Significance of Serum Leucine Aminopeptidase Isozyme in Hepatobiliary Diseases

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Serum leucine aminopeptidase (LAP) is used in diagnosing hepatobiliary diseases. Increased serum LAP is noted not only in carcinoma of pancreatic head, hepatic carcinoma, carcinoma of bile duct, cholelithiasis and hepatitis but also in pregnancy and is not necessarily limited to any specific disease. We[1] have examined the serum LAP zymograms in a wide variety of diseases and found that patients with hepatobiliary diseases show serum LAP iszymes which differ from that in normal persons and that particularly patitents with hapatobiliary obstruction show characteristic isozyme patterns. There is an increase in serum LAP activity in hepatitis also but LAP isozyme in most cases is not different from that in normal persons. Thus, it appeared that besides the liver function tests used heretofore examination of LAP zymograms may have special significance in the differentiation of hepatobiliary diseases. Therefore, we have made a further review of this point.

MATERIAL AND METHOD

The sera of 140 cases of hepatobiliary disease (84 cases of hepatitis, 15 cases of liver cirrhosis, 19 cases of hepatic carcinoma, 17 cases of cholelithiasis, one case of cholecystitis, 3 cases of malignant biliary obstruction and 2 cases of congenital biliary obstruction) were used. LAP zymograms were prepared according to the above stated method.[2] The same material was used to determine the serum LAP,[3] icteric index or bilirubin, alkaline phosphatase, GPT and A/G ratio.[4]

RESULT AND DISCUSSION

The sera of cases of hepatobiliary disease show 3 types of patterns on LAP zymogram, namely, types Aα_1, A$\alpha_1+\alpha_2$ and A$\alpha_1+\alpha_2+\alpha_2\beta$. Isozyme α_2 and $\alpha_2\beta$ are not seen in normal serum (These shall be referred to as pathological isozymes hereinafter). Since these pathological isozymes are often seen in disease with biliary obstruction, it was first suspected that the obstruction of out flow of bile might be the cause of the appearance of these pathological isozymes. Therefore, the cases selected as material were roughly divided into 2 group; namely, the group with icterus (icteric index more than 8) and the group without icterus

(icteric index less than 7) to investigate the distribution of the isozyme types. The frequency of appearance of pathoiogical LAP activity bands, namely, types $A\alpha_1 + \alpha_2$ and $A\alpha + \alpha_2 + \alpha_2\beta$ in the icteric group was 50 % and that in the non-icteric group was 46 %. Thus, both groups showed almost the same fre-

Table 1. Relationship between Jaundice and LAP Isozyme Pattern.

Jaundice / Isozyme pattern / Diseases	Non-jaundice (57 cases)			Jaundice (83 cases)		
	$A\alpha_1$ type	$A\alpha_1+\alpha_2$ type	$A\alpha_1+\alpha_2+\alpha_2\beta$ type	$A\alpha_1$ type	$A\alpha_1+\alpha_2$ type	$A\alpha_1+\alpha_2+\alpha_2\beta$ type
Hepatitis	24	20		29	11	
Liver cirrhosis	2			9	4	
Hepatic cancer	3	3	1	3	7	1
Cholelithiasis	1	2			7	7
Cholecystitis	1					
Malignant biliary obstruction					1	2
Congenital biliary obstruction					2	
Total	31	25	1	41	32	10

quency with no significant difference (Table 1). In other words the appearance of these new LAP activity bands is not necessarily parallel to the increase in icteric index or bilirubin concentration. A general tendency was noted that sera with high bilirubin concentration show increases in activity bands. However, pathological LAP activity bands are detected even in a fairly large number of cases with low bilirubin concentration. Therefore, icterus cannot be considered as the first cause of the appearance of pathological isozymes (Table 2).

Table 2. LAP Isozyme Pattern and Liver Function Tests.

Tests \ Isozyme pattern		$A\alpha_1$ type (72 cases)	$A\alpha_1+\alpha_2$ type (57 cases)	$A\alpha_1+\alpha_2+\alpha_2\beta$ type (11 cases)
A/G ratio	<1.2	94 %	100 %	99 %
	<0.7	25	34	42
Increased icteric index (Bilirubin)		71	44	41
AP	>4.0 units	21	70	66
LAP	>30 units	44	79	100
GPT	>10 units	72	82	83
	>50 units	32	16	83

The next possibility is that even normal serum may have a minimal amount of pathological isozyme, the activity of which is too low to be detected and appear on zymograms only when the serum LAP increases. In other words, it was sus-

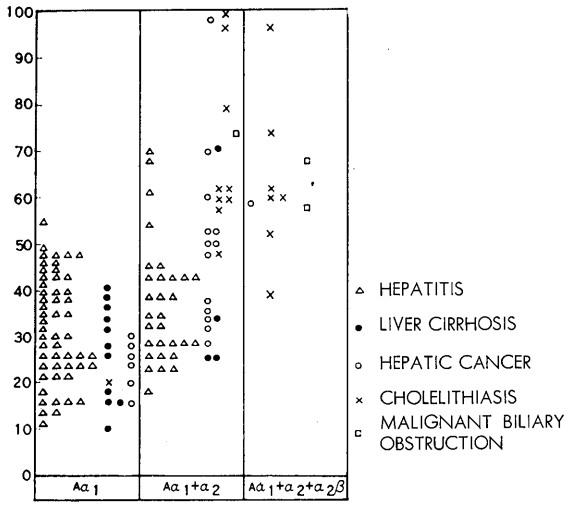

Fig. 1. Relationship between LAP Activity and LAP Isozyme Pattern.

