangzhou, Meizhou, Shantou, and Shaoquan) of Guangdong as research targets and analyzed hospitalized data of patients with AP in multicenter of Guangdong for 15 years, which was the first largest patient series with HLAP investigating the incidence, severity, and outcome in China. The first aims of this study were to establish the incidence and clinical features (presentation, severity, complications, and outcome) for HLAP in Guangdong. Further aims were to assess trends over time in incidence and to investigate variation in incidence geographically across Guangdong.

MATERIALS AND METHODS

Patients

From January 1990 to July 2005, all patients who have AP and admitted to Guangzhou First People’s Hospital that is affiliated to Guangzhou Medical University (represents Cantonese culture), Meizhou People’s Hospital (represents Hakka culture), Yue Bei People’s Hospital of Shaoguan (represents mountainous area), and Shantou Central Hospital (represents Chaoshan culture) were included. Patients were excluded if they did not undergo serum lipid detection within 24 hours after hospitalization. This study was approved by the ethics committees of the hospitals.

Diagnosis

The diagnostic criteria for AP formulated at revision of the 1992 Atlanta Classification of AP were used.10

SAP was diagnosed when signs of organic dysfunction (shock, systolic arterial blood pressure of <90 mm Hg; respiratory dysfunction; <60 mm Hg PaO2; renal dysfunction, serum creatinine level >20 mg/dL) and/or local complications (necrosis, pancreatic abscess, or a pseudocyst) were present.

Two etiologies of AP (gallstone and HTG) were distinguished as follows: biliary-induced pancreatitis (ABP) was defined if gallstones were identified in the gallbladder or in the biliary tract or in both by radiologic examinations (ultrasonography or computed tomographic [CT] scan), and HLAP was diagnosed if serum triglyceride level reached 11.3 mmol/L or above 5.6 mmol/L with lactic serum on admission.

Methods

The inpatient medical and radiologic records were reviewed, and demographic profile, etiology, presentation, disease severity scores (Ranson score and Balthazar CT severity index [CTSI]), complications (local or organic dysfunction), deaths, length of hospital stay, and recurrence rates were recorded and analyzed.
All patients with AP admitted to hospitals were divided into 3 groups by the following diagnostic dates: 1990 to 1994, 1995 to 1999, and 2000 to 2005. The number of AP and HLAP and the proportion of etiologic factors (gallstone and hyperlipidemic) were compared among these 3 periods.

According to etiology, these patients were divided into HLAP group (n = 123) and ABP group (n = 828). A comparison of the demographic profile, disease severity scores, complications, and deaths was made in between the 2 groups.

Statistical Analysis

Data were expressed as mean (SD) or percentage. Data in normal distribution were analyzed using t test. Data in abnormal distribution were analyzed using Wilcoxon rank sum test. Categorical data were analyzed using $\chi^2$ test. $P$ value less than 0.05 was considered statistically significant.

RESULTS

Trends in Incidence of HLAP

During the 15 years, AP was diagnosed in 2367 patients in 4 tertiary hospitals. However, 785 (33.2%) cases of patients who did not undergo serum lipid detection on admission within 24 hours were excluded. In total, 1582 cases of patients who were hospitalized with AP were included in this series.

The overall number of AP in Guangdong increased significantly, especially rapid growth after 2000 (Fig. 1). The percentage of patients who underwent serum lipid detection was 24.3% (274/1132 patients) in 1990 to 1994, 59.4% (439/633 patients) in 1995 to 1999, and 76.9% (1055/1372 patients) in 2000 to 2005 ($P < 0.05$). Failure to investigate HTG may lead to an underestimation of HLAP. Hyperlipidemia as the etiology of AP got more and more attention by the clinicians over the past 15 years.

