The Natural History of Esophageal Varices and Effecting Factors

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Summary: *We studied the rate of development and the factors effecting with large oesophageal varices in 40 cirrhotic patients who had Child-Pugh score A or B and without large oesophageal varices and no history of digestive bleeding.*

As a conclusion, during the follow-up period the factors effecting the occurence of large eosophageal varices and change of the variceal size were: initial size of varices and alterations in Child-Pugh score, serum albumin level and prothrombin time.

Key Words: Large esophageal varices, natural history and effecting factors.

Esophageal varices (EV) are the consequence of portal hypertension produced by liver cirrhosis. The most frequent cause of upper gastrointestinal haemorrahage in cirrhosis is oesophageal variceal bleeding. A bleeding episode is encountered usually in a year after first diagnosis and mortality is about 40-50% in first episode of bleeding (1). Survival rate is near 30% in the following year (2). Bleeding is most frequently seen in those patients who have larger sizes varices with red spots, and have concominant gastric varices (3-6). Bleeding is also more frequent in Child-Pugh score B or C and in alcoholic cirrhosis (6).

The natural history of EV have not been investigated and documented well. In this study the EV of the patients who had not bled were investigated and the natural history with possible factors effecting this course were searched.

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PATIENTS AND METHODS

Patients carrying the following criteria were included in the study: Age below 75, cirrhosis diagnosed either histologically biochemically, clinically and/or ultrasonographically; with cirrhosis which have been diagnosed not earlier than 6 months; no history of upper gastrointestinal bleeding; free of hepatic carcinoma; Child-Pugh A or B cirrhosis; and with grade 0 ve 1 varices; and with no medications which could effect portal haemodynamics.

Fourty patients who have been followed with liver cirrhosis in TYIH, Department of Gastroenterology since 1983 and who fit the criteria mentioned were included in the study. The duration of the disease; the size of the spleen and liver; the presence of ascite or encephalopathy; the serum albumin, bilirubin, ALT and AST levels; prothrombin time and the Child-Pugh classifications were recorded at 6 monthly. Intervals ultrasonograhic and endoscopic findings were also noted.

Mortality and variceal bleeding were considered as the endpoint of the follow-up.

The size of the EV were classified as suggeted by Japanese society for portal hypertansion (7).

Grade 0: no oesephageal varices;
Grade 1: oesophageal varices flattened by insufflation;
Grade 2: oesophageal varices that were not flattened by insufflation and were separated by areas of the normal mucosa;
Grade 3: confluent esophageal varices that were not flattened by insufflation.

The mean age of the patients was 45 (range 16-67). Twenty nine were males and 11 were females. Cirrhosis was due to HBV in 28, alcohol in 3, primary biliary in 2, and cryptogenic in 7. The diagnoses were verified histopathologically in 24 (60%). The median oberved duration of cirrhosis was 36 months (range 12-102). The mean follow-up was 30 months (range 6-96). Nineteen were graded as Child-Pugh A and 21 as B. The varices graded 0 in 28 (70%) and 1 in 12 (30%) at the beginning.

Statistical Analysis

Data was analysed by factorial analysis and were saperated by Varimax method. Statistical significance was looked with Mann-Whitney U test and $p>0.05$ was considered as not significant.

RESULTS

In 12 (30%) of the patients the variceal grade remained stable whereas in 28 (70%) varices increased in size during follow-up. No new varices developed in 8 of 28 (28.6%) patients who had no varices (grade 0) at initial diagnosis. Fourteen (50%) turned into grade 1,5 (17.8%) turned into grade 2 and 1 (3.6%) turned into grade 3. The variceal sizes did not changed in 4 of 12 (33.3%) who had grade 1 varices. Initially four (33.3%) turned into grade 2 and 4 (33.3%) turned into grade 3. Garde 2 varices developed in 9 (22.5%) and grade 3 varices developed in 5 (12.5%) patients (Figure 1).

The number of patients who did not developed large sized varices at the and of the first year

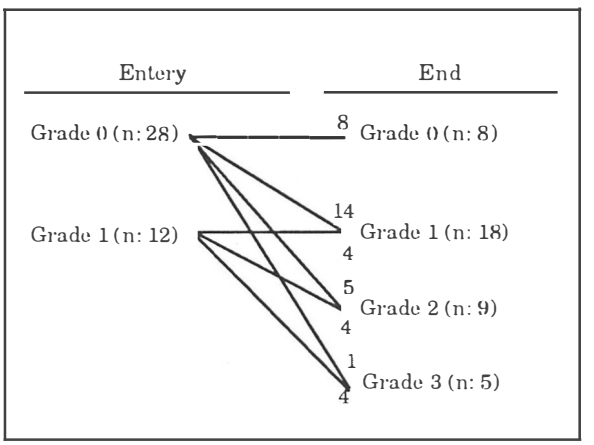

Figure 1: The changes in variceal grades during the follow-up period.

was 32 (80%), at the and of the second year was 29 (72.5%), at the and of the third year was 27 (67.5%) and at the and of fourth year was 26 (65%) (Figure 2).

