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RELATIONS BETWEEN THE HAEMATOLOGICAL HYPERSPLENISM AND SPLENOMEGALY IN PATIENTS WITH HEPATIC CIRRHOSIS

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Abstract: *Even though the relation between the hypersplenism and hepatic cirrhosis has been long known, the complete explanation of its mechanisms is not completely understood. The numerous clinical observations have shaped the notion of haematological hypersplenism and have related it to portal hypertension and increased volume of the spleen Attempts to infer the intensity of hypersplenism based on various clinical or paraclinical criteria have had controversial results. Trying to find correlations between any possible predictive factors of hypersplenism in cirrhotic patients this study shows that splenomegaly is not a predictive factor for hypersplenism and that the most predictive factor for thrombocytopenia was the viral plus alcoholic aetiology of chirrosis*

Key words : *hypersplenism, splenomegaly, cirrhosis, portal vein.*

1. Introduction

Changes in the peripheral blood associated with hepatic cirrhosis and splenomegaly, known under the name of hypersplenism, have been described for the first time in 1894 by Banti. They most frequently consist of thrombocytopenia and more rarely of leukopenia and anaemia. In 1929 King found that in 20% (1/5) of the number of cirrhotic patients the number of platelets was low, whereas only one out of fifteen (1/15) concomitantly had prolonged clotting times [1].

The concept of hypersplenism within the framework of cirrhosis has never been proved beyond any reasonable doubt, but it has been accepted for lack of an alternative explanation [2]. The simplest intuitive mechanism turned the intermediate portal hypertension into the main missing link in the drop of the figurative elements of blood, through their mechanical destruction in the trabecular spaces of the red pulp and through secondary splenomegaly. Nevertheless, the spleen's volume increase does not only have a haemodynamic cause, but is also due to hyperplasia and the fibrosis of the splenic

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tissue [3], this being a second mechanism of hypersplenism. Even though there had been suspicions for a long time about the existence of a colony-stimulating factor of the platelet production, thrombopoietin was cloned by five independent groups of scientists only in 1994, thus making obvious another link, between thrombocytopenia and the liver, a different one from portal hypertension. Thrombopoietin is predominantly produced in the liver and it depends on the mass of functional hepatocytes [2], and the drop in it is a third mechanism involved in the concept of hypersplenism. In a study made in 2010, Djordjević J. was unable to find any correlation between the size of the spleen and the number of thrombocytes suggesting the existence of two more mechanisms: one represented by the myelosuppression induced by the multiplication of the hepatic viruses or by the toxic effect of alcohol, and a second one, related to the presence of antithrombocytic antibodies [4].

Correlations have been described between the size of the spleen, thrombopenia and the age of onset of the liver disease. The hypersplenism is characterized by severe thrombocytopenia in young patients with large spleens more often than in elder patients [5].

The prognostic significance of hypersplenism is unclear in cirrhotic patients even more because it is unknown why some patients, regardless of the degree of splenomegaly, develop severe forms of hypersplenism, whereas others display no sign of it. In this context, it is natural to wonder whether severe hypersplenism is a predictive factor for oesophageal variceal rupture or spontaneous bacterial peritonitis, two of the redoubtable complications of cirrhosis [6].

2. Aim

The study of relationshep beetween haematological hypersplenism, spleen and portal vein saize evaluated by abdominal echography.

3. Material and Methods

3.1. Design

A transversal, observational and prospective study in 290 patients with cirrhosis admitted in the Departments of Gastroenterology and Internal Diseases of the Clinical Emergency Hospital in Brasov City during the year 2012.

The patients were diagnosed with cirrhosis of different aetiology and Child-Pugh stages and randomised in order of their admission in the hospital. According to the aetiology the group included 174 patients with alcoholic cirrhosis (60%), 84 patients with viral cirrhosis (29,3%), 17 patients with mixed cirrhosis (6,2%) and 15 patients with idiopathic cirrhosis (5,5%). The patients were evaluated using hemogram (number of platelets, leucocytes and haemoglobin), abdominal ultrasound to measure the diameter of the portal vein and the spleen size. In 75 patients a upper digestive endoscopy was performed to quantify the degree of the oesophageal varices as small, average and large size. The serum concentration of iron was determined in 26 of the subjects. The types of hypersplenism analysed were: pancytopenia, bicytopenia and thrombo-cytopenia.

The hypersplenism in was defined by platelet count < 150,000/mm^3 , leukocyte count < 4000/mm^3 and anemia by Hb <12g%. Using these criteria 74 patients were diagnosed with haematological hypersplenism. Isolated thrombocytopenia was seen in 184 patients (63%). Pancytopenia was present in 20 patients (6,9%) and bicytopenia (thrombocytopenia and leukopenia) in 35 patients (12%).

3.2. Statistical analysis

The statistical analysis used the SPSS 17 software and comprised different modules of univariate and multivariate anaysis of the observed parameters. Averages, medians, the dispersion analysis and data normality were used to calculate the confidence interval of 95% (C.I. 95%).

