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Recommended Citation

Shahid, A., Zuberi, S. J., Siddiqui, A., Muhamined A. Waqar, M. M. (1997). Genetic Markers and Duodenal Ulcer. *Journal Of Pakistan Medical Association*, 47(135), 135-137.

Available at: http://ecommons.aku.edu/pakistan_fhs_mc_bbs/269

Genetic Markers and Duodenal Ulcer

Pages with reference to book, From 135 To 137

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Abstract

Serum pepsinogen, ui-antitrypsin (ui-AT) and blood groups were studied as genetic markets in 32 patients with endoscopically proven duodenal ulcer and 44 control subjects with no family history of ulcer disease. Serum pepsinogen was detennined by the modified method of Edward et al⁷, a1-AT by single radial hnmunodiffusion⁸ (RID) and phenotyping was carried out by isoelectric focusing (IEF)⁹. Duodenal ulcer patients with hyper- pepsinogenemia (28%) and low serum ui-AT (35%) had a dominant blood group O, lower mean age, an early onset of disease, a higher frequency of gastrointestinal (GI) bleeding and ulcer perforation. These parameters were found considerably different in patients with normal serum pepsinogen and ui-AT. Phenotype analysis of a1-AT revealed that four duodenal ulcer patients had partial deficiency of the protease inhibitor and none of the normal exhibited the deficiency pattern. The etiology of the disease appears to be genetic anomaly in 28% of patients while the rest (72%) had ulcers as a result of neuroendocrinological or environmental factors (JPMA 47:135,1997).

Introduction

Duodenal ulcer is a common disorder which is believed to have existed in families. Due to its heterogeneity¹ and multiple causative factors it often becomes difficult to assign a single agent responsible for this disease. It is therefore, widely accepted that interaction of certain environmental, genetic and other factors such as stress might collectively produce alteration of gastric secretions to such extent that it leads to low resistance of gastric mucosal cells which in turn detennines the predisposition to the development of duodenal ulcer. The genetic markers that have been proposed to be linked with this disorder include ABO blood groups², secretor and non-secretor status³, I{LA typing⁴, serum pepsinogen⁵ and serum alpha 1 antitrypsin⁶. Those who have been considered prone to develop duodenal ulcer include individuals with blood group O (35%) and non-secretors (50%). In addition to these, persons with raised serum pepsinogen, low levels of ui-AT and increased frequency of HLA, B-5 have also been identified among the predisposed group²⁻⁶. Like many of the well known disonlers of genetic origin, researchers have also been looking for suitable markers for this disease. If one or more suitable markers can be identified for the duodenal ulcer it is hoped that this information would provide considerable help not only in the successful management of patients, but also in the development of strategies for control and prevention of disease. This study was conducted to find out whether the etiology of duodenal ulcer in our population is genetic or some other factors play a role in causation of the disease.

Patients and Methods

Thirty-two patients with endoscopically proven duodenal ulcer and forty-four healthy subjects with no history of peptic ulcer disease were selected as patients and controls respectively. Patients written consent and an approval of the Ethical Conunittee, Jinnah Postgraduate Medical Centre, Karachi were taken, All sera were stored at -70°C until analysed. Serum pepsinogen was determined by the modified

method of Edward et al. Quantitative measurement of serum α -1AT was carried out by single RID technique using M. Partigen immunodiffusion plates (Behring Diagnostic, Germany)⁸ and phenotyping was performed by ultrathin layer polyacrylamide gel IEF⁹. We used gels containing 2% ampholytes in the pH range 4.2-4.9. At the end of IEF run, pH at each 1 cm segment across the gel length was measured using a surface pH electrode. α 1-AT bands were visualized by staining the gels with Coomassie Blue R-250. Further confirmation of ui-AT phenotyping was done by immunofixation⁹. For this purpose cellulose acetate membrane presoaked in 1:2 diluted antiserum to ui-AT, was layered over the surface of JEF gel. After an hour the membrane was washed exhaustively in saline and stained with amido-black to locate ui-AT-antibody complexes.

Results

Serum pepsinogen, ui-AT and blood groups were determined in 32 patients with duodenal ulcer and 44 controls. The patients age ranged between 18-77 years (mean 41 years) and in controls from 18-82 years (mean 35 years). There were 26 males and 6 females with a male to female ratio of 4.3:1. The mean values and ranges for total serum pepsinogen, serum ui-AT and blood groups in controls and patients with duodenal ulcer are shown in Table I. The range of serum pepsinogen in controls was 9-140 units/ml. Considering this as normal range, 72% patients were normal pepsinogenemic and 28% were hyperpepsinogenemic. The values of controls and patients with duodenal ulcer do not appear significantly different (Table I).