In total, HLAP was diagnosed in 7.8% (n = 123) of all patients with AP. Meanwhile, the proportion of HTG as etiologic factor of AP was 3.4% (3/88 patients) in 1990 to 1994, 5.9% (26/439 patients) in 1995 to 1999, and 8.9% (94/1055 patients) in 2000 to 2005. The incidence of HLAP in 2000 to 2005 was 2.3 (61/26) in patients age younger than 44 years. Most patients with HLAP were young male; male/female ratio was 1.9 (81/42) in all patients with HLAP, and 0.7 (336/492) in all patients with ABP, respectively ($P < 0.05$). Male/female ratio was 1.5 (52.9% vs 24.3%) in patients age younger than 44 years. Male/female ratio was 1.5 (52.2% vs 46.6%) in 1990 to 1994, 52.6% (439/828 patients) in 1995 to 1999, and 52.9% (558/1055 patients) in 2000 to 2005 ($P > 0.05$).

Geographic Variation of HLAP

There was a clear geographic variation of HLAP. Table 1 shows the number of patients with AP collected from the 4 tertiary hospitals, percentage of serum lipid detection, and incidence of HLAP across Guangdong. Hyperlipidemia was considered the cause in 5.7% of cases from Guangzhou, 5.9% from Shantou, 15.5% from Meizhou, and 3.3% from Shaoguan. At the regional level, the highest rates were in Hakka area (Meizhou), and the lowest rates were in the mountainous area (Shaoguan).

Demographics of Patients With HLAP

The mean (SD) age was 40.8 (10.9) years in HLAP, and 58.8 (15.6) years in ABP, respectively. The mean age for HLAP is significant lower than ABP ($P < 0.05$). Most of the patients with HLAP are young and middle-aged, approximately 95.1%. Only 4.9% of the patients with HLAP are elderly (age older than 60 years). However, 52.5% of the patients with AP are elderly ($P < 0.05$). Male/female ratio was 1.9 (81/42) in all patients with HLAP, and 0.7 (336/492) in all patients with AP, respectively. Most patients with HLAP were young male; male/female ratio was 2.3 (61/26) in patients age younger than 44 years.

Medical History of HLAP

Patients with HLAP often have more comorbid conditions that go hand in hand with hypertriglyceridemia. Diabetes mellitus was diagnosed in 32% of the patients, diabetes history in 33.3% (13/39) of the patients, and diabetes established on admission in 66.7% (26/39) of the patients. Only 19% of the patients gave a history of alcohol use or abuse. There was a history of overeating in approximately 10% of the patients. A total of 27% of the patients had a history of smoking. Fifty-five (approximately 45%) patients gave a history of fatty liver. Four (3.3%) women had AP attack during pregnancy. Approximately 40% of the patients had nondiabetic, nonalcoholic, and nondietary factors.

Clinical Features of HLAP

Table 2 shows symptoms and signs on admission. Compared with APB, there was no significant difference among the symptoms of HLAP. The biliary obstruction–related symptom such as jaundice is more common in APB (8.9%) than that in HLAP (0.8%). Ascites and abdominal distension are more common in HLAP than that in APB (11.4% vs 5.9%, 22.8% vs 11.8%).

Table 3 shows initial laboratory values and complications. Serum amylase elevations were higher than normal in 81.2% of the patients with HLAP but only 2 times greater than normal in 17.1% of the patients and 3 times greater than normal in 37.6% of the patients, whereas amylase elevations were higher than normal in 89.8% of the patients with APB; 2 times greater than normal in 11.0% of the patients, and 3 times greater than normal in 66.0% of the patients, respectively ($P < 0.05$). The mean (SD) serum triglyceride (TG) values in HLAP were significantly higher than in APB (13.6 [7.2] vs 1.2 [1.14] mmol/L). Calcium average levels of patients with HLAP are less than that of patients with APB; diabetes was diagnosed in 31.7% of the patients with HLAP, so patients also have high average blood glucose levels.

Compared with APB, HLAP had a higher frequency of SAP, higher CTSI scores, and higher incidence of complications (respiratory or renal or heart failure). Hyperlipidemic acute pancreatitis also had a higher recurrence rate (30.1%) and...
mortality (4.1%) and the time of death within 1 week of admission, but there were no significant differences in the Ranson score and frequency of local complications between HLAP and ABP.