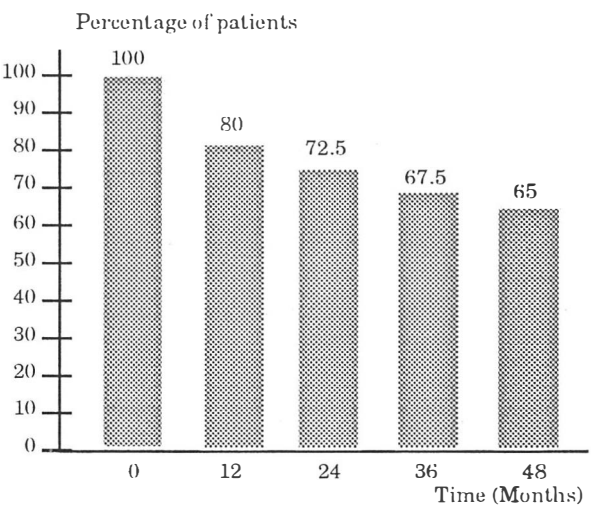

Figure 2: The distribution of patients who the variceal size did not changed.

Of the nineteen patients with Child-Pugh A cirrhosis 7 (36.8%) became Child-Pugh B and 7 (36.8%) became Child-Pugh C. Child-Pugh classification did not changed in 5 (26.4%) Child-Pugh A patients of the 21 patients with Child-Pugh A cirrhosis 14 (66.7%) became Child-Pugh C whereas 7 (33.3%) did not changed.

The changes in Child-Pugh classification in the patients in whom oesophageal variceal size altered were as follows; 3 patients remained in A, 7 patients became B and 5 patients became C of 15 Child-Pugh A patients. 3 patients remained in B and 10 became C of 13 Child-Pugh B patients. The changes in Child-Pugh classification in whom variceal size did not altered were as follows; 2 patients became C and 4 remained A in 6 of Child-Pugh A patients. 4 patients became c and 4 remained B in 8 of Child-Pugh B patients.

The aetiology of cirrhosis who developed large varices were as follows 8 of 28 HBV cirrhosis, 2 of 4 alcoholic cirrhosis, 3 of 6 cryptogenic cirrhosis and one of 2 primary biliary cirrhosis.

Four patients were exculuded from the study (in 3 because of bleeding and in 1 because of death due to hepatic failure). The patients who had bled from varices were managed by endoscopic injection sclerotherapy and by medical means. Bleeding varices were initially grade 1 and developed larger varices. Thus the bleeding rate in grade 1 varices was 25% and in the larger varices group was 21%.

The clinical and laboratory parameters of the group which varices changed in size and did not changed in size are shown in Table I.

Table I: The distribution of parameters according to patients

		Variceal size not changed		Variceal size changed	
		Entry	End	Entry	End
Ascite	+	4	9	3	17
		8	3	25	11
Liver Size	HM	2	1	0	4
	N	9	2	21	12
	A	1	7	4	16
SM	+	6	10	19	2
		6	2	9	4
Fundal varices	+	0	0	0	2
		12	12	28	26
BIL. mg/dl	<2	9	5	16	10
	2-3	0	4	10	11
		3	3	2	7
ALB. mg/dl		1	7	6	10
	3-3.5	4	3	16	6
	>3.5	7	2	6	4
ALT IU/L	<100	9	9	21	19
	>100	3	3	7	9
AST IU/L	<100	10	10	24	20
	>100	2	2	4	8
PT (sec)	<14	4	4	15	9
	14-20	8	8	13	
	>20	0	0	0	1
CPS	0-6	4	2	15	3
	7-9	8	4	13	10
	10-15	0	6	0	15

Abbraviations: HM: Hepatomegali, N: Normal, A: Atrophy SM: Splenomegali,
BIL: Bilirubin, ALB: Albumin, PT: Prothrombin Time, CPC: Child-Pugh Score.

Statistical Results

At the initiation of the study: the significant variables as cirrhosis duration (CD), liver size (LS), ascite (A), splenomegali (SM), albumin (ALB), bilurubin (BIL), prothrombin time (PT), ALT, AST and Child-Pugh score (CPS) were reduced to two factors (FI, F2) which explain the 58% of general variance. The rank of the variable effecting these factors are; CPS, AST, ALT and ALB.

