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Leprous Hepatitis: Clinico-Pathological Study and Therapeutic Efficacy of Liv.52*

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Fifty cases of leprosy were studied for clinico-biochemical and histological features pertaining to hepato-biliary system involvement. Therapeutic efficacy of an indigenous drug Liv.52 was also studied for its hepatic restorative and protective effects in leprous hepatitis.

Specific granulomatous lesions suggestive of leprous hepatitis was mainly seen in lepromatous leprosy (40%). Granulomata in liver were seen in all types of leprosy (70%). Some of the hepatic lesions progressed to stellate fibrosis and early cirrhotic changes (40%). Functional derangement was the main feature in lepromatous cases irrespective of the extent and duration of the disease. Uniform elevation of normal level of total serum proteins was mainly due to increase in serum globulin with reversal of A:G ratio, indicating deranged hepatocyte function and hyperplasia of reticulo-endothelial cells. Hyperbilirubinaemai (highest level of serum bilirubin 5.6 mg%) was chiefly seen in lepromatous leprosy.

A study to evaluate the efficacy of treatment of leprous hepatitis with an indigenous drug 'Liv.52' was also undertaken in these 50 cases—20 cases served as control and 30 cases received Liv.52 along with the antileprosy drug. The clinical and bio-chemical with histopathological response was significant in Group A (Liv.52 treated cases) as it cut short the duration course and severity of the disease and showed remarkable improvement towards normal values without any untoward side-effects.

We feel that Liv.52 richly deserves to be used as a routine treatment specially in all cases of lepromatous leprosy, as incidence of hepato-biliary system involvement is much more in our country.

INTRODUCTION

Amongst the various systemic effects produced by leprosy, hepatobiliary system is the most commonly affected (Contreras *et al,* 1969; Karat *et al*, 1971; Nigam, *et al*, 1976). The hepatic involvement is seen in the early stage of the disease (Dogliotti and Fazio 1960; Thomas *et al* 1966). Besides the frequent presence of granulomata, a few of the lesions may mimick cirrhosis of liver. The studies of the hepatic functional status revealed minimal derangement in tuberculoid leprosy, whereas marked derangement in one test or the other in lepromatous leprosy.

Liv.52, an indigenous drug of The Himalaya Drug Co., has been claimed as remedy for various hepatic disorders with some encouraging results (Jogelkar and Leevy, 1970; Prasad 1975). Certain indigenous plants from our country (India) have been claimed to have hepatic restorative and protective effects. Hence it was thought of taking a trial on Liv.52 in cases of leprous hepatitis.

MATERIAL AND METHODS

The present study comprises 50 cases of leprous hepatitis. All the patients were thoroughly examined clinically and were categorised according to various clinical types (Indian Classification – Dharmendra 1967; Nigam *et al* 1976). Biochemical liver function tests were done by standard techniques and included serum proteins, albumin, globulin, A:G ratio, serum bilirubin, thymol turbidity, serum transminases, alkaline phosphatase and serum cholesterol. Percutaneous liver biopsy was performed under aseptic technique with Silverman's biopsy needle wherever possible. Haematoxylin and Eosin stained sections were histologically examined. Acid-fast bacilli were demonstrated by modified Fite Faraco's technique (Samuel and Chaterjee, 1971).

Patients were grouped into Group A (Study group of 30 cases receiving Liv.52) and Group B (Control group of 20 cases). The study group patients were given Liv.52 two tablets three times a day alongwith antileprosy drug (Dapsone). Follow up was made every week for the first two months. Then monthly for next 6 months and finally once in 3 months. Patients, who could not be followed, were excluede from the study. The clinical assessment of recovery of patients was judged by the clinical improvement and return of liver function tests to normal values.

OBSERVATIONS

Out of the 50 cases of leprosy studied, 27 were of lepromatous, 10 of dimorphous and remaining 13 of tubercuolid leprosy (Table 1): There were 38 males and 12 females. The majority of the cases were from 4th and 5th decades of life. The duration of the illness varied from 3 months to 10 years with the mean duration of illness 2 years 3 months. All patients had clinical manifestations of liver dysfunction.

Table 1: Age and sex distribution in various clinical types of leprosy with duration of illness

Clinical forms of Leprosy	Sex	Age groups in years					Total	Incidence
		0-20	21-30	31-40	41-50	Above 50		
Lepromatous leprosy	Male	2	3	9	6	1	21	42%
	Female	1	1	3	1	–	6	12%
Dimorphous leprosy	Male	–	1	4	1	1	7	14%
	Female	–	–	1	2	–	3	6%
Tuberculoid leprosy	Male	1	2	4	2	1	10	20%
	Female	–	1	1	1	–	3	6%
Total		4	8	22	13	3	50	
Incidence		8%	16%	44%	26%	6%	100%	

Age range = 9-72 years, Mean age = 29.5 yeas. Sex ratio = male: female :: 3.16 : 1.
Duration of illness = 3 months - 10 years. Mean duration of illness = 2 years 3 months.