**DISCUSSION**

In this study, we investigated the trends of incidence, clinical features, severity, and mortality of HLAP in a large consecutive case series of patients in Guangdong. All diagnosed cases in a 15-year period were collected; thus, we believe that this group of patients can correctly reflect the clinical spectrum of the disorder. The retrospective nature of this study may limit the accuracy of the information provided. Despite these limitations, we believe that our study can supply some useful information to incidence and clinical features of HLAP in Guangdong.

**Incidence of HLAP**

Hyperlipidemia is a well-recognized cause and the most common etiology of AP next to gallstone and alcohol-induced disease. Both primary and secondary disorders of lipoprotein metabolism are associated with HLAP. The frequency of HTG in patients with AP is reported to be 32.5% to 56%, but most of these studies have mild degrees of hypertriglyceridemia. Mild-to-moderate elevations in TG are very common in the early phase of AP of any cause. It is generally believed that a serum TG level above 1000 mg/dL (approximately 11.3 mmol/L) or between 500 and 1000 mg/dL (approximately 5.6–11.3 mmol/L) and accompanying lactic acid serum should be considered as etiologies of AP.

Following these criteria, Fortson et al. reported that the frequency of HTG as an etiologic factor ranged from 1.3% to 3.5% in a review of 70 HLAP cases collected over 12 years. The investigation of AP in 5 European countries reported approximately 6.3% to 12.3%, and the cohort study found that AP occurred in 20.2% in patients with severe hypertriglyceridemia. In our study, in the 4 hospitals of Guangdong, the incidence of HLAP ranged from 3.3% to 15.5% (average, 7.8%), which is similar to Taiwan and Greece but slightly higher than the 5 European countries.

Interestingly, the incidence of HLAP in Guangdong increased gradually year by year, which had increased approximately 2.6 times during the 15 years. The US and European studies from time trends suggest that AP has increased sharply over the past several decades, especially when caused by gallstone disease, but it did not report any researches on HLAP. In Japan, there were 4 pancreatitis cases associated with HTG in the 1970s, 12 cases in the 1980s, and 17 cases in the 1990s. The number of cases increased possibly because of Westernization of diet habits and better recognition of this disease. Our data are similar as those in Japan. The most likely explanation is that China had led to a rise in the frequency of HTG. Studies showed that the prevalence of hypertriglyceridemia in China was 13.3% in 1992. By 2002, the prevalence was 30.2%.

In this study, data also show geographic variation in incidence of HLAP across Guangdong. At the regional level, the highest rates were in the northeast of Guangdong (Meizhou, Shantou, and Shaoguan) compared to the southwest (Guangzhou and Shantou). This may be related to the different diet habits and lifestyle in these regions.

**TABLE 1. Number of Patients Admitted in 4 Hospitals With AP (Total Number Overall as well as Number Due to Biliary, HTG, or Other Causes)**

<table>
<thead>
<tr>
<th>Hospitals</th>
<th>Cases of AP</th>
<th>Percentage of Lipid Test</th>
<th>Cases of HLAP, n (%)</th>
<th>Cases of ABP, n (%)</th>
<th>Cases of Other AP, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guangzhou</td>
<td>613</td>
<td>68.8%</td>
<td>35 (5.7)</td>
<td>387 (63.1)</td>
<td>191 (31.1)</td>
</tr>
<tr>
<td>Shantou</td>
<td>529</td>
<td>80.9%</td>
<td>31 (5.9)</td>
<td>273 (51.6)</td>
<td>225 (42.5)</td>
</tr>
<tr>
<td>Meizhou</td>
<td>349</td>
<td>72.7%</td>
<td>54 (15.5)</td>
<td>122 (34.9)</td>
<td>173 (49.6)</td>
</tr>
<tr>
<td>Shaoguan</td>
<td>91</td>
<td>26.6%</td>
<td>3 (3.3)</td>
<td>46 (50.6)</td>
<td>42 (46.2)</td>
</tr>
<tr>
<td>Total</td>
<td>1582</td>
<td>66.8%</td>
<td>123 (7.8)</td>
<td>828 (52.3)</td>
<td>631 (39.9)</td>
</tr>
</tbody>
</table>