The normality of the variable distributions was assessed by calculating the skewness and kurtosis coefficients of data.

For the correlation of the scalar data, a graph matrix of the bivariate correlations was used, and then the partial correlations were studied. The testing of the statistical significance was done using the Pearson „r" coefficient and the R^2 coefficient of determination. The simple linear regression equation was pointed out.

The correlation between the haematological hipersplensim and age, gender, chirrosis aetiology, spleen size and portal vein diameter used the multinomial logistic regression analysis (statistically significancy for $p < 0.05$). B coefficients (with the statistical significance and the confidence intervals of 95% – 95% C.I.) were calculated, as well as the odds ratio values (ExpB) with 95% C.I. and the matched model indexes for every variable included in the table.

4. Results and Discussion

4.1. Analysis of the characteristics of the studied population

The mean age of the patients was 56 (CI 95%[54.8 – 57.4]; min 20, max 86). With a predominance of females (63% vs 37%) in our study group, the gender proportion was unballanced. A binomial test indicates a very high significance of this difference ($p < 0.001$). As there is no biological explanation, this is interpreted as a particularity of the study group. It was a high proportion of the alcoholic aetiology (47.5%) among female.

The average values of the haematological parameters of hypersplenism are shown in Table 1.

Mean of haematologic parameters (Nr./mm^3) Table 1

	Trombocytes	Leucocytes	Hb
Mean	140279	6483	12.1
Std. Deviation	94332	2814	2.67
Skewness	1.309	.904	-.420
Kurtosis	1.581	1.287	.566

The histogram of the platelet and leukocyte distribution suggests a positive "skew" of the normality curve, anticipating the relation between hypersplenism and the hepatic cirrhosis that is presented in Figure 1.

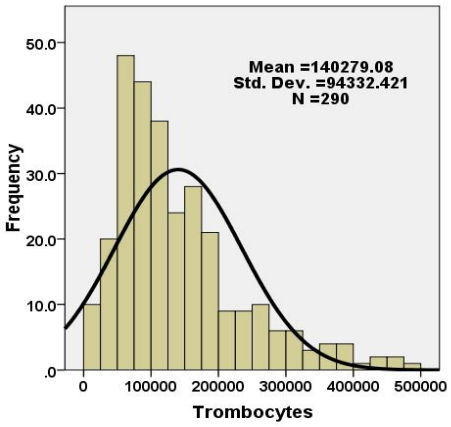

Fig.1. *Trombocytes distribution*

The severity of oesophageal varices in the 75 patients who underwent oesophagoscopy shown that in 40 patients (53%) the varices were small, in 13 patients (18%) there was an average grade of varices and that 22 patients (30%) had large oesophageal varices. This parameter was used as an indirect sign of the severity of the portal hypertension, alongside the volume of the spleen and the diameter of the portal vein, whose statistical description can be seen in Table 2.

Table 2

Mean of the spleen and portal vein (mm)

	Spleen	**Portal vein**
Mean	134	12.9
Std. Deviation	27	2.16
Skewness	.059	.433
Kurtosis	.276	.900

The mean value of the iron serum concentration was 107 μg (SE ±16,5 μg). There was a lack of correlation between the values of haemoglobin and iron serum level, (Pearson's correlation: $r = 0,23$; $R^2 = 0,05$; $p=0,26$), suggesting that in these patients the low values of hemoglobin could be also explain by other mechanisms including hypersplenism.

4.2. The correlations between hypersplenism and the spleen and portal vein size

The drop in the figurative elements of blood has been analysed in relation to the spleen size and portal vein diameter in a matrix of graphs of bivariate correlation (Fig. 2).

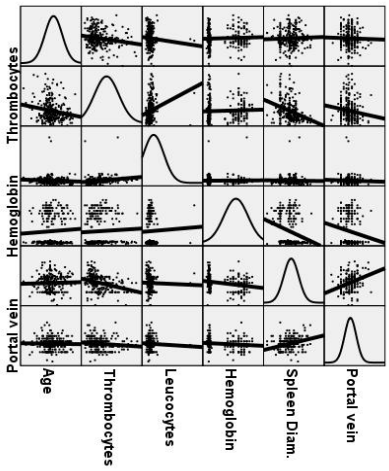

Fig. 2. *Matrix of bivariate correlations*

There was a highly positive correlation between platelets count, leukocytes count and haemoglobin values, underling the involvement of all three lines of haematophoesis in the haematological hypersplenism of cirrhotic patients.

Our data show also a statistical significant negative correlation between platelets count, leukocytes count, haemoglobin values and spleen size and portal vein diameter in cirrothic patients (Table 3). Even though the statistical significance of the connection is very important, the calculation of the determination coefficients (Table 3) shows a modest influence of the spleen volume in the determination of thrombocytopenia, i.e. only 10%.

