Alpha-Fetoprotein in Liver Disease

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SUMMARY

The serum concentration of alpha-fetoprotein (AFP) was measured by radio-immunoassay in 98 patients with liver disease including hepatoma, chronic active hepatitis, alcoholic cirrhosis, and acute virus B hepatitis. Raised AFP levels, above 30 ng/ml, were found in 87% of patients with acute viral hepatitis, in 82% of patients with primary liver cell carcinoma, in 58% with chronic active hepatitis and in 14% of patients with alcoholic cirrhosis. However, levels above 1000 ng/ml were found only in patients with hepatoma and in acute viral hepatitis.


Alpha-fetoprotein (AFP), a naturally occurring fetal serum protein, appears in fetal plasma after 1 month of gestation, reaches a peak serum concentration of $3 \times 10^6$ ng/ml at 12 weeks, and remains constant until 32 weeks, after which it declines rapidly and steadily until it reaches adult levels of 30 ng/ml at the end of the second year of life. While markedly elevated levels of AFP in primary liver cell carcinoma have been well documented, increased plasma values of AFP in other liver diseases are less well established. We report the results of AFP estimations in patients who attended the Liver Clinic at Groote Schuur Hospital over the 2-year period 1975-1976.

RESULTS

The AFP levels of the patients are shown in Fig. 1.

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Date received: 3 October 1977.
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Patients with chronic active hepatitis had a range of 4.7-462 ng/ml, with a mean of 85.9 ng/ml and a standard error of 37.9 ng/ml. Seven of the 12 patients had levels which exceeded the upper limit of normal. Elevated AFP levels were only seen in patients with active disease, as evidenced by raised serum glutamic oxalo-acetic transaminase (SGOT) levels.

Patients with alcoholic cirrhosis had a range of 5.8-118 ng/ml, with a mean of 21.1 ng/ml and a standard error of 2.8 ng/ml. The AFP level exceeded the upper limit of normal in only 14% of these patients.

Patients with virus B hepatitis had a range of 18-3794.2 ng/ml, with a mean of 608.7 ng/ml and a standard error of 458 ng/ml. Eighty-seven per cent had elevated AFP levels.

The 35 patients with primary cancer had a range of 4.7-6441 328.8 ng/ml with a mean of 600 302.2 ng/ml and a standard error of 243 665.3 ng/ml. Eight per cent had AFP values above the upper limit of normal.

Because of known differences in aetiology and pathogenesis, the 35 patients with primary liver cancer were grouped according to race, and the AFP levels were compared (Fig. 2). While the small number of White patients precludes statistical analysis, only 1 out of 4 had levels in excess of 1000 ng/ml. Thirteen out of 15 Black patients, and 6 out of 12 Cape Coloured patients had AFP levels above 1000 ng/ml (Fig. 3).

The mean age of Black patients was 44 years (range 14-69 years), that of Cape Coloured patients was 51.2 years (range 33-69 years), and that of White patients was 65 years (range 50-77 years).

Five of the 8 patients with virus B hepatitis had serial AFP and SGOT estimations from time of admission until complete recovery or death; details are shown in Fig. 4. In all patients in whom early samples were available the AFP levels rose at a time when the SGOT levels were falling. Patient 4 was studied late in the course of the disease and here both SGOT and AFP levels were falling. This patient suffered a clinical and biochemical relapse 50 days after admission, as reflected by a levelling off of the AFP level owing to renewed synthesis. Patient 1 was admitted in deep coma, and apart from a slight rise in level of consciousness on days 15-22, remained comatose until his death 25 days after admission. From day 22, SGOT and lactate dehydrogenase (LDH) levels rapidly increased, while the AFP level con-

Fig. 2. Frequency histogram of AFP levels in Black, White and Cape Coloured patients with primary liver cancer at 3 levels, i.e. high (above 1 000 ng/ml), medium (30-1 000 ng/ml) and low concentration (less than 30 ng/ml).

Fig. 3. Distribution of AFP (ng/ml) in 35 hepatoma patients separated according to race and sex. The upper limit of normal is 30 ng/ml.
SERUM AFP, LDH, GOT IN AU AG POSITIVE HEPATITIS

Fig. 4. Levels of AFP, SGOT and LDH during illness, from the onset of symptoms to recovery or death, at weekly intervals. In case 4 the logarithmic AFP scale shows a biphasic response with a sudden doubling of the body pool of AFP after 50 days but a normal half-time of 8 days. A logarithmic scale for case 1 shows a half-time of AFP of 4 days — the shortest half-time we have observed.

Fig. 5. Mean values of AFP and SGOT at weekly intervals from onset of symptoms in all cases of virus B hepatitis. The AFP peaks at 14 days after onset of symptoms. The insert shows the linear regression of AFP and SGOT with the half-times as indicated. The mean and standard deviations for AFP and SGOT are indicated at weekly intervals.

Fig. 5. Mean values of AFP and SGOT at weekly intervals from onset of symptoms in all cases of virus B hepatitis. The AFP peaks at 14 days after onset of symptoms. The insert shows the linear regression of AFP and SGOT with the half-times as indicated. The mean and standard deviations for AFP and SGOT are indicated at weekly intervals.

continued to fall. The AFP half-time of 4 days in this patient suggests accelerated catabolism of this protein.

