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New Clinical Criteria for the Assessment of Liver Involvement in Hodgkin's Disease

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Abstract—*The hepatic involvement in Hodgkin's disease, histologically verified in 133 patients who underwent laparotomy or laparoscopy, proved to be singly related to the following clinical findings: result of the liver isotopic scan, liver and/or spleen enlargement, serum albumin* $\leqslant 3.5$ *g/dl, GOT and/or GPT* $\geqslant 20$ *mU/ml, serum alkaline phosphatase (SAP)* $\geqslant 210$ *mU/ml, BSP retention at* 45 min $\geqslant 6.5\%$ *and* ESR $\geqslant 51$ mm *at* 1 hr. *Such clinical findings were jointly evaluated and further selected by means of a logistic discriminant analysis, and the simplest function with the best discriminant ability between involved and non-involved liver was made by liver scan, spleen enlargement, BSP retention and GOT (89.5% of correct diagnoses). Since the Ann Arbor clinical criteria for liver involvement showed correct diagnoses in 69–80% of the cases, more reliable criteria can be proposed. So, liver involvement is highly probably (a) when three or more of the five variables indicated above are abnormal, or (b) when a markedly abnormal liver scan is associated with alteration of at least one of the other four parameters: otherwise liver will be non-involved.*

INTRODUCTION

THE INVOLVEMENT of the liver in Hodgkin's disease (HD) is a critical step in the clinical course of the disease. Generally, the spreading of HD into the liver occurs by haematogenous dissemination from distant organs [1]; there is evidence that often the previously involved spleen is recognizable as the main source of diffusion to the liver, via the splenic vein and the portal tract [2, 3]. Moreover, the liver is one of the most common extranodal organs to be involved in the advanced phases of HD [1] and such an event affects prognosis and treatment [4, 5].

The clinical assessment of liver involvement usually provides some problems. Many liver function tests have been suggested as indicators of hepatic HD [6–13] but they all have proved to be rather unreliable when singly considered [14], and it is general experience that the Ann Arbor clinical criteria—using two or three tests together [15]—show only slightly greater accuracy. So, an exact evaluation of liver involvement requires multiple biopsies either guided by laparoscopy or performed during a careful staging laparotomy [5].

In this work we investigated the clinical, humoral and instrumental findings that prove to be better correlated with liver involvement. Our purpose was to arrange a battery of clinical tests with the relatively greatest ability of predicting the HD hepatic involvement or non-involvement, irrespective of any other associated liver pathology.

MATERIALS AND METHODS

We reviewed the clinical records and the surgical protocols of 133 patients with HD who underwent staging laparotomy with splenectomy and multiple liver biopsies between January 1971 and December 1980. Seventy-eight of them were male, 55 female, 14–54 years of age.

After staging laparotomy 20 patients (15%) showed evidence of liver involvement by HD while 113 had non-involvement; in this second group 11 cases of unspecified portal inflammation, seven of mild steatosis and one of chronic alcoholic hepatitis were observed.

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None of the 113 patients without liver involvement at diagnosis relapsed with either proved or even suspected liver disease within 16 months from laparotomy. Four patients are known to have relapsed with liver involvement at 17, 19, 25 and 39 months respectively from pathological staging.

By means of contingency tables [16] a selection was made of the pre-laparotomy physical, humoral and instrumental findings that showed to be more related to the involvement (or non-involvement) of the liver. The clinical parameters we have taken into account are listed in Table 1.

Enzymatic assays were performed with an optimised kinetic test [17] using Merck kits (Darmstadt, West Germany); the BSP retention was evaluated by standard methods [18].

Liver and spleen enlargement were judged merely on physical findings, i.e. by the semeiological evaluation of the whole size of these organs and with the exclusion of simple lower displacement.

After selection of the best tests an attempt was made to handle these as binary variables for ease and uniformity of data elaboration.

Parameters with more than two discrete values (e.g. the histology) were converted when possible into dichotomous ones by the analysis of the differences between the observed and expected frequencies of their values. Such a reduction could not be made for the results of lymphography and of liver and spleen scans, for which three types of results had to be tolerated: positive, negative and dubious.

The laboratory tests, whose values are variable over a wide range, were transformed into dichotomous parameters according to whether or not their values exceeded a fixed threshold value; this was chosen as intermediate between the means recorded among patients with involved and non-involved liver respectively. The 'like normal' distribution of data in the two groups of patients (see also Fig. 1) made such an approach possible.