Clinical Features: Before the appearance of jaundice there were non-specific constitutional and gastrointestinal symptoms (Table 2), which lasted for about one week. Later on with the appearance of jaundice, anorexia (84%) and other symptoms also developed. This was latter on followed or accompanied by alteration in bowel habits (36%), nausea and or vomiting (34%). Liver was palpable in all the cases and only in some advanced cases the spleen was found to be enlarged.

Liver Function Tests: Liver function tests were much more deranged in lepromatous leprosy (Table 3). Serum bilirubin was raised with clinically detectable jaundice. The highest serum bilirubin noted was 5.6 mg% with direct positive Vandenbergh Test. Hepatic dysfunction and damage was also noted by raised thymol turbidity and raised levels of serum transaminases and alkaline phosphatase. There was uniform elevation of serum proteins (6.8 - 9.4 gms%) with lowered levels of serum albumin and raised serum globulin, resulting in altered albumin/globulin ratio. This alteration was irrespective of the extent and duration of the disease.

Table 2: Presenting clinical features			
Sl.No.	Clinical features	No. of cases	Incidence
1.	Diminished/lost appetite	42	84%
2.	Fever	14	28%
3.	Nausea and/or vomiting	17	34%
4.	Yellow mustard oil colour urine	48	96%
5.	Pain in abdomen	38	76%
6.	Jaundice	49	98%
7.	Distension abdomen	21	42%
8.	Loose motions	3	6%
9.	Constipation	15	30%
10.	Oedema	6	12%
11.	Ascites	3	6%
12.	Enlarged tender liver	50	100%
13.	Splenomegaly	4	8%

Table 3: Biochemical values in liver function tests				
Liver function tests (1)		Clinical Types of Leprosy		
		Lepromatous (27 cases) (2)	Dimorphous (10 cases) (3)	Tuberculoid (13 cases) (4)
Serum bilirubin (mg%)	=mean	3.8	3.0	2.6
	=range	1.8-5.6	1.6-3.6	1.4-3.2
Thymol turbidity (units)	=mean	16.8	12.0	13.8
	=range	13-19	9-14	10-15
Alkaline phosphatase (K.A. units)	=mean	25.2	16.5	16.2
	=range	20-28.2	12.8-21.8	10.8-20
SGOT (units)	=mean	60.8	61.l2	58.9
	=range	50-72	50-70	46-68
SGPT (units)	=mean	80.9	72.8	76.8
	=range	60-92	58-80	56-89
Serum cholesterol (mg%)	=mean	126	119	108.6
	=range	104-160	100-125	102-114
Serum proteins (gms%)	=mean	8.2	7.8	7.2
	=range	6.8-9.4	6.4-8.6	6.0-7.6
Serum albumin (gms%)	=mean	3.9	3.4	3.4
	=range	3.4-4.8	3.6-4.8	3.2-4.6
Serum globulin (gms%)	=mean	5.2	4.8	4.6
	=range	4.2-6.4	3.9-6.2	4.0-5.8
A : G Ratio	=mean	1.49	2.04	2.08
	=range	1.2-1.9	1.6-2.4	1.4-2.4

Histopathological Changes in Liver: The histopathological lesions of leprosy yielded significant results. The histological changes were grouped as follows (Table 4):

1. Specific changes of granuloma suggestive of leprous hepatitis (21 cases) (Figure1).
2. Progression of hepatic lesion to fibrosis (12 cases) (Figure 2).
3. Changes of non-specific nature with or without fibrosis (7 cases).

Liver architecture was preserved in majority of cases. Granulomata is the main lesion seen which vary in size. Multiple and extensive granulomata were seen in lepromatous leprosy, pushing aside the surrounding liver tissue. Acid-fast bacilli can be seen in lepromatous and dimorphous leprosy cases (Figure 3). Granulomata comprised various types of cells predominantly foam cells with scattered irregular histocytes and lymphocytes (Figure1). Foam cells were arranged in groups.