pected that the number of isozymes may increase merely to increases in LAP activity. Therefore, the relation between serum LAP activity and LAP zymograms was studied (Figure 1). It was found that many of the cases with low LAP activity show the $A\alpha_1$ type and that with increase in LAP activity types $A\alpha_1+\alpha_2$ and $A\alpha_1+\alpha_2+\alpha_2\beta$ appear. It is certain that the higher the serum LAP activity is, the more the number of activity bands on the zymograms is. However, there are some cases with low serum LAP determinations which show 2 activity bands (about 20 %). On the other hand, there are some cases with high activity which show only one activity band. Therefore, it cannot be concluded that the appearance of pathological isozyme is simply a quantitative problem.

In cholelithiasis, the frequency of increased activity bands is very high, but when the obstruction is corrected by surgery, LAP isozymes α_2 and $\alpha_2\beta$ disappear and $A\alpha_1$ type appears. Thus, the appearance of this isozyme appears to be a reversible phenomenon caused by accumulation of bile LAP. However, the LAP activity bands of the bile appear at positions which correspond to α_1-globulin and α_2-globulin so that it is difficult to consider that mere biliary stagnation can cause LAP isozymes α_2 or $\alpha_2\beta$ to appear. From the above result, the appearance of LAP iszymes α_2 and $\alpha_2\beta$ is considered to be closely related to complication by hepatobiliary disturbances.

The summary of the results of liver function tests done on cases showing LAP isozymes α_2 and $\alpha_2\beta$ reveals that almost all cases show decreased A/G ratio and that many cases show increased alkaline phosphatase and increased GPT (Table 2). The serum icteric index (bilirubin) is not necessarily increased. Evidently, the appearance of pathological isozyme is generally accompanied by some degree of hepatic parenchymal disturbances. It is interesting that $A\alpha_1+\alpha_2$ type is found in only a small number of cases with GPT exceeding 50 units, that $A\alpha_1+\alpha_2+\alpha_2\beta$ type is found in most cases with GPT greater than 50 units. The appearance of isozyme $\alpha_2\beta$ may be related to some specific hepatic cell disturbances.

Review of the frequency of pathological serum LAP isozymes by the type of hepatobiliary disease reveals that the frequency in hepatitis is 39 % in the icteric group and 45 % in the non-icteric group. There is little difference between these 2 groups and the frequency of appearance of pathological serum LAP isozyme was low (Table 1). In liver cirrhosis, no pathological serum LAP isozyme was detected in the non-icteric group. The frequency of pathological serum LAP isozyme in hepatic carcinoma was 72 % in the icteric group and 70 % in the non-icteric group. This is a high frequency irrespective of whether there was icterus or not. In all cases of cholelithiasis or malignant biliary obstruction accompanied by icterus, pathological LAP isozymes type $A\alpha_1+\alpha_2$ or $A\alpha_1+\alpha_2+\alpha_3\beta$ were detected. In 2 out of 3 cases of cholelithiasis without icterus, $A\alpha_1+\alpha_2$ type was detected. Thus, when icteric serum shows increased LAP isozyme activity bands, the presence of obstruction of the intrahepatic bile duct or the bile ducts can be considered. Especially, $A\alpha_1+\alpha_2+\alpha_2\beta$ type (3 activity bands) can be said to be limited only to cholelithiasis or malignant biliary obstruction. However, benign obstruction and malignant obstruction cannot be differentiated on the basis of the number of activity bands.

In some cases of severe hepatic parenchymal disturbances such as hepatitis, hepatic cancer or liver cirrhosis, new LAP activity bands were detected, but this is considered, as reported previously, to be the result of obstruction within the hepatic bile ducts. Hepatic cancer is more likely to cause biliary obstruction than hepatitis, and this may be the cause for the frequency of appearance of pathological isozyme to be higher in the former.

CONCLUSION AND SUMMARY

The serum LAP zymograms of 140 cases of hepatobiliary diseases were examined. Normal cases show only one activity bands, but 48 % of cases of hepatobiliary diseases showed 2 or 3 activity bands. The appearance of this pathological LAP isozyme is not necessarily parallel to increases in serum LAP activity or bilirubin concentration.

A certain degree of hepatic parenchymal disturbances is necessary for pathological isozyme to appear. However, when there is no bile duct obstruction, no matter how severe parenchymal disturbances may be, no pathological isozyme appears. This pathological isozyme is almost specific to obstruction of the bile duct.

When an icteric patient shows 2 pathological serum isozymes, there is a very strong possibility of this case being probable cholelithiasis or malignant bile duct obstruction.

Cases of bile duct obstruction with no increase of serum GPT show only one pathological LAP isozyme and those which have increased serum GPT show 2

pathological isozymes.

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