Genetic Markers in Duodenal Ulcer Disease

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Abstract

A study has been carried out on 100 endoscopically proven duodenal ulcer patients and in 100 healthy controls to examine the role of genetic factors in the development of duodenal ulcer disease. Serum pepsinogen levels, serum alpha-1-antitrypsin, haptoglobin phenotyping and ABO blood groups served as genetic markers. Hyperpepsinogenemia, deficiency of alpha-1-antitrypsin, haptoglobin 2-2 typing and 'O' blood group were found to be associated with duodenal ulcer disease.

Key words: *Duodenal ulcer, genetic markers, association.*

The role of genetic factors in the pathogenesis of duodenal ulcer has been described by several workers[1-3], who have reported an increased frequency of the disease in first degree relatives of patients, and greater concordance between monozygotic twins than dizygotic twins.[3] Other markers such as ABO blood groups,[4] secretor and non secretor status,[5] HLA typing[6] and serum pepsinogen[1,7] have been studied. But, there has been no report of multiple markers studied in the same individual. The present study was carried out by taking four markers (serum pepsinogen, serum alpha-1-antitrypsin, haptoglobin phenotyping (Hp) and ABO blood groups) in the same patients as well as in healthy controls, to see the role of these markers, in the predisposition to duodenal ulcer disease.

Methods

One hundred duodenal ulcer patients of both sexes and aged between 22 and 58 years (mean age 37.6 ± 11.2) were studied at the Department of Gastroenterology, Osmania General Hospital, Hyderabad. The presence of a duodenal ulcer was confirmed by endoscopy. One hundred healthy age and sex matched individuals, none of whom had a history of duodenal ulcer, dyspepsia or any other disease, were selected as controls.

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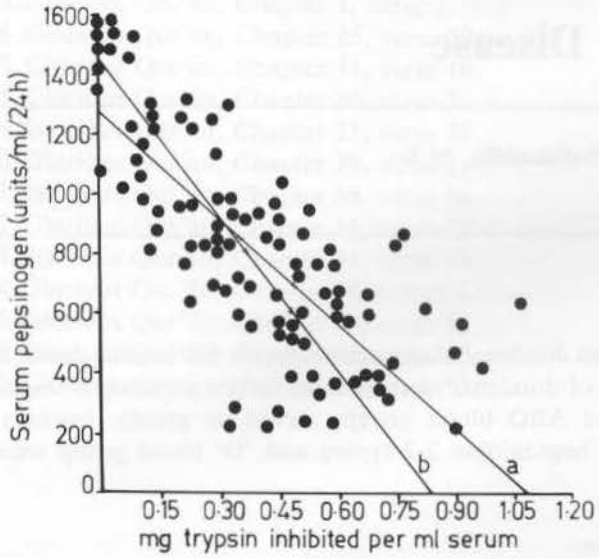
Blood samples were collected from patients and controls for the estimation of serum pepsinogen, serum alpha-1-antitrypsin and for the analysis of ABO blood groups and haptoglobin phenotypes. The ABO blood group frequencies of the general population of Hyderabad reported by Padma et al[8] were used as controls against which the blood group frequencies of duodenal ulcer patients were compared. Serum alpha-1-antitrypsin was estimated in the form of serum trypsin inhibitor capacity (STIC) by the method of Jaccobson[9] using hemoglobin as a substrate. Serum pepsinogen levels were determined by the method of Mirsky et al[10] using hemoglobin as a substrate. The slide agglutuation technique was followed for the analysis of ABO blood groups. Haptoglobin phenotypes were analysed by the method of Clark.[12]

The statistical significance of the difference in distribution of STIC and total serum pepsinogen in controls and patients as determined by student 't' tests. Pearson's correlation coefficient was calculated for the relationship between STIC and serum pepsinogen levels. Scatter diagrams showed the relationship between these two and appropriate regression lines were fitted in the figure. The frequency of blood groups and Hp types in the patients were compared with that of controls and the variation was then evaluated statistically using Chi-square test.

Results

Serum trypsin inhibitor capacity was expressed as normal, intermediate and low according to Eriksson's criteria (i.e. low levels < 0.5 mg/ml represent homozygous state, intermediate 0.5-1.0 mg/ml called heterozygous state and > 1.0 mg/ml represent normal state of STIC). The mean STIC in healthy controls was 1.00 ± 0.7 mg/ml. In healthy controls



Figure

Regression lines for data on serum alpha-1-antitrypsin and serum pepsinogen levels in duodenal ulcer disease ($r = -0.621$, $p < 0.001$). The regression of y on x (line a) has the equation $y = 1122.2-845.7x$. The regression of x on y (line b) has the equation $x = 0.6772-0.0004y$.

