Hiroshima Journal of Medical Sciences
Vol.35, No.2, 171~175, June, 1986
HIJM 35-26

Familial Aggregation of Duodenal Ulcer and an Autosomal Dominant Inheritance of Hyperpepsinogenemia I

Koji SUMII, Naomi UEMURA, Akira INBE, Ken HARUMA, Yoshiro INABA, Akira TARI, Masaharu YOSHIHARA, Masaki SEKITOH, Tadashi TOKUTOMI, Goro KAJIYAMA and Akima MIYOSHI*

The First Department of Internal Medicine, Hiroshima University School of medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan
* *Shizuoka General Hospital, Kitaando, 4-27-1-2, Shizuoka 420, Japan*
(Received March 25, 1986)

Key words: Duodenal ulcer, Hyperpepsinogenemia I, Autosomal dominant inheritance

ABSTRACT

To clarify genetic factors involved in the familial aggregation of duodenal ulcer, serum pepsinogen I levels were determined by radioimmunoassay in patients with duodenal ulcer and their affected and unaffected relatives.

There existed relationship between an elevated pepsinogen I level and susceptability of duodenal ulcer, and the familial aggregation of duodenal ulcer. The segregation analysis revealed that hyperpepsinogenemia I was inherited as an autosomal dominant inheritance, and in some families this trait was responsible for familial aggregation of duodenal ulcer. But in other families normopepsinogenemic I duodenal ulcer has segregated and association to pathophysiological factors of this trait was obscure. These data provide evidence that genetic factors play a role in pathogenesis of duodenal ulcer, and that hyperpepsinogenemia I is one of genetic markers of this disease.

A significant proportion of duodenal ulcer patients have positive family history of this disease. The results of family studies are consistent with the hypothesis that genetic factors play a role in the cause of duodenal ulcer[2,4,5,7]. The observation on blood group 0 and non-secretor status consisted early important evidence for the role of genetic factors in duodenal ulcer[1,3,5,6]. Resently some studies have shown that hyperpepsinogenemia I is inherited as an autosomal dominant trait[8,9]. We therefore planed to determine serum pepsinogen I levels in patients with duodenal ulcer and their unaffected relatives with or without positive family history of duodenal ulcer to substanciate that hyperpepsinogenemia I plays a role on familiar aggregation of duodenal ulcer.

SUBJECTS AND METHODS

In 26 patients, duodenal ulcer was diagnosed with endoscope in Hiroshima University Hospital. And their 93 relatives were surveyed upon duodenal ulcer. Thirty-two duodenal ulcers were found in them. So, totally in this study, 58 patients with duodenal ulcer and 61 unaffected relatives of 26 families were, investigated. These 26 families were divided into two groups; one group was those who had at least one other first degree relatives of duodenal ulcer, the other was those who had no relatives of duodenal ulcer. Diagnosis of duodenal ulcer was made only by endoscope. No patients had been performed vagotomy or gastric resection before present investigation. The subjects of familial survey consisted of 38 parents and 72 siblings and 9 children, and familial aggregation of duodenal ulcer was recorded in 18 families.

Control subjects consisted of 38 patients with negative family history of peptic ulcer, who visited hospital with complaints resembling duodenal

ulcer, and found no gastroduodenal lesion by endoscopy.

All patients were explained the purpose of this study, and each one gave informed consent.

Serum pepsinogen I levels were determined by radioimmunoassay (CIS, RIA-KIT). According to the previously established normal range[12], those whose serum pepsinogen I level was above 95 ng/ml were defined as hyperpepsinogenemia I.

Student's t-test and chi-square test were used for the calculation of the statistical significance.

RESULTS

1. Serum pepsinogen I levels in subjects with or without family history

The serum pepsinogen I level was 112.0 ± 7.1 ng/ml (mean ± SE) in duodenal ulcer patients with positive family history, and 112.8 ± 18.0 ng/ml in those without family history. The mean serum pepsinogen I level (77.5 ± 5.6 ng/ml) in unaffected relatives with positive family history was significantly higher ($p<0.05$) than that (61.4 ± 4.5 ng/ml) in unaffected relatives with negative family history, and were not different from that of control subjects (Table 1).