Mean values of SGOT and AFP, measured at weekly intervals from the onset of symptoms, are shown in Fig. 5 and demonstrate the rise in AFP at a time when the SGOT is already falling. The AFP reaches a peak 14 days after the onset of symptoms, and declines in an exponential manner, with a half-time of 5.5 days (Fig. 5), whereas the SGOT reaches its peak in the first 7 days and declines more slowly, with a half-time of 11 days (Fig. 5).

DISCUSSION

The value of AFP determinations in the diagnosis of primary liver cancer is well established. Indeed, AFP levels in excess of 1 000 ng/ml are extremely rare in other liver conditions. These high levels occur more often in the 'African' variety of primary liver cancer than in that seen in Europe or North America. Our results indicate that high AFP levels (above 1 000 ng/ml) occur more frequently in South African Blacks than in Cape Coloureds or Whites with primary liver cancer (Fig. 1). In the latter groups the tumours appear to grow more slowly and usually develop in livers which have been cirrhotic for some time. The high AFP levels seen in the more florid tumours in Blacks have not been found to correlate with tumour weight or with the weight of residual liver.

While elevated AFP levels were found in patients with alcoholic cirrhosis and chronic active hepatitis, these never exceeded 1 000 ng/ml. In chronic active hepatitis the AFP values appear to correlate with the activity of the disease as evidenced by elevated SGOT levels. This may also be true of alcoholic cirrhosis, but our data are insufficient for any conclusion to be drawn.

In contrast to chronic active hepatitis and alcoholic cirrhosis, very high levels of AFP were found in acute viral hepatitis, but these were always transient. This finding is in keeping with the experience of others. In viral hepatitis the elevation of AFP has been claimed to be due to regenerative activity in the liver and to constitute a favourable prognostic sign. Bloomer et al. found elevated AFP levels in 9 out of 12 patients with fulminant hepatic necrosis. Eleven of these patients died and autopsy confirmed the clinical diagnosis. Histological evidence of regeneration was found in every patient with an elevated AFP level. In our experience the elevation of SGOT, an index of necrosis, preceded that of AFP in all the patients studied serially from the early stage of the illness. This finding is in keeping with the hypothesis that AFP is synthesized in response to injury rather than released from damaged cells. The finding that the half-time of AFP in viral hepatitis (5.5 days) was similar to the half-time of AFP when cord blood was injected into adult male volunteers (5.75 days) and to the postnatal degradation rate of AFP in maternal plasma, suggests that AFP is synthesized for a short time only. Continued synthesis can be ruled out by the half-time of 4-8 days seen in our patients. One patient (case 4) suffered a clinical and biochemical relapse after
50 days, and the levelling off of the AFP at this time may well reflect a second short period of synthesis. The mechanism by which the adult non-malignant liver is stimulated to synthesize this fetal protein is not clear. Our data suggest that synthesis may well occur as a result of regenerative activity.

REFERENCES


Vitamin B₆ and Aspartate Aminotransferase Activity in Chronic Liver Disease

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SUMMARY

Serum aspartate aminotransferase (AST) concentrations are commonly determined to detect hepatocellular damage. However, discrepancies between serum AST values and histological signs of active liver damage sometimes occur in patients with cirrhosis.

The enzyme AST requires pyridoxal-5-phosphate (PLP) (active vitamin B₆) as a co-enzyme to express its activity. Since approximately 90% of patients with severe cirrhosis are vitamin B₆-deficient, it has been suggested that vitamin B₆ supplements given to these patients might cause an elevation of falsely low serum AST concentrations.

Treatment of 8 vitamin B₆-deficient cirrhotic patients with pyridoxine hydrochloride (50 mg intravenously twice daily for 1 week) increased their serum AST concentrations from 121 ± 18 (mean ± SEM) to 136 ± 26 IU/l, while treatment of a second group of 9 patients with the active co-enzyme PLP increased AST concentrations from 118 ± 17 to 146 ± 20 IU/l. Neither of these increases was statistically significant. Plasma PLP increased from 2.4 ± 0.7 to 18.5 ± 7.6 ng/ml after pyridoxine, and from 3.3 ± 0.7 to 27.0 ± 6.2 ng/ml after PLP supplementation.

It is concluded that B₆ deficiency is unlikely to be an important determinant of serum AST concentrations in patients with chronic liver disease.


Serum aspartate aminotransferase (AST) concentrations are widely used to detect hepatocellular damage. Elevated serum AST values in hepatic injury are presumably due to leakage of the enzyme from damaged hepatocytes. In acute hepatic damage, e.g. viral hepatitis, the rise in serum AST values precedes hyperbilirubinaemia. Serial AST estimations have been proposed for the early detection of hepatic drug reactions. Serum AST concentrations are used to monitor the progress and response to treatment of patients with chronic active hepatitis. In cirrhosis, serum AST is usually only minimally elevated, or it may even be normal. A normal AST value in cirrhosis is explained by calling the cirrhosis ‘inactive’