



IJCRR

Section: Healthcare
 Sci. Journal
 Impact Factor
 4.016
 ICV: 71.54

Assessment and Comparison of Liver Functions in Leprosy

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ABSTRACT

Leprosy is chronic infectious disease of man, caused by Mycobacterium leprae, affecting peripheral nerves, skin and sometimes other tissues. Hepatic involvement is seen in all stages of the leprosy, more so in lepra reactions.

Aim: The present study was undertaken to evaluate hepatic status by studying the various liver function tests in leprosy patients as well as in patients of lepra reaction.

Methodology: Sixty untreated leprosy patients (30 Multibacillary, 30 Paucibacillary) with duration of illness varying from one month to three years were considered. Hepatic functional status was evaluated by estimation and comparison of variations in the levels of liver enzymes, proteins (Albumin, Globulin) and Australia antigen in paucibacillary, multibacillary leprosy and type I&2 lepra reactions.

Results: Decreased levels of serum albumin were noted in all forms of leprosy except in type II reaction while serum globulins were decreased only in paucibacillary leprosy. Raised levels of SGOT were found in all forms of leprosy including lepra reactions. However SGPT was significantly raised in type II lepra reaction. Serum bilirubin was raised in type II lepra reaction while raised levels of serum alkaline phosphatase were observed in type I lepra reaction. Serum cholesterol levels were decreased in all forms of leprosy except in type I reactions.

Conclusion: We found that liver is significantly affected in leprosy and in lepra reactions. Assessment of liver functions is useful to measure the severity of affection of the liver in leprosy and for monitoring the patients on antileprosy treatment.

Key Words: Leprosy, Liver Function Tests (LFT), Multibacillary (MB), Paucibacillary (PB)

INTRODUCTION

Leprosy is chronic infectious disease of man, caused by mycobacterium leprae, affecting peripheral nerves, skin and sometimes other tissues.¹ In individuals having no cell mediated immunity against mycobacterium leprae, a widespread clinical form of leprosy is seen. This form is called lepromatous leprosy. The continuous bacillema of lepromatous leprosy, estimated at 105 organisms/ml blood, ensures the constant bombardment of internal organs by mycobacterium leprae. The reticuloendothelial system acts as a filter to the circulating bacteria which accumulate in macrophages in the liver, spleen, bone marrow and several groups of lymph nodes especially in lepromatous leprosy.

The liver lesions in lepromatous leprosy are fairly common and are well described.^{2,3} Histopathological examination shows prominent Kupffer cells and numerous miliary

lepromas.⁴ Involvement of liver, of a milder nature and degree is also seen in other types of leprosy such as tuberculoid leprosy. Tuberculoid granulomas in the liver of leprosy patients are known to occur especially during the reactive phase and have been well described.⁵ The involvement of liver in leprosy is well reflected in serum enzymes denoting liver function which have been found to be elevated mainly in lepromatous leprosy. There are reports of increased serum bilirubin, reversal of albumin globulin (A: G) ratio⁵ and increased SGOT⁶ and also SGPT⁷, increased serum gamma globulins⁶ but decreased serum cholesterol.⁸

The aim is to collect a comprehensive data regarding biochemical parameters of liver in leprosy with comparison of the collected data between the two groups of leprosy (i.e. Paucibacillary and multibacillary) and lepra reactions (Type I and Type II) with the control.

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Received: 20.01.2017

Revised: 14.02.2017

Accepted: 24.02.2017

MATERIALS AND METHODS

The present study was conducted over a period of two years in 60 patients attending outpatient department of Skin and Sexually Transmitted Disease (STD) in a government hospital, Kolhapur. After ethical consideration and written consent, patients without prior history of leprosy or prior history of leprosy treatment i.e. freshly diagnosed leprosy cases were chosen from the outpatient department depending on their willingness to undergo investigations.

A detailed history was taken to rule out chronic alcoholism, recent history of jaundice, liver disease or recent intake of any hepatotoxic drugs. Patients with such history were excluded from the study. Remaining patients were then subjected to careful clinical examination to determine the extent of the disease. The clinical type of the disease was determined according to Ridley and Jopling's classification⁹ (1966) and findings were entered in proforma. After that, patients were subjected to special investigation called "skin clip".

Skin clip

The skin clip was done by 'Slit and Scrape' method of Wade. Smears were made from suspected lesions as well as from sites commonly affected in lepromatous leprosy – forehead, ear lobules, chin, extensor aspect of forearm, buttocks, nasal cavity etc. The smear was stained by Ziehl-Neelsen method for staining for acid fast bacilli.

Recording of smear reports

About 50 to 100 fields were examined with oil immersion lens and results were noted as positive or negative. In cases of positive finding, results were recorded as follows:

- 6+ Very numerous – more than 1000 bacilli; or globi per oil immersion field.
- 5+ Numerous – 100 to 1000 bacilli per oil immersion field.
- 4+ Moderate – 10 to 100 bacilli per oil immersion field.
- 3+ Few – 1 to 20 bacilli per oil immersion field.
- 2+ Very few – 10 to 100 bacilli per entire slide (100 fields).
- 1+ Rare – 1 to 10 bacilli per entire slide (100 fields).

Bacteriological Index (BI) was calculated by adding the degree of positivity of all smears and dividing the total by number of smears examined. Those patients with positive bacteriological index were grouped under multibacillary group and those with negative bacteriological index in paucibacillary group. In each group, 30 patients were included to make a total of 60 patients for our study. Also 30 normal healthy individuals were chosen as control group. All these 90 patients were subjected to special investigation of liver function tests.