Table I. Genetic markers in duodenal ulcer.

| | Serum Pepsinogen (u/ml) | α ₁ -antitrypsin | | Blood Group |
|---------------------------|----------------------------|--|---------------------------------|-------------------------------|
| | Mean \pm S.E. (Range) | IEF Phenotype | RID (g/l) (mean \pm SE) | |
| Duodenal Ulcer (32) | 99 \pm 14 (10-320) | M=22 M ₁ M ₂ =06 SZ=03 S=01 | *1.99 \pm 0.14 (0.52-3.52) | A=05 B=11 AB=03 O=13 |
| Controls (44) | 70 \pm 6.5 (9-140) | M=33 M ₁ M ₂ =11 | 2.70 \pm 0.12 (0.52-5.50) | A=11 B=16 AB=04 O=13 |

*P<0.001

IEF: Isoelectric focussing

RID: Radial Immunodiffusion

Subjects having values less than 2 gm/l of serum ui-AT were regarded as being ui-AT deficient. Among the patients 65% had normal and 35% below normal ui-AT levels. A significant difference (P<0.001) was observed between the mean values of controls and patients (Table I). IEF patterns indicated that four duodenal ulcer patients with low serum ui-AT had at least partial deficiency of the protease inhibitor. Blood group O was dominant among patients with raised serum pepsinogen and low ui-AT. Comparing patients with blood group O versus those with groups other than O indicates that these patients had a lower mean age, raised mean serum pepsinogen and low mean ui-AT (Table II).

Table II. Comparison of age, sex, serum pepsinogen and serum α_1 - Antitrypsin in DU patients with Blood group O Vs Patients with Blood groups other than O.

| | | DU patients with blood group O | DU patients with blood groups other than O |
|-------------------------------|---------|--------------------------------------|---|
| | | (13) (Mean \pm SE (Range) | (19) Mean \pm SE (Range) |
| Age | (Years) | 39 \pm 4.0 (22-77) | 42.5 \pm 4.0 (18-77) |
| Sex | Male | 12 | 14 |
| | Female | 01 | 05 |
| Serum pepsinogen | U/ml | 127 \pm 27 | 80.4 \pm 12.7 |
| Hyper-pepsinogen | | (11-320) | (10-182) |
| Normo-pepsinogen | | 6 (46%) | 3 (16%) |
| | | 7 (54%) | 16 (84%) |
| Serum α_1 -Antitrypsin | | 1.8 \pm 0.22 | 2.1 \pm 0.18 |
| Radial immunodiffusion | (g/L) | (0.52-3.25) | (0.52-3.25) |
| Low | | 6 (46%) | 5 (26%) |
| Normal | | 7 (54%) | 14 (74%) |
| Isoelectric focusing | | MM=10 | MM=12 |
| | | M ₁ M ₂ =02 | M ₁ M ₂ =04 |
| | | S=01 | SZ=03 |

Discussion

Duodenal ulcer manifesting raised serum pepsinogen and low α_1 -AT is reported to be a genetically determined entity. Other characteristic features among these patients include dominant blood group O, lower mean age, an early onset of the disease and an increased frequency of gastrointestinal bleeding and perforation¹⁰. These findings confirm the strong association of duodenal ulcer with genetic markers, which in the present study seems to hold true only in a small number of patients i.e., only 28% of the patients had raised serum pepsinogen while 35% had low α_1 -AT. Among these patients, blood group O was found dominant. Role of genetic factors in duodenal ulcer disease has been suspected

since long because of an increased incidence of the disease among first degree relatives of patients³. A greater concordance for duodenal ulcer in monozygotic than in dizygotic twins¹¹ and an increased frequency of blood group 0 and blood group non-sector status in patients with duodenal ulcer have been reported. Blood group 0 and non-sector status although associated with the disease, are not useful for this purpose as the magnitude of the association appears very weak², however, an elevated serum pepsinogen level occurs with increased frequency in patients with established duodenal ulcer^{12,13} and has been found to identify those at an increased risk for the development of the disease^{14,15}. Hereditary deficiency of the protease inhibitor, resulting in low levels of α_1 -AT (synthesized by hepatocytes) is another factor reported in duodenal ulcer⁶. Recognizing phenotypes of α_1 -AT is clinically important as it is an acute phase reactant protein and its quantitative estimation in duodenal ulcer and in other inflammatory conditions can be misleading¹⁶.

Duodenal ulceration is a common gastrointestinal problem but to date no studies have been conducted on local population in screening various genetic markers and establishing the etiology of the disease either to be of genetic or non-genetic in origin. An earlier study⁵ reported a high percentage (83%) of duodenal ulcer patients with hyperpepsinogenemia. Such an ulcer was considered to be of genetic etiology termed as primary duodenal ulcer. The observations are different in our study, only 28% of the patients had raised serum pepsinogen while serum α_1 -antitrypsin was low in 35% of the patients. Other findings in the patients include dominant blood group 0, lower mean age, an early onset of the disease, an increased frequency of gastrointestinal bleeding and ulcer perforation, thereby confirming the strong association of duodenal ulcer with all the markers. But this association seems to hold true only in a small number of patients included in this study. From the preceding discussion it appears that the genetic etiology of the disease existed in just 28% of the patients while the rest comprising a large majority of the patients (72%) had ulcers which could be the result of neuroendocrinological or environmental factors which are also known to cause the disease. Individual differences in character tendencies, psychological and emotional adaptability, responses and adaptive abilities of the humoral system to stress are also closely related with the development of ulcer. Severe psychological stresses imposed upon children and adults because of the complex psycho-social circumstances may be the root cause of the disease and should be seriously considered.

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