The parameters which singly showed the highest relation with liver involvement were jointly inter-connected in a logistic discriminant analysis in order to draw a predictive rule for liver involvement. In the linear function the values 1 or 0 were assigned to the dependent variable—the histological aspect of the liver—whether it was involved or not; the same values 1 or 0 were given to the predictive variables—the pre-operative clinical findings—according to whether they were positive or negative respectively (or present or absent, higher or lower than the fixed threshold value); the dummy value 0.5 was given only to the dubious result of liver and spleen scans and of lymphography.

Such statistical approaches have been better detailed elsewhere and proved to be successful [19–21].

RESULTS

Tables 2, 3 and 4 report the frequency of normal and altered clinical findings related to the involvement of the liver verified histologically by multiple biopsies in the course of staging laparotomy.

Table 2 shows that liver involvement is not associated with a particular sex or histological type; it is relatively more frequent when general symptoms are present (B stages) and it is strictly related to both liver and, separately, palpable spleen enlargement.

Table 3 suggests that liver involvement is frequently recognized by liver scan, but it is also often related to abnormal spleen scan (a true, histologically proven involvement of the spleen accompanied that of the liver in 17 out of our 20 cases). Lymphographic positivity of retroperitoneal lymph nodes was not significantly associated with liver involvement.

Table 1. Clinical findings recorded before laparotomy with multiple liver biopsies and evaluated in relation to the involvement of the liver by HD

Discrete variables		Continuous variables
Sex		Erythrocyte sedimentation rate (ESR), mm at 1 hr
Histological type (LP, NS, MC, LD)		Fibrinogenaemia (Fb), mg/dl
General symptoms (A or B)		Serum copper (Cu), μg/dl
Palpable liver enlargement		Albuminaemia (Alb), g/dl
Palpable spleen enlargement		α_2-globulinaemia (α^2), g/dl
Liver scan (rose bengal—[^{131}I] or [^{99m}Tc])	positive or negative or dubious	Serum total bilirubin (Bil), mg/dl
Spleen scan ([^{197}Hg] or [^{99m}Tc])		Serum glutamic oxaloacetic transaminase (GOT), mU/ml
Bipedal lymphoangiography		Serum glutamic pyruvic transaminase (GPT), mU/ml
		Serum gamma-glutamyl-transpeptidase (GGT), mU/ml
		Serum alkaline phosphatase (SAP), mU/ml
		Bromosulphophthalein retention (BSP), % at 45 min

Table 2. Frequency of some biological and clinical findings recorded before laparotomy related to the involvement (inv.) and non-involvement (n-inv.) of the liver verified after laparotomy

Parameter		Liver inv.	Liver n-inv.	*P*	Parameter		Liver inv.	Liver n-inv.	*P*
Sex	male	13	64	0.808	Symptoms	A	9	73	0.096
	female	7	39			B	11	40	
Histotype	LP	1	18	0.684	Liver enlargement	Yes	16	54	0.008
	NS	10	35			No	4	59	
	MC	6	43						
	LD	3	17		Spleen enlargement	Yes	15	42	0.006
						No	5	71	

Table 3. Results of roentgenologic and isotopic investigation related to the involvement (inv.) or non-involvement (n-inv.) of the liver, histologically verified

		Liver inv.	Liver n-inv.	*P*			Liver inv.	Liver n-inv.	*P*			Liver inv.	Liver n-inv.	*P*
Liver scan	Positive	9	17	0.002	Spleen scan	Positive	11	24	0.016	Lympho-graphy	Positive	12	54	0.537
	Dubious	7	30			Dubious	4	23			Dubious	1	12	
	Negative	4	66			Negative	7	66			Negative	7	47	

Table 4. Humoral alterations related to the involvement (inv.) or non-involvement (n-inv.) of the liver by HD

Test		Liver inv.	Liver n-inv.	*P*
ESR	≥51 mm 1 hr	13	47	0.053
	<51 mm 1 hr	7	66	
Fb	≥413 mg/dl	12	44	0.079
	<413 mg/dl	8	69	
Cu	≥183 µg/dl	10	54	0.855
	<183 µg/dl	10	59	
Alb	≥3.5 g/dl	7	69	0.029
	<3.5 g/dl	13	44	
α2	≥0.95 g/dl	8	33	0.335
	<0.95 g/dl	12	80	
BSP	≥6.5%	12	39	0.031
	<6.5%	8	74	
Bil	≥0.75 mg/dl	10	41	0.244
	<0.75 mg/dl	10	72	
GOT	≥20.0 mU/ml	9	19	0.004
	<20.0 mU/ml	11	94	
GPT	≥20.0 mU/ml	9	22	0.013
	<20.0 mU/ml	11	91	
GGT	≥48.5 mU/ml	8	28	0.157
	<48.5 mU/ml	12	85	
SAP	≥210 mU/ml	8	16	0.008
	<210 mU/ml	12	97	

Table 4 indicates that the only single humoral indices statistically related to liver involvement are: serum alkaline phosphatase (SAP), BSP retention at 45 min, glutamic pyruvate transaminase (GPT), serum albumin (Alb) and glutamic oxaloacetic transaminase (GOT) (see also Fig. 1).