Table 4: Histopathological changes in liver (30 cases)				
Sl. No.	Histopathological changes	Clinical Types of Leprosy		
		Lepromatous (16 cases)	Dimorphous (6 cases)	Tuberculoid (8 cases)
1.	Specific granulomata (Fig. 1) (suggestive of leprous hepatitis)	12	4	5
2.	Progress of hepatic lession to fibrosis (Figure 2) = early stelate fibrosis = fibrosis resembling cirrhosis	6 6 2	2 1 1	2 2 –
3.	Non-specific changes	3	2	2
4.	Normal histology	1	–	1
5.	Demonstration of A.F.B. (Figure 3)	13	4	–

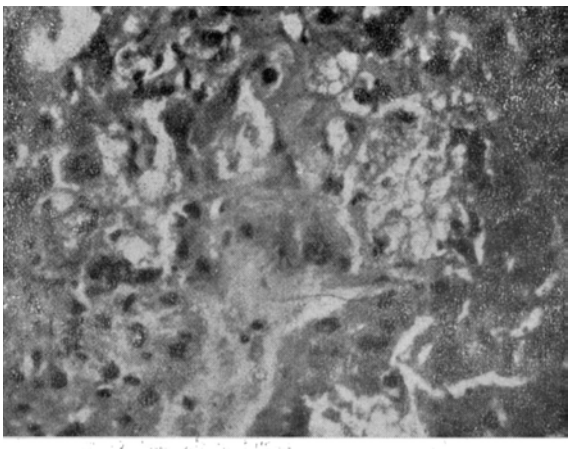

Fig. 1. Microphotograph of liver showing typical granuloma with large number of foam cells. (H & E x 280).

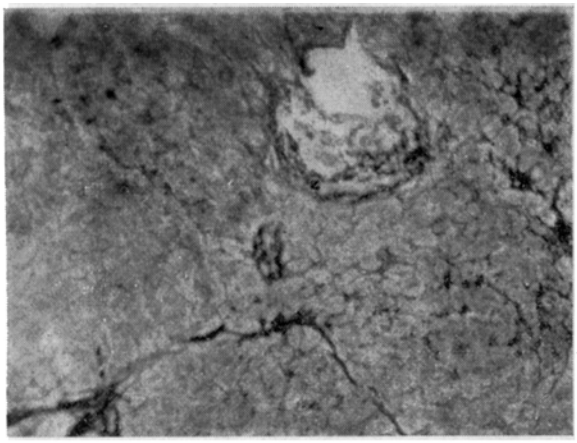

Fig. 2. Microphotograph of liver showing condensation of reticulum and increased periportal fibrosis. (Reticulum stain x 70).

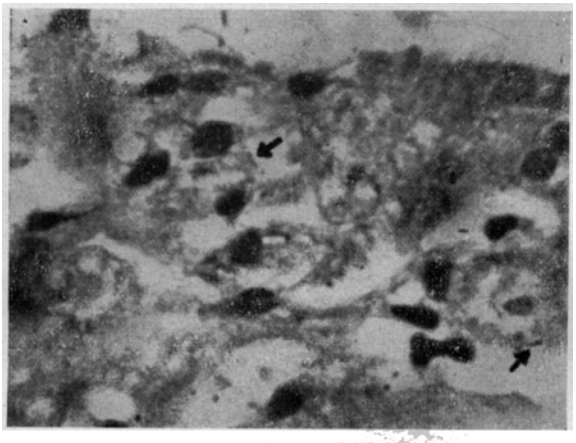

Fig. 3. Microphotograph of liver with modified Fite Faraco stain showing lepra bacilli in the histiocytes.

Therapeutic response: The average period of therapy pertaining to hepatic dysfunction was 8 weeks in group A but were followed to a maximum period of one year. At times Liv.52 was repeated as and when indicated.

The average number of days for the clinical disappearance of jaundice in groups A and B were 16 and 25 days respectively (Table 5). Improvement in relief of symptoms of nausea, vomiting, abdominal pain and return of appetite was quicker in group A cases. The diminution of liver size was rapid in group A cases, receiving Liv.52.

Table 5: Average time taken for improvement of symptoms with therapy		
Symptoms	Group A (30 cases)	Group B (20 cases)
Fever	4^{th} day	4^{th} day
Anorexia	8^{th} day	11^{th} day
Nausea and/or vomiting	3^{rd} day	5^{th} day
Jaundice	16^{th} day	25^{th} day
Irregular bowel habits	3^{rd} day	5^{th} day
Pain in abdomen	4^{th} day	6^{th} day
Flatulence and dyspepsia	8^{th} day	8^{th} day

Earlier restoration of liver function to normal occurred in group A cases than group B patients (Table 6). Serum bilirubin levels, which were raised in the earlier stage, returned to near normal level earlier with regression in clinical jaundice. Serum transaminases, alkaline phosphatase levels, which were initially higher, returned to normal in two weeks time.