Table 1. Serum pepsinogen I levels in subjects (mean ± SE)

	n	PGI(ng/ml)
Control	38	66.8 ± 4.4
Duodenal ulcer		
Positive family history	50	112.0 ± 7.1
Negative family history	8	112.8 ± 18.0
Unaffected relatives		
Positive family history	39	77.5 ± 5.6
Negative family history	22	61.4 ± 4.5

* $p<0.05$ **$p<0.001$

2. Incidence of hyperpepsinogenemia I and duodenal ulcer in siblings

In 32 out of 72 siblings, hyperpepsinogenemia I was found. In positive family history group, hyperpepsinogenemia I was found in 51.9% (27/52) of siblings, and in negative family group, 25.0% (5/20) (Table 2. $X^2=4.240$ $p<0.05$). A significantly large proportion (75%) of siblings with hyperpepsinogenemia I were revealed to be duodenal ulcer (Table 3. $X^3=7.659$ $p<0.01$).

3. Segregation analysis

Segregation analysis was done on two subsets of the data. The first subset included those siblings in which at least one of subjects of the first degree relatives was hyperpepsinogenemia I (siblings of hyperpepsinogenemic I family). The second subset included the siblings whose either parent was hyperpepsinogenemia I.

Let p be the probability that sibling be hyperpepsinogenemia I, the frequency of family with 0 to s of hyperpepsinogenemic I siblings in family size (number of siblings) s is estimated as

$$(p + q)^s$$

where $p=0.5$, if hyperpepsinogenemia I is inherited as an autosomal dominant fashion. For example, the probability of 0, 1 or 2 of siblings being hyperpepsinogenemia I in families with 2 siblings are 25%, 50% or 25%, and in the families with 3 siblings, that of 0, 1, 2 or 3 are 12.5%, 37.5%, 37.5% or 12.5%.

The families without hyperpepsinogenemic I sibling tended to be excluded, as probands were usually patients with duodenal ulcer, and a half

Table 2. Occurrence of hyperpepsinogenemia I (hPGI) and normopepsinogenemia I (nPGI) in 72 siblings with positive or negative family history of duodenal ulcer

Family history	hPGI	nPGI	Total
Positive	27	25	52
Negative	5	15	20
Total	32	40	72

$x^2=4.240$ $p<0.05$

Table 3. Occurrence of duodenal ulcer in siblings with hyperpepsinogenemia I and normopepsinogenemia I

	Duodenal ulcer	Normal	Total
hPGI	24	8	32
nPGI	17	23	40
Total	41	31	72

$x^2=7.659$ $p<0.01$

Table 4. The expected proportion of affected individuals in truncate ascertainment under autosomal dominant hypothesis

Size of sibling (S)	Proportion of sibships unascertained (q=(1/2))	Proportion of sibships ascertained (p=1-(1/2))	Proportion of affected individuals in ascertained (Z)	Variance (δ)
1	$(1/2)^1=1/2$	1/2	1.0000	0.0000
2	$(1/2)^2=1/4$	3/4	1.3333	0.2222
3	$(1/2)^3=1/8$	7/8	1.7142	0.4898
4	$(1/2)^4=1/16$	15/16	2.1333	0.7822
5	$(1/2)^5=1/32$	31/32	2.5806	1.0822
6	$(1/2)^6=1/64$	63/64	3.0476	1.3786

$Z=SP/(1-q^s)$ $p+q=1$
$\delta=SP(1-q^s-spq^{s-1})/(1-q^s)^2$

Table 5. The observed and expected number of hyperpepsinogenemic I siblings in hyperpepsinogenemic I families