**TABLE 2. Admission Findings of HLAP and ABP**

<table>
<thead>
<tr>
<th>Complication</th>
<th>HLAP</th>
<th>ABP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>123 (100)</td>
<td>824 (99.5)</td>
<td>0.574</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>93 (75.6)</td>
<td>654 (79.0)</td>
<td>0.395</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>28 (22.8)</td>
<td>98 (11.8)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Jaundice</td>
<td>1 (0.8)</td>
<td>74 (8.9)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Fever</td>
<td>28 (22.8)</td>
<td>225 (27.2)</td>
<td>0.302</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>108 (87.8)</td>
<td>688 (83.1)</td>
<td>0.187</td>
</tr>
<tr>
<td>Guarding</td>
<td>32 (26.0)</td>
<td>172 (20.8)</td>
<td>0.186</td>
</tr>
<tr>
<td>Ascites</td>
<td>14 (11.4)</td>
<td>49 (5.9)</td>
<td>0.023*</td>
</tr>
</tbody>
</table>

Values are presented as n (%).

*P < 0.05. Differences between the two groups were evaluated using χ² test or t test.

2% and 6.9%, respectively. In the Asia-Pacific region, Taiwan reported approximately 6% to 12.3%, and the cohort study found that AP occurred in 20.2% in patients with severe hypertriglyceridemia. In our study, in the 4 hospitals of Guangdong, the incidence of HLAP ranged from 3.3% to 15.5% (average, 7.8%), which is similar to Taiwan and Greece but slightly higher than the 5 European countries.

**TABLE 3. Clinical Features of HLAP and ABP**

<table>
<thead>
<tr>
<th>Complication</th>
<th>HLAP</th>
<th>ABP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum amylase, mean (SD), mmol/L</td>
<td>571.8 (541.3)</td>
<td>922.1 (842.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>TG, mean (SD), mmol/L</td>
<td>13.6 (7.2)</td>
<td>1.2 (1.14)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Glucose, mean (SD), mmol/L</td>
<td>10.7 (5.7)</td>
<td>7.6 (3.2)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Calcium, mean (SD), mmol/L</td>
<td>2.08 (0.4)</td>
<td>2.16 (0.2)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Ranson score, mean (SD)</td>
<td>1.4 (1.3)</td>
<td>1.4 (1.2)</td>
<td>0.764</td>
</tr>
<tr>
<td>CTSI, mean (SD)</td>
<td>0.9 (1.0)</td>
<td>0.4 (0.7)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Frequency of SAP, %</td>
<td>17</td>
<td>8.7</td>
<td>0.004*</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td>19 (15.4)</td>
<td>26 (3.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Organ failure</td>
<td>7 (5.7)</td>
<td>17 (2.1)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8 (6.5)</td>
<td>4 (0.5)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6 (3.3)</td>
<td>5 (0.6)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (5.7)</td>
<td>28 (3.4)</td>
<td>0.201</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>5 (4.1)</td>
<td>5 (0.6)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Shock</td>
<td>37 (30.1)</td>
<td>155 (18.7)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>5 (4.1)</td>
<td>11 (1.3)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Mortality</td>
<td>15.3 (13.1)</td>
<td>17.2 (13.6)</td>
<td>0.302</td>
</tr>
</tbody>
</table>

Values are presented as n (%).

*P < 0.05. Differences between the two groups were evaluated using χ² test or t test.