60% had STIC in the normal range, 25% had heterozygous deficiency and 15% showed homozygous deficiency of STIC. In ulcer patients, the mean STIC was 0.345 ± 0.24 mg/ml, which is significantly lowered when compared with the mean values of controls ($p < .001$). Seventy-three percent of patients had a homozygous deficiency of STIC, 25% had heterozygous levels and only two patients were in the normal range. The mean serum pepsinogen level in healthy controls was 511.5 ± 116.5 units/ml/24h. The values ranged between 280 and 745 units. Any value beyond 745 units was regarded as hyperpepsinogenemia. The mean value of serum pepsinogen levels in patients was 830.37 ± 371.86 units/ml/24 h. This was significantly elevated compared with the controls ($p < 0.001$).

Statistical analysis of the data revealed a strong negative correlation ($r = -0.621$, $p < 0.001$) between serum alpha-1-antitrypsin and serum pepsinogen levels in patients with duodenal ulcer disease (Figure).

The distribution of ABO blood groups and Hp types in healthy controls and in patients with duodenal ulcer is presented in Tables 1 and 2. Relative incidence was claculated to show the incidence of the disease in people with blood group O as compared to people with blood group A, B and AB. Similarly the relative incidence was calculated to show the incidence of the disease in people with Hp type 2-2 as compared to people with Hp types 2-1 and 1-1. The incidence of duodenal ulcer in people with blood group O was 1.7 compared with an incidence of 1.0 in people with blood group A, B and AB. Patients with Hp 2-2 type have a relative risk of 3.00 ($X^2 = 4.2$, $df = 1$, $p < 0.05$) compared with an incidence of 1.0 in patients with other Hp types.

Table 1. ABO blood group distribution in controls and patients with duodenal ulcer disease (percent).

Blood group	Controls	Patients
O	36	55
A, B, or AB	64	45
A	24	18
B	33	25
AB	7	2

Comparison of the distribution of blood group O versus other blood groups between controls and patients. The difference is statistically significant ($X^2 = 23.1$, $P < 0.001$).

Table 2. Distribution of haptoglobin types in duodenal ulcer patients and controls (percent).

Hp types	Patients	Controls
2-2	90	68
2-1	9	28
1-1	1	4
Total	100	100

Comparison of the distribution of Hp type 2-2 versus the other types between patients and controls. The difference is statistically significant, $p < 0.05$

Discussion

In this study 73% of the patients had a homozygous deficiency of alpha-1-antitrypsin. The site of synthesis of this protein is the liver cell, with the defect being in the synthesis of the carbohydrate moiety of a glycoprotein.[13] The basic defect in the glycoprotein is in the sialic acid at the terminal residue, which makes the glycoprotein non transportable from the liver into the circulation. This defect causes emphysema, chronic obstructive lung disease and cirrhosis in Indian children. The same defect may also present in many duodenal ulcer patients. About 25% of the patients in our study also had emphysema, or chronic obstructive lung disease.

In the patients where the deficiency of alpha-1-antitrypsin were recorded, hyperpepsinogenemia was also seen. Twenty-seven percent of the patients had intermediate levels of alpha-1-antitrypsin (heterozygous state) and in these patients most were associated with normal pepsinogen levels. Intermediate levels of alpha-1-antitrypsin in these pa-

tients may indicate the disease is in the early stages where there is only partial accumulation of this protein into the liver cells. Similarly in the early stage of the disease, the pepsinogen levels may not exceed the normal range.

Fifty-five percent of the patients with hyperpepsinogenemia and a deficiency of alpha-1-antitrypsin, also had an 'O' blood type. The serum pepsinogen levels were highly elevated in the blood group O patients when compared with other blood group A, B and AB patients. According to Hanley's report[14] the extent of peptic secretory cell mass is influenced by sex, by ABO blood genes, and the serum pepsinogen levels and probably reflects the size of the gastric secretory cell mass. Their experimental results[15] revealed that the gastric secretory cell mass is larger in group 'O' phenotypes than in group 'A' phenotypes. Our results are in agreement with these reports.

In patients with hyperpepsinogenemia, and deficiency of alpha-1-antitrypsin, Hp 2-2 types were also recorded.

Thus the combination of blood group 'O', Hp 2-2 type, hyperpepsinogenemia and deficiency of alpha-1-antitrypsin represent increased risk factors in the development of duodenal ulcer disease.

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