Size of sibling (s)	No. of sibships (a)	Total no. of individuals (sa)	No. of affected individuals		Variance
			Observed	Predicted (saz)	
1	1	1	1	1	0
2	6	12	8	7.9998	1.3332
3	9	27	13	15.4278	4.4082
4	1	4	1	2.13333	0.7822
5	0	0	0	0	0
6	2	12	9	6.0952	2.7572
Total	19	56	32	32.6561	9.2808

of whom were having normopepsinogenemia I. Families with many hyperpepsinogenemic I siblings are more likely to be selected than families with only one affected sibling, and when hyperpepsinogenemic I parent has no affected children, the proportion of affected children will be as shown in Table 4. The observed and predicted number of hyperpepsinogenemic I siblings in the first subset were shown in Table 5.

The segregation ratios were 0.4989 ± 0.0821 under truncate ascertainment and 0.3514 ± 0.0822 under single ascertainment, and chi-square analysis revealed no significant difference between observed and predicted segregation ratios of 0.5, assuming an autosomal dominant inheritance for hyperpepsinogenemia I in normal-by-affected matings. The segregation analysis of hyperpepsinogenemia I in the second subset also gave segregation ratios consisting with autosomal dominant inheritance (Table 6).

4. Incidence of hyperpepsinogenemia I according to pepsinogen I levels of their parents in siblings with positive family history of duodenal ulcer.

When both parents or either parent had hyperpepsinogenemia I, 100% or 65.2% of their offsprings had hyperpepsinogenemia I in subjects with positive family history of duodenal ulcer. When both parents had normopepsinogenemia I, a few offsprings (21.4%) had hyperpepsinogenemia I, and 72.7% of their offsprings with duodenal ulcer had normopepsinogenemia I (Table 7).

Table 6. Segregation analysis of hyperpepsinogenemia I in siblings

	Subset	
	Siblings in hPGI family	Siblings with hPGI parent
Proband	19	10
Siblings	56	29
hPGI	32	17
Segregation analysis		
Truncate	0.4989 ± 0.0821	0.6365 ± 0.1185
Single	0.3514 ± 0.0822	0.5000 ± 0.1179

Table 7. Occurrence of hyper- and normopepsinogenemic I siblings according to mating of parents in subjects with positive family history of duodenal ulcer

	No. of family	Siblings							
				Duodenal ulcer			Normal		
		a) No.	b) hPGI (b/a)	c) No.	d) hPGI (d/c)	e) nPGI (e/c)	No.	hPGI	nPGI
Both parents hPGI	1	2	2 (100)	2	2 (100)	0 (0)	0	0	0
Either parent hPGI	8	23	15 (65.2)	13	9 (69.2)	4 (30.8)	10	6	4
Both parents nPGI	5	14	3 (21.4)	11	3 (27.3)	8 (72.7)	3	0	4

(%)

DISCUSSION

This study has shown that hyperpepsinogenemia I is inherited as an autosomal dominant trait in families with duodenal ulcer. The incidence of hyperpepsinogenemia I was significantly higher in siblings with positive family history of duodenal ulcer than those without such history, and duodenal ulcer was assigned more frequently in siblings with hyperpepsinogenemia I than in those with normopepsinogenemia I. Thus the familial aggregation of hyperpepsinogenemia I appears to contribute to the familial aggregation of duodenal ulcer.

The segregation analysis done on siblings of the first subset and of the second subset was consistent with autosomal dominant inheritance of hyperpepsinogenemia I. The first subset consisted of siblings with hyperpepsinogenemia I subjects in their first degree relatives. The second subset gave information about parents, and it was normal-by-affected matings. When hyperpepsinogenemia I is inherited as an autosomal dominant transmission, the predicted ratios were 0.5 in normal-by-affected matings. The chi-square value for goodness of fit of the observed data in truncate and single ascertainment to the dominant hypothesis in the first and the second subset was not significant. Therefore not in all families but in some families, familial aggregation of duodenal ulcer can be attrebuted to an autosomal dominant inheritance of hyperpepsinogenemia I.