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15.5%), and the lowest rates were in the north (Shaoguan, 3.3%). Incidence was similar in southeast and south central regions of Guangdong (5.9% and 5.7%, respectively). The diet studies of Guangdong have shown that dietary intake of fat and sodium in Hakka area is higher than those in Cantonese and Chaoshan area. It may due to the highest HLAP incidence rates of Meizhou. However, research data are currently very limited and need further study. Chylomicrons are product of dietary fat absorption. A fasting state after onset of symptoms or after diagnosis of AP allows rapid metabolism of the TG-rich chylomicrons. A delay in the consideration of diagnosis or failure to investigate HTG may lead to an underestimation of HLAP and false conclusions about the cause of AP. The lowest HLAP rates of Shaoguan may be due to the lowest serum lipid detection rates. Thus, it is important to consider and investigate HTG in AP.

Clinical Feature of HLAP

Some authors believed that the clinical features of patients with HLAP are not different from patients with AP of other causes, but there is some evidence that demonstrated difference between HLAP and AP recently.

Ohmoto et al\textsuperscript{18} and Sekimoto et al\textsuperscript{19} demonstrate that the average age for HTG-induced AP is lower than the one for other causes, and the disease has been more common in women than in men because it has often been associated with pregnancy. In a cohort study, 20\% of patients presented with AP referred for severe hypertriglyceridemia; most subjects were male (80\%), with a mean age of 37.5 years.\textsuperscript{16} We also found that the average age for HLAP is lower than ABP too. The age of patients with HLAP is more concentrated in middle-aged and fewer over the age of 60 years (only 4.9\%), but unlike the data in Japan, patients younger than 40 years are mostly male in Guangdong.

Although the initial presentation of HLAP is similar to AP because of other etiologies, some features should lead to the consideration of HLAP — poorly controlled diabetes, alcoholism, obesity, pregnancy, prior pancreatitis, and personal or family history of HTG with suggestion of HLAP. In some studies, the prevalence of diabetes in HTG-induced pancreatitis is around 30\%.\textsuperscript{20} In our study, 31.7\% of patients have a history of diabetes, established either before or at the time of admission for HLAP. The second presentation is the patient with alcoholism who is found to have hypertriglyceridemia or lacaescent serum at the time of admission. Patients with hypertriglyceridemia who do not have diabetes and alcoholism, which are diet or drug or pregnancy induced, seem to account for approximately 40\% of HLAP in this study.

There are a few animal studies showing that HTG intensifies the course of pancreatitis.\textsuperscript{21} Older studies reported that the clinical course in patients with pancreatitis with concomitant hypertriglyceridemia is often more severe with increased attendant complications.\textsuperscript{8,9} Fortson et al\textsuperscript{2} reported that in a single-center research, hyperlipidemic pancreatitis had a more severe clinical course and was more commonly associated with complications. However, when a larger number of patients were studied to include those in nonreferral hospitals, no difference in prognostic criteria, course of illness, or complications were recognized. A recent cohort study showed that the severity of pancreatitis in the HLAP (71.5\%) is higher than that of pancreatitis provoked by gallstone and alcohol.\textsuperscript{16} Another recent study also showed a trend toward more severe disease in patients when the patients with dyslipidemia were compared with those who had normal lipid profiles.\textsuperscript{26} In this 15-year large multicenter study, we found that HLAP has a higher frequency of organ failure, higher mortality, and recurrence rate, approximately 1.6 times that of ABP. There is evidence for a more severe trend and poor prognosis in HLAP than in pancreatitis of other causes.

Many authors had reported the lack of sensitivity and low levels of initial serum pancreatic enzymes in patients with HLAP.\textsuperscript{22,23} Similar to other researches, the level of serum amylase was 3 times greater than normal only in 36\% of patients with HLAP. Therefore, careful diagnosis is necessary. In such patients who presented with abdominal pain and normal serum amylase, CT scans have diagnostic and prognostic values.

In summary, the incidence of HLAP in Guangdong had increased during the past 15 years, and with a clear geographic variation, HLAP still has remarkable severity and recurrent trend. Hypertriglyceridemia is closely related to the prognosis and course of AP.

REFERENCES