A linear discriminant analysis was made on all the clinical parameters of Tables 2, 3 and 4 that showed the best correlation with liver involvement: there were nine of these and are those underlined in each table. The statistical evaluation of the coefficient of discrimination of every parameter made possible the selection of the smallest number of clinical variables associated with a relative maximum of diagnostic accuracy. Four of them could be omitted because of strong mutual inter-correlation: albumin, GPT, liver enlargement and spleen scan. The discriminant function with the remaining five clinical parameters is reported in Table 5 with its threshold values.

Involvement is predictable when, after the addition of the coefficients of all the present or positive clinical variables, the function assumes a value higher than the threshold one; non-involvement can be deduced for lower values. The error of discrimination between involved and non-involved liver in the population of 133 patients is 10.5% and increases at any further reduction in the number of the clinical variables employed.

Table 6 makes a comparison between the diagnostic accuracy of this discrimination function and that of the Ann Arbor criteria with respect to liver involvement; this comparison was made both on the 133 patients of this study and on 18 other patients observed after December 1980. The discrimination by the linear function (87.5–89.5%) was better than that by any one of the Ann Arbor criteria (70.0–79.7%) in both series of patients.

Particularly, it can be seen that the sensitivity of the clinical diagnosis is greatly enhanced by the

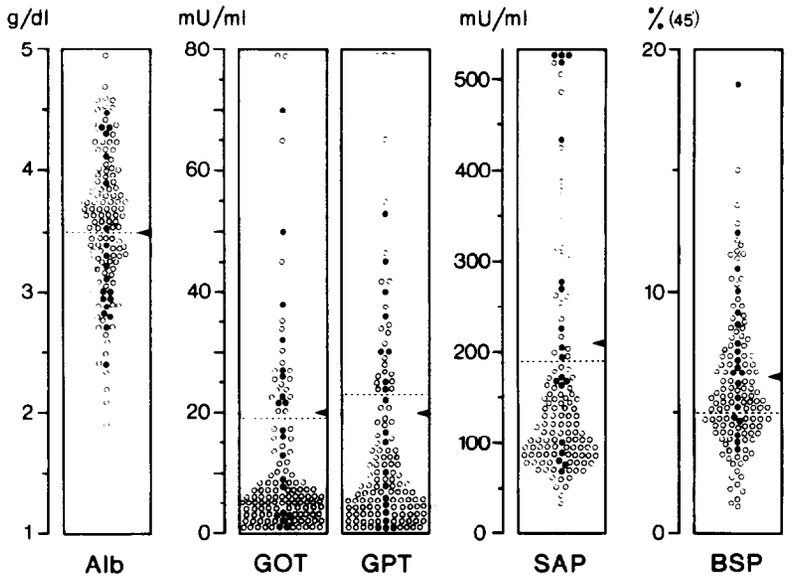

Fig. 1. Scattergram of the data of the main liver function tests related to the involvement (full points) or non-involvement (empty points) of the liver. The arrows indicate the working threshold value, while the dashed lines correspond to the normal limit.

Table 5. Linear discriminant function of the clinical variables of Tables 2, 3 and 4 that proved better related to the involvement of the liver (involvement is predictable when, after addition of all the coefficients of the abnormal tests, the function shows a value higher than the threshold one; otherwise liver will be probably non-involved)

Variables	Liver scan*	SAP ≥0.210	Spleen enlargement	BSP ≥6.5	GOT ≥20.0	Threshold value
Coefficients	×0.339	×0.260	×0.146	×0.132	×0.103	0.381
$P(t)$	($\underline{2\times10^{-6}}$)	($\underline{5\times10^{-4}}$)	($\underline{0.005}$)	($\underline{0.034}$)	(0.091)	

§When scan is dubious its coefficient must be multiplied by 0.5 before adding it.

