LIVER, BILIARY AND PANCREAS

 α_1 Antitrypsin phenotypes and alcoholic pancreatitis

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Abstract

Altered frequencies of α_1 antitrypsin phenotypes have been reported in patients with chronic pancreatitis, suggesting a possible genetic basis for individual susceptibility to this disease. α_1 antitrypsin phenotypes, with particular regard to alcoholic pancreatitis, were studied. Patients with alcoholic pancreatitis were compared with alcoholic control subjects with no history of pancreatic disease. Serum α_1 antitrypsin concentrations were raised in pancreatitis patients sampled within one month of an acute attack of pancreatitis, but otherwise values were similar to those of control subjects. There were no significant differences in α_1 antitrypsin phenotypes between alcoholics with pancreatitis and alcoholic control subjects. This study of α_1 antitrypsin phenotypes provides no evidence of an inherited susceptibility to alcoholic pancreatitis.

Only a minority of alcoholics develop clinical evidence of pancreatitis. The reasons for individual susceptibility to this disease are unknown.

A genetic predisposition to pancreatitis has been suggested by reports of increased incidences of various HLA antigens (Aw 23¹, Aw 24¹, B 13², Bw 39³, B 40⁴) as well as blood groups O⁵ and Le(a-b-).⁶ These studies, however, have generally failed to control for either racial differences in the distribution of genetic markers or the presence of alcoholism, which itself may have an inherited component.

α_1 Antitrypsin is the major protease inhibitor of serum. The protein exhibits appreciable genetic polymorphism and a variety of phenotypes have been described. Mortality of experimental pancreatitis is increased with reduced concentrations of circulating α_1 antitrypsin.⁸ Furthermore, pancreatic fibrosis has been reported in association with the deficient ZZ phenotype.⁹ Therefore, it is possible that genetically determined variations in this protein mediate susceptibility to alcoholic pancreatitis.

Two previous studies^{10,11} have reported conflicting results regarding α_1 antitrypsin phenotype patterns in patients with chronic pancreatitis. However, racial heterogeneity between groups (which is known to affect α_1 antitrypsin phenotype distributions)¹² may have affected the results obtained in both studies. Furthermore, the control subjects were blood donors and it is not possible to determine

whether any differences in phenotype distribution were associated with pancreatitis *per se* rather than with the presence of alcoholism.

The present study was designed to determine whether α_1 antitrypsin phenotypes are linked to the development of symptomatic pancreatitis in an alcoholic population. To correct for a possible confounding effect of alcoholism, the control subjects were alcoholics without clinically evident pancreatic disease.

Methods

All subjects were white and gave a history of alcohol abuse. There were two study groups, group 1 comprised alcoholics with pancreatitis and group 2, alcoholics without pancreatitis (control group).

Patients were interviewed by an experienced gastroenterologist. A medical history was obtained. This incorporated a structured interview concerning drinking behaviour and an estimate of alcohol consumption was obtained using quantity/frequency estimates, similar to the method described by Robertson *et al.*¹³ Where possible, corroborative information was obtained from friends and relatives. Duration of alcohol abuse was calculated to the onset of clinical disease in the case of pancreatitis subjects and to the time of entry into the study in the case of alcoholic controls.

Physical examination was performed. Liver disease was considered present if two or more of the following signs were present: hepatomegaly, unexplained splenomegaly, spider naevi, palmar erythema, or gynaecomastia.

At the time of interview, blood was obtained for determination of the α_1 antitrypsin concentration and phenotype, liver function tests, fasting serum triglycerides, and serum calcium.

ENTRY CRITERIA*Alcoholics with pancreatitis*

These were patients of Prince Henry, Prince of Wales, St Vincent's, and Royal Prince Alfred Hospitals, Sydney. All suffered from pancreatic disease thought to be caused by alcohol abuse. Pancreatic disease was diagnosed by the presence of at least one of the following criteria: (1) previous acute attacks of pancreatitis with severe abdominal pain, abdominal tenderness, and serum amylase or lipase activities greater than three times the upper limit of normal; (2) chronic

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abdominal pain with pancreatic calcification on abdominal x ray or computed tomogram; (3) severe abdominal pain and endoscopic pancreatographic changes of moderate or severe pancreatitis according to the criteria of Sarner and Cotton;¹⁴ (4) histopathological changes of chronic pancreatitis in tissue obtained at operation or necropsy in a patient with a history of severe abdominal pain suggestive of pancreatitis.