At the and of the study when the same variable were considered it was reduced to 3 fastors explaining the 73% of general variance (F'1, F'2, F'3). The rank of the variable effecting these factors are AST, CPS, PT, ALT and ALB.

The factors were made of the following variables;

F1: CD, ALB, BIL, PT, CPS; F2: LS, ALT, AST, A, SM; F'1: ALB, PT,CPS; F'2: ALT,AST; F'3: CD, LS,BIL,SM, A.

When the group in which varices changed in size was compared to group which the size did not changed. At the initiation of the study there was no significant difference between (F1)s and (F2)s (F1:$p>0.05$, F2:$p>0.05$). At the and of the study there was significant difference between (F'1)s, (F'1:$p<0.001$), but there no differences in (F'2)s and (F'3)s, (F'2:$p>0.05$, F'3:$p>0.05$).

DISCUSSION

The investigation of natural history of esophageal varices should begin in the earliest phase of cirrhosis, because in the late phase of the disease the inclusion criteria alters the evaluation of the results.

Only the patients with not more than 6-month-history of cirrhosis and who had not bled were included in this study. Therefore the natural history of EV could be investigated as good as possible.

There are not many reports about the natural development of EV. Preliminary articles about the subject were reported by Dagradi and Olsson (8,9). Dagradi investigated the EV of alcoholic cirrhotic patients; in one group the patients had given up alcohol where as in the other group the patients werek still consumers. Olsson investigated the relation between cirrhosis and EV in autopsy material in his resrospective study.

Dagradi reported that the time needed for development of large varices was approximately 50 months in alcohol consumers (8).

In his study Czaja reported that EV development rates after diagnosis of cirrhosis was 8% in after one year and 13% after five years. But all of his cases had severe chronic active liver disease treated with prednisone and varices were diagnosed by X-Ray (10).

Christensen showed that the cumulative persentage of the patients in whom EV had been shown by radiography but who had not experienced bleeding increased from 8 to 83% over 10 years. Nevertheles the actual percentage of patients with EV might have been less, since this calculation did not take into account the proportiton of patients in whom variceal size regressed (1).

The Mayo Clinic group showed that EV occured in 31% of patients with primary biliary cirrhosis followed for a median of six years (11).

Cales reported that in patients with alcoholic cirrhosis who had grade 0 or 1 EV, the size did not changed in 49%, increased in 43% and decreased in 8% and at the and a median follow-up of 16 months large EV developed ın 31% (12).

In our study the EV size remained stable in 30% and increased in 70%. No decrease in EV size was observed. Large EV developed in 32.5% of the patients in 36 months.

Cales observed that large EV developed in 74% of patients at the and of first year and in 52% at the and of the second year, and large EV development rate increased linearly in two years (12).

Dagradi also oberved variceal size increased faster in first year after their discovery than later on (8).

Our results showed that the percentage of patients free of large varices was 80% at the and of first year, 72.5% in second year, 67.5% third year and 65% fourth year. The variceal grade increased linearly with the duration of cirrhosis. This increase was greater in the first two years. But we did not observed any relation between the change of EV size and the duration of cirrhosis ($p>0.05$).

Cales suggested that the initial size of EV and variation in Child-Pugh score and the dura-

tion of cirrhosis were the major factors effecting the development of large varices (12).

We also found that initial size of EV was important. Large EV developed was 24% of patients with grade 0 and 66.6% of grade 1 patients. In some studies no relation between initial Child-Pugh score and development of large EV. But some observed significant relation between variation in Child-Pugh score and development of large EV (12). And some other authors found relation between the mean Child-Pugh score and size of EV (4). The predictive value of hepatic dysfunction was shown important for the occurence of EV in Primary biliary cirrhosis (11).

We did not find any relation between the initial Child-Pugh score and EV developement, but there was a significant relation with the variation of the Child-Pugh score ($p<0.001$). There were also no relations between the albumin, bilirubin, ALT, AST, PT, liver and spleen size, and ascite parameters at initial diagnosis and occurence large EV. But the relation between variation size of EV and albumin and PT in time was significant ($p<0.001$). This shows that the most important factor effecting EV grade was the level of hepatic dysfuction.

Clinically, the change of the size of EV and the rate of occurence of large EVs are important, because bleeding is the most frequent cause of death in cirrhosis (13). Bleeding rate increases as the EV size increases (3,4,6,8,12). On the other hand, bleeding rate is also higher in Child B and C patients (7,14). EV wall rupture is impossible if hepatic venous pressure is 12mmHg or less, although there is no significant relation between EV bleeding and portal pressure (3).

There is also relation between the variceal size and endoscopic predictive signs of possible bleeding (4). Considering all of the subjects discussed above, it seems suitable that the prophlactic measures, either medical, endoscopic or surgical should be taken.

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