Table 6: Comparative evaluation of biochemical improvement in liver function tests with therapy

Liver function tests	Duration of therapy			
	3 weeks		6 weeks	
	Group A (30 cases)	Group B (20 cases)	Group A (30 cases)	Group B (20 cases)
Serum bilirubin <5 mg%	10 (33.3%)	6 (30%)	28 (93.3%)	16 (80%)
SGOT <40 I.U.	9 (30%)	6 (30%)	27 (90%)	16 (80%)
SGPT <40 I.U.	18 (60^)	9 (45%)	29 (96.6%)	15 (75%)
Alkaline phosphatase <14 I.U.	24 (80%)	13 (65%)	30 (100%)	18 (90%)
Thymol turbidity <5 units	21 (70%)	11 (55%)	29 (96.6%)	16 (80%)
Urine=absence of bile elements	25 (83.3%)	12 (60%)	29 (96.6%)	19 (95%)

DISCUSSION

In the present study alteration in important liver function tests mainly in lepromatous leprosy is enough testimony of involvement and affection of hepato-biliary system.

Taking the liver function tests individually, it was observed that the level of serum bilirubin was significantly higher in lepromatous leprosy and dimorphous leprosy, confirming the findings of Dhople and Balkrishna (1968). Clinically jaundice was seen in these cases, which has not been mentioned in the literature.

Lepromatous cases have shown significantly raised level of alkaline phosphatase in contrast to the findings of Gupta *et al*, (1974) and Lodha *et al* (1974), but it is in confirmity to the findings of Dhople and Balkrishna (1968), and Nigam *et al* (1976). The serum transaminases levels were found to be increased in all types of leprosy. This rise might be due to combination of hepatic dysfunction and muscular involvement, whereas Mohanty and Murty (1973) stressed mainly on muscular involvement.

Other functional abnormalities in the form of increased globulin and decreased albumin, abnormal thymol turbidity and lowered serum cholesterol level, have been reported by different workers (Thomas and Ananthachari, 1966; Dhople and Balkrishna, 1968; Nigam *et al* 1976). The alteration in serum protein profile in lepromatous and dimorphous leprosy might be due to the deranged hepatocyte function and hyperplasia of the reticulo endothelial cells (Lodha *et al* 1974). The normal or slightly altered functions in the other forms of leprosy suggest that the presence of granulomatous lesions do not necessarily diminish liver functions and it may neither have any clinical consequence of hepatic dysfunction e.g., hepatomegaly or jaundice etc. as observed in the present series of cases.

The pathological lesions of liver in 28 cases out of 30 cases were in general agreement with other workers (Verghese and Job, 1966; Dhople and Balkrishna, 1968; Gupta *et al,* 1974; Lodha *et al,* 1974; Nigam *et al,* 1976). Two types of lesions encountered i.e., granulomata specific of leprosy and non-specific collection of mononuclear cells in the liver parenchyma and around portal area. The granulomata in the liver in leprosy cases has been given the term of leprous hepatitis (Contreras *et al,* 1969; Nigam *et al,* 1976). Both types of lesions progressed to portal scarring in due course of time in 12 cases. Out of these 12 cases, 8 were of lepromatous leprosy. This might be due to drug, nutritional factors or the end result of the disease itself.

Many indigenous plants of India have empirically been used in liver diseases and claimed to have beneficial results. Liv.52, a preparation from indigenous plants of India, has been proved beneficial, safe and non-toxic drug with its multiple actions (Kirtikar and Basu, 1933; Jogelkar and Leevy, 1970; Dave *et al,* 1972; Prasad, 1975) i.e., hepatic stimulant, chloretic anabolic and hepato-protective against various toxic agents. It stimulates hepatic function and possibly by reducing intrahepatic congestion by its anti-inflammatory action it relieves cholestasis and clears the jaundice, which in words of Bradley (1963) is the clinical manifestation of hyperbilirubinaemia.
In our observations the improvement in relief of symptoms nausea, vomiting, abdominal pain, return of appetite was quicker in the patients getting Liv.52. The serum bilirubin, an index of deranged hepatic function, had dropped significantly in the group A cases (93.3%). This indicates that the cholestasis was greatly relieved possibly due to reduced intrahepatic oedema and cellular infiltration. The cellular regeneration is also rapid. This hypothesis is supported by the histopathological observations of Joglekar *et al* (1963, 1970). In vitro studies it has been found that it stimulates the liver cells directly to excrete the bilirubin into culture media (Prasad 1975). Clinically such action has also been reported by Dayal *et al* (1971). At the same time the decrease in serum transaminases levels indicate that Liv.52 probably prevents liver parenchyma damage with quick regeneration. Moreover, the activity of the liver cells and the regenerative process could be confirmed by the levels of alkaline phosphatase. It has been suggested that the water soluble fraction of Liv.52 probably also acts directly on the liver and stimulates it to restore the function and normalise the cells (Prasad 1975).

The exact mechanism of the protective effect of Liv.52 in leprous hepatitis remains still unexplained and requires further elucidation.

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