Patients were excluded if other potential causes of pancreatitis were found. Gall stones were excluded by ultrasound or oral cholecystography. Fasting serum triglycerides were less than twice the upper limit of normal. Serum calcium was normal, and there was no relevant drug history.

Alcoholics without pancreatitis

Alcoholic controls were recruited from an alcoholism detoxification and rehabilitation hospital (The Langton Clinic, Sydney) or two general Sydney metropolitan teaching hospitals (The Prince Henry and Prince of Wales Hospitals). There was no history of clinical pancreatic disease. Patients with a history of abdominal pain, tenderness, or hyperamylasaemia were excluded.

BIOCHEMICAL ANALYSIS

Concentrations of α_1 antitrypsin in serum were determined by nephelometry.¹⁵ α_1 Antitrypsin phenotyping was performed by isoelectric focussing.¹⁶ Where required, narrow range gels (pH 4.2–4.9) were used to differentiate M subtypes (M1, M2, M3). Analyses were performed without knowledge of the clinical history.

ETHICS COMMITTEE APPROVAL

The study was approved by the ethics committees of the Eastern Sydney Area Health Service and the Royal Prince Alfred Hospital. Written informed consent was obtained from each patient.

STATISTICAL ANALYSIS

Results were expressed as mean (SEM). Results obtained in cases and control subjects were compared using Student's *t* test.¹⁷ χ^2 Analysis was used to compare the α_1 antitrypsin phenotype distributions.¹⁷

Results

PATIENT CHARACTERISTICS

Age and sex distribution

The pancreatitis patients and the alcoholic control subjects were well matched for age and sex (Table I).

Alcohol consumption

The mean duration of alcohol abuse was similar in the two groups (Table I). Daily consumption, however, was less in the pancreatitis group. A measure of cumulative alcohol consumption was derived from the product of daily alcohol intake and the number of years of heavy drinking. Cumulative alcohol consumption was significantly less in the pancreatitis group (Table I).

Liver disease

The prevalence of signs of liver disease was similar in the two groups of patients (Table I). The liver function test results were similar in the study groups, other than serum albumin. Pancreatitis patients had significantly lower values for albumin, but the mean values for both groups were within the normal range (Table I).

SERUM α_1 ANTITRYPSIN VALUES

Serum α_1 antitrypsin values for pancreatitis patients were significantly higher than for alcoholics without pancreatitis (Table I). The α_1 antitrypsin values for 33 patients sampled within one month of an acute attack of pancreatitis were 3.85 (0.26) g/l, and 2.70 (0.12) g/l in the remaining 57 pancreatitis patients. This difference was statistically significant ($p < 0.0001$) and accounted for the difference in α_1 antitrypsin concentrations between patients with alcoholic pancreatitis and alcoholic controls.

SERUM α_1 ANTITRYPSIN PHENOTYPES

The distributions of α_1 antitrypsin phenotypes for the two study groups are shown in Table II. The MM Phenotypes were the most common in both study groups. The distributions were also similar for the less common phenotypes. There were no statistically significant differences between α_1 antitrypsin phenotype distributions in alcoholics with pancreatitis compared with alcoholics without pancreatitis.

Discussion

This study found no significant differences in α_1 antitrypsin phenotype distributions between subjects with well documented clinical alcoholic pancreatitis and alcoholic control subjects. Serum α_1 antitrypsin concentrations were raised only in pancreatitis patients sampled shortly after an acute attack of pancreatitis, but were similar to controls where patients were sampled at other times.

Individual susceptibility to alcoholic pancreatitis is variable and remains unexplained. Variations in the type of alcohol consumed and patterns of consumption^{18,19} do not correlate with

TABLE I Characteristics of the two study groups, including estimated alcohol consumption and evidence of liver disease (values mean (SEM))

	Alcoholics with pancreatitis	Alcoholics without pancreatitis	<i>p</i>
No	90	188	
Sex (% male)	73.6	79.8	NS
Age (yrs)	43.8 (1.3)	44.1 (0.9)	NS
Alcohol consumption:			
Daily intake (g)	132 (8.1)	190 (7.7)	<0.0001
Duration of abuse* (yrs)	20.9 (1.2)	19.4 (0.7)	NS
Consumption index† (kg ethanol)	992 (96.4)	1366 (75.2)	<0.0001
Serum α_1 antitrypsin (normal 1.8–3.5 g/l)	3.13 (0.13)	2.63 (0.06)	<0.0001
Signs of liver disease	25.6%	33.0%	NS
γ Glutamyl transferase (normal <50 IU/l)	123 (18.0)	90.3 (9.6)	NS
Serum albumin (normal 35–55 g/l)	39.5 (0.68)	42 (0.40)	<0.0001

*Calculated to time of diagnosis of pancreatitis or to entry into the study for controls.