Rotter et al[9] determined serum pepsinogen I levels in patients with duodenal ulcer and their normal siblings. They ascertained the presence of duodenal ulcer in siblings with different procedure for diagnosis, using either radiography or endoscopy, and some were diagnosed at surgery or even by their clinical history alone. Differing from previous studies, in our study only endoscopy was used for the conformation of the presence of duodenal ulcer in probands and also in their siblings. Endoscopy presents the incidence of active and healed duodenal ulcer more precisely than any other methods.

We do not know whether an elevated gastric acid secretion was determined genetically, since there was no study on it in a familial basis. Pepsinogen I is derived from the chief cells and mucous neck cells in fundic gland mucosa of stomach[10] and a significant relationship exists between the serum pepsinogen I level and acid secretory capacity[11]. If elevated level of serum pepsinogen I concentration was determined genetically, and an elevated gastric acid secretion was also genetically determined in such manner, the hypersecretion of hydrochloric acid and pepsin in gastric juice may contributed to the development of duodenal ulcer in affected siblings.

About a half of duodenal ulcer siblings was normopepsinogenemia I, and in some duodenal ulcer families normopepsinogenenia I also seggregated. As the most striking feature of duodenal ulcer is elevated acid secretion, although overlap with normal subjects exists, there is no pathophysiological role of normopepsinogenemia I itself in the development of duodenal ulcer in these families. Other genetic factors linked with inheritance of pepsinogen I level may have a pathophysiologic significance.

REFERENCE

1. **Clarke, C.A., Edwards, J.W., Haddock, D.R.W., Howel Evance, A.W., McConnell, R.B. and Sheppard, P.M.** 1956. ABO blood groups and secrator character in duodenal ulcer. Br. Med. J. **2**:725—731.
2. **Doll, R. and Buch, J.** 1950. Hereditory factors in peptic ulcer. Ann. Eugen. **15**:135—146.
3. **Gotlieb Jensen, K.** 1980. Genetics of peptic ulcer. Scand. J. Gastroenterol. **15 Supple 63**:11—15.
4. **Jirasek, V.** 1971. Hereditary factors in the etiology of peptic ulcer. Acta Univ. Carol **17**:383—456.
5. **Kubickowa, Z. and Vesely, K.T.** 1972. The value of the investigation of the incidence of peptic ulcer in families of patients with duodenal ulcer. J. Med. Genet. **9**:39—42.
6. **Lam, S.K. and Ong, G.B.** 1976. Duodenal ulcer, early and late onset. Gut **17**:169—179.
7. **Monson, P.R.** 1970. Familial factors in peptic ulcer, the occurrence of ulcer in relatives. Am. J. Epidemiol. **91**:453—466.
8. **Rotter, J.I., Sones, J.Q., Samloff, I.M., Richardson, C.T., Gursky, J.M., Walsh, J.H. and Rimoin, D.L.** 1979. Duodenal-ulcer disease associated with elevated serum pepsinogen I. N. Engl. J. Med. **300**:63—66.
9. **Rotter, J.I., Petersen, G., Samloff, I.M., McConnell, R.B., Ellis, A., Spence, M.A. and Rimoin, D.L.** 1979. Genetic heterogeneity of hyperpepsinogenemic I and normopepsinogenemic I duodenal ulcer disease. Ann. Int. Med. **91**:372—377.
10. **Samloff, I.M.** 1971. Cellular localization of group I pepsinogens in human gastric mucosa by immunofluorescence. Gastroenterology **61**:185—188.
11. **Samloff, I.M., Secrist, D.M. and Passaro, E., Jr.** 1975. A study of the relationship between serum group I pepsinogen levels and gastric acid secretion. Gastroenterology **69**:1196—1200.
12. **Uemura, N., Sumioka, M., Sumii, K., Kajiyama, G. and Miyoshi, A.** 1984 Clinical significance of serum pepsinogen I levels. I Bunpitsu Kenkyu-kaishi **16**:29—32 (In Japanese).