Table 6. Number and correct predictions of involved and non-involved liver by the discriminant function of Table 5 and, separately, by each of the three criteria proposed at the Ann Arbor Conference

Clinical prediction by:		Liver histology in 133 studied patients		Liver histology in 18 control patients		Incorrect diagnoses %
		inv.	n-inv.	inv.	n-inv.	
Discriminant function	inv.	17	11	2	3	10.5–12.5
	n-inv.	3	102	0	13	
		(0.85)	(0.90)	(1.00)	(0.81)	
Ann Arbor criteria						
(a) Liver enlargement + abnormal SAP	inv.	6	13	2	4	20.3–12.5
	n-inv.	14	100	0	12	
		(0.30)	(0.88)	(1.00)	(0.75)	
(b) Two abnormal function tests	inv.	11	31	2	5	30.1–27.8
	n-inv.	9	82	0	11	
		(0.55)	(0.73)	(1.00)	(0.68)	
(c) Positive scan + one abnormal test	inv.	6	12	1	4	19.5–22.2
	n-inv.	14	101	1	12	
		(0.30)	(0.89)	(0.50)	(0.75)	

The comparison was made both on the 133 patients evaluated for statistical analysis and in 18 others taken as control. Sensitivity and specificity coefficients are given in brackets under involved and non-involved livers respectively.

discriminant function (from 0.30–0.55 to 0.85 in the study group, while the control group has too few patients with involved liver to give a reliable confirmation). Specificity is only slightly increased, from 0.73–0.89 to 0.90 in the study group and from 0.68–0.75 to 0.81 in the control group.

Practically, and without numbers, the clinical significance of the linear function can thus be reassumed: liver should be considered involved (a) when three or more out of the five variables of Table 5 are positive or abnormal (dubious scan included among these), or (b) when a markedly abnormal liver scan is associated with alteration of at least one of the other four parameters; otherwise, liver should be considered non-involved. These criteria reduced to less than one-half of the uncorrect clinical evaluations allowed by the Ann Arbor requirements for liver involvement.

DISCUSSION

Histologic examination of the liver seems the only reliable method for the assessment of its clinical status in HD [5, 15, 21]; for such evaluation adequate amounts of tissue, drawn from selected areas, can be provided only by staging laparotomy or peritoneoscopy [14, 22–24]. The clinico-pathological correlations allowed by such surgical procedures have proved the poor reliability of all the biochemical and instrumental tests which have been proposed for the detection of liver involvement: SAP and its isoenzymes, bilirubin, GOT, GPT and gamma-glutamyl transpeptidase, 5'-nucleotidase [5, 6–10, 22, 25]. SAP has been shown to be relatively less misleading [10, 12] and our results confirm this, but its accuracy, even taking into account SAP isoenzymes, is far from being satisfactory [10, 14, 22].

Besides, many clinical conditions coexisting with HD can enhance alterations of many function tests [22]; in some cases such alterations proved to be dependent on a mere reactive process with absence of any histological abnormality [25]. On the other hand, there is evidence that normality of both functional and instrumental tests does not always mean non-involvement of the liver by HD [5, 9, 10].

Also, the three combinations of clinical requirements for liver involvement proposed at the Ann Arbor Conference have proved to be somewhat disappointing; it was suggested that they were equivalent to each other, but uncertainty still remains regarding the importance of some given tests when compared with others.

Moreover, the surgical risk of laparotomy and also the discomfort and the limitations of liver biopsy (with or without laparoscopy control) still stimulate interest in evaluating liver involvement in patients with HD by means of clinical investigations.

So, lacking a specific non-invasive test for liver involvement in HD, we thought to apply a battery of several contemporary tests whose profile on the whole seems to be less unspecific than each single test alone.

It must be underlined that the 'threshold' value

which has been used for each serum test was calculated empirically by the data from our population. This value, using the discrimination function, should not be mistaken for the limit of normality of that test, even though the similarity of the two values (see Fig. 1) seems a good sign of clinical reliability of the applied statistics.

Furthermore, only the discrimination of involvement and non-involvement by HD interests our research; every other pathology of the liver is considered here only from the point of view of 'non-involvement by HD', and any further distinction is beyond the scope of the discrimination.

Nevertheless, the criteria proposed here seem a small but discrete improvement in the clinical evaluation of the liver in HD, particularly by reducing the number of false negative diagnoses (see Table 6). Such clinical criteria can become of value when liver biopsy is contra-indicated (infectious fever, severe jaundice, haemorrhagic diathesis, etc.) or cannot be performed because of technical reasons (patient unable to collaborate with the operator, presence of adhesive peritonitis, etc.). In such cases these new criteria are proposed as more reliable than the Ann Arbor ones for non-invasive assessment of hepatic involvement in HD.

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