†The product of daily consumption and duration of alcohol abuse.

NS, not significant.

TABLE II α_1 Antitrypsin phenotype distributions in alcoholic pancreatitis and alcoholic controls

Phenotype	Alcoholics with pancreatitis (%)	Alcoholics without pancreatitis (%)
M1 M1	59.3	69.6
M1 M2	11.0	13.3
M2 M2	8.8	3.7
M. M3	5.5	3.7
M. S	9.9	5.9
M. Z	5.5	2.7
Others	0.0	1.1

$\chi^2 = 5.37$ df, $p = 0.37$.

susceptibility. Hypertriglyceridaemia may theoretically potentiate the toxicity of alcohol²⁰ but is found infrequently.²¹ Some studies have indicated that dietary factors may play a permissive role,²² but others have challenged this view.^{18, 23}

In a study of the determinants of individual susceptibility to a disease, the choice of controls is critical. Racial differences may influence the incidence of genetic markers as may the presence of alcoholism itself. We have controlled for these factors by ensuring that all patients were racially similar (white) and alcoholic. Although it is recognised that some diversity in α_1 antitrypsin phenotypic distributions persists, even amongst white populations,¹² major racial differences between the index and control groups were minimised in this study by confining the investigation to white subjects drawn from the same community. Although asymptomatic pancreatic abnormalities are frequently found at necropsy, this study has investigated individual susceptibility to clinically evident pancreatitis by selecting a control group without overt disease. Therefore, the index and control groups differed by only one major factor – the presence or absence of clinically evident pancreatitis.

It is interesting to note that the cumulative alcohol consumption of patients with pancreatitis (calculated to the onset of clinical disease) was significantly less than for the control group (at the time of entry into the study). Quantifying alcohol consumption was attempted primarily to ensure that the control group had consumed, on average, at least as much alcohol as the pancreatitis group. This was done to forestall the criticism that some control subjects destined to develop pancreatitis may not have consumed enough alcohol at the time of entry into the study. The finding that control subjects consumed on average more than the index group was unexpected and its importance should not be overemphasised given the difficulties in measuring alcohol consumption in alcoholics. Nevertheless, this study suggests that in addition to alcohol consumption, other factors contribute to the development of pancreatitis in alcoholics.

It has traditionally been accepted that alcoholic pancreatitis and alcoholic liver disease do not frequently coexist. In this study, however, signs of alcoholic liver disease occurred in 26% of patients with alcoholic pancreatitis. This finding is consistent with recent studies which show that the two diseases do frequently occur together.²⁴

Novis *et al*¹⁰ studied a South African cohort with chronic pancreatitis of mixed aetiology and

found a significantly greater proportion of MZ α_1 antitrypsin phenotypes when compared with control subjects. However, racially mixed groups were studied and the controls (blood donors) were not alcoholic, making any useful conclusions about the incidence of α_1 antitrypsin phenotypes in alcoholic pancreatitis impossible. Braxel *et al*¹¹ found no relation between α_1 antitrypsin phenotypes and pancreatitis. However, this study included patients with a variety of causes for pancreatitis and did not specifically address the issue of susceptibility to alcoholic pancreatitis with appropriate controls.

Serum α_1 antitrypsin concentrations were greater in patients with pancreatitis who were sampled shortly after an acute attack of pancreatitis compared with pancreatitis patients sampled at other times or alcoholic controls. α_1 Antitrypsin concentrations have been shown to rise during acute pancreatitis in humans, and return to baseline values after recovery.²⁵⁻²⁷ The higher results obtained in patients with alcoholic pancreatitis in this study are consistent with these previous reports, and similar to other published reports.²⁸ The increased values observed after acute attacks of pancreatitis may be part of the non-specific inflammatory response (the 'acute phase response'), since a similar response is also observed after several types of operative stress.²⁹ The importance of this response in pancreatitis is unclear, since severe deficiency of α_1 antitrypsin is not associated with an increased mortality from pancreatitis.³⁰

The absence of a relation between α_1 antitrypsin phenotypes and alcoholic pancreatitis suggests either that genetic factors are not important in the pathogenesis of alcoholic pancreatitis or that α_1 antitrypsin phenotypes are not useful genetic markers in this regard. In addition, since the deficient phenotypes were not more common in patients with alcoholic pancreatitis, a protective role for α_1 antitrypsin in this disease seems unlikely.

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