Correlations between trombocytes and other parameters Table 3

		Age	**Leucocytes**	**Hb**	**Spleen Diam**	**Portal vein**
Trombo-cytes	Pearson Correlation	-.179**	.375**	.142*	-.323**	-.124*
	Sig. (2-tailed)	.002	.000	.016	.000	.035
	Coef. of determ. (R^2)	.030	.14	.02	.10	.01

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

As quite a tight connection has been proven between the diameter of the spleen and that of the portal vein, such connection being directly proportional to the size of the portal hypertension, a partial correlation has been made between the platelet count and the spleen size, with the portal vein diameter as a control parameter, but the correlation coefficient between the platelet count and the spleen size did not improve. This suggest only a modest influence of the spleen size in the developement of thrombocytopenia.

The age, the aetiology of cirrhosis, spleen size and portal vein size has been proven to not predict pancytopenia and bicytopenia in hepatic cirrhosis (Tables 4a and 4b).

Pancytopenia Table 4a

	B	Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Age	.038	.101	1.038	.993	1.086
Gender(1)	.137	.805	1.147	.386	3.410
Etio		.283			
Etio(1)	.467	.453	1.596	.471	5.411
Etio(2)	1.456	.052	4.287	.990	18.557
Etio(3)	-18.009	.999	.000	.000	.
Spleen	.007	.422	1.007	.989	1.026
Constant	-6.215	.002	.002		

Bicytopenia Table 4b

				95% C.I.for EXP(B)	
	B	Sig.	Exp(B)	Lower	Upper
Age				.998	1.071
Gender(1)				.174	.969
Etio		.735			
Etio(1)	.284	.558	1.328	.514	3.432
Etio(2)	.798	.274	2.222	.531	9.293
Etio(3)	-18.668	.998	.000	.000	.
Spleen	.019	.009	1.020	1.005	1.034
Constant	-6.341	.000	.002		

If only the thrombocytopenia has been analysed, age and the spleen diameter are recorded as predictors, with *odds ratio* very close to 1. The strongest positive predictors of thrombocytopenia have been mixed etiology (*odds ratio* 38,3 ; C.I. 95% 5,4–271) and female gender (*odds ratio* 4,1 ; C.I. 95% 2–8,2). (Table 5, Figure 3).

Thrombocytopenia Table 5

	B	Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Age	.027	**.036**	1.027	1.002	1.053
Gender(1)	-1.415	**.000**	.243	.121	.487
Etio		**.002**			
Etio(1)	-.485	**.181**	.616	.302	1.253
Etio(2)	1.765	**.027**	5.843	1.225	27.869
Etio(3)	-1.882	**.004**	.152	.042	.547
Spleen	.024	**.000**	1.025	1.014	1.036
Constant	-3.039	**.003**	.048		

Predicted Probability is of Membership for YES
The Cut Value is ,50
Symbols: N – NO; D - YES
Each Symbol Represents 1 Case.

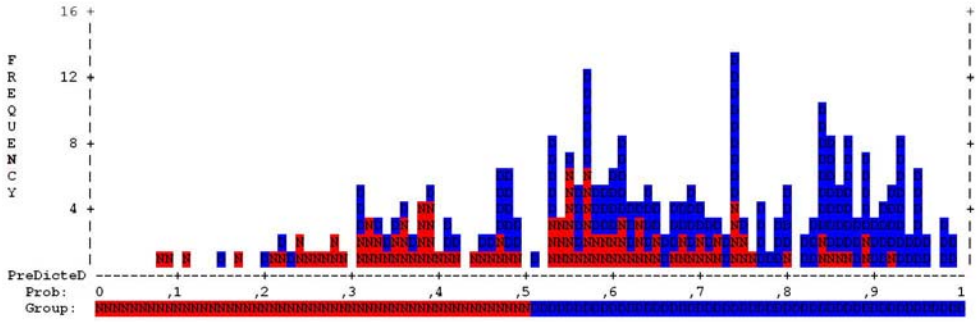

Fig. 3. *Observed Groups and Predicted Probabilities*

The R2 Naghelkerke coefficient is 0.26, which should be interpreted in the sense that only 26% of the platelet variation may be explained through the other four parameters (age, gender, aetiology and splenomegaly). This value indicates a relatively modest relation and there are other factors that the size of thrombo-cytopenia depends upon. The efficiency of this model of prediction of thrombocytopenia caused by hyper-splenism based on the four parameters is 70% and this is not a very high predictive power.

In our study it was a positive correlation between thrombocytopenia and age. Even if week, the positive correlation between the platelet count and age might be interpreted, most likely, as being associated to the age of the disease. McCormick et al. reported a positve correlation between the age of patients and the onset of the disease [5].

5. Conclusions

The haematological hypersplenism in cirrhotic patients occurred in two third of patients, is about 4 times higher in female and the most involved haematopoesis line is the thrombocytic one.

Splenomegaly was not a powerful predictive factor for haematological hypersplenism. The most powerful predictive factor for thrombocytopenia was the mixed (viral plus alcoholic) aetiology. The inclusion of age, gender and splenomegaly does not increase the predictability of thrombo-cytopenia.

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