Liver function tests: ¹⁰

About 20 ml of blood was collected, usually on the day of admission by venepuncture using aseptic technique following liver function tests were carried out.

- Total plasma proteins, serum albumin and globulins (Biuret method for total proteins and albumin by bromocresolgreen method).
- Serum bilirubin (Malloy and Evalyx method).
- Serum glutamic pyruvic transaminase (SGPT) (Calorimetric method of Reitman and Frankel).
- Serum glutamic oxaloacetic transaminase (SGOT) (Calorimetric method of Reitman and Frankel).
- Serum alkaline phosphatase (king Armstrong method).
- Serum cholesterol (ferroham method).
- Australia antigen (Latex Agglutination).

Due to difficulty in performing electrophoresis of protein fractions to find out differential proteins (alpha, beta, gamma proteins) in our institute, this was not done.

Statistical method: Independent sample 't' test was used to compared the data. $P < 0.05$ was considered as significant and evaluated by ANNOVA method.

OBSERVATIONS

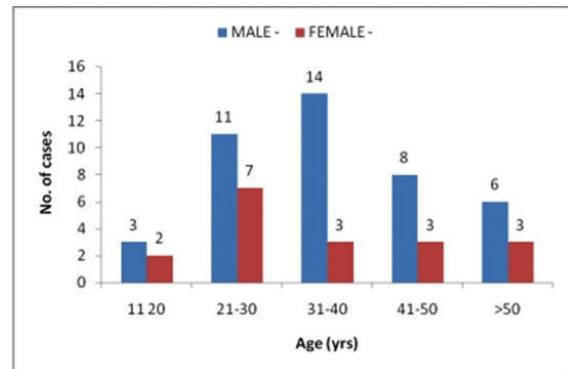
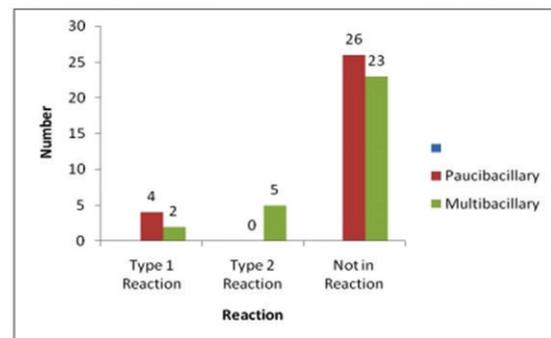
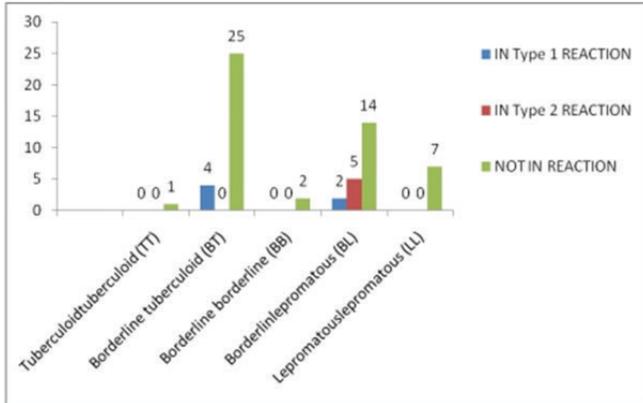


Figure 1: Age and Sex wise distribution of leprosy patients.



$\chi^2 = 5.85$, d.f = 2, $p = 0.054$ (Not significant)

Figure 2: Distribution based on bacillary index and, their reactional status.



$\chi^2 = 11.77$, d.f = 8, $p = 0.019$ (statistically highly significant)

Figure 3: Distribution of leprosy patients according to Redley Joplings classification (1966), and their reactional status.

Table 1: Results of Liver function tests in paucibacillary patient vs Control

Variable	Paucibacillary (n=26)		Control (n=30)		"t" - value	"p" - value
	Mean	Sd	Mean	Sd		
Total Proteins	6.01	0.44	6.57	0.96	2.73	0.008 **
Serum Albumin	3.15	0.24	3.49	0.47	3.33	0.002 **
Serum globulin	2.86	0.34	3.15	0.57	2.26	0.027 *
Serum bilirubin	0.60	0.14	0.64	0.12	1.15	0.25 (NS)
SGPT	16.23	8.25	16.2	5.62	0.06	0.98 (NS)
SGOT	16.08	4.62	13.5	4.18	2.19	0.033 *
Serum alk. phosphatase	7.10	3.04	6.47	1.60	0.98	0.33 (NS)
Serum cholesterol	185.85	50.05	216.4	34.59	2.68	0.01 *

*= statistically significant, **= statistically highly significant, NS = not significant

Table 2: Results of Liver function tests in multibacillary patient vs Control

Variable	Multibacillary (n=23)		Control (n=30)		"t" - value	"p" - value
	Mean	Sd	Mean	sd		
Total Proteins	6.19	0.56	6.57	0.96	1.68	0.09 (NS)
Serum Albumin	3.01	0.33	3.49	0.47	4.16	0.000 **
Serum globulin	3.18	0.67	3.15	0.57	0.17	0.86 (NS)
Serum bilirubin	0.67	0.18	0.64	0.12	0.73	0.47 (NS)
SGPT	22.04	14.86	16.2	5.62	1.98	0.05 (NS)
SGOT	21.13	13.90	13.5	4.18	2.85	0.006 **
Serum alk. Phosphatase	6.85	3.78	6.47	1.60	0.49	0.62 (NS)
Serum cholesterol	178.57	81.92	216.4	34.59	2.28	0.03 *

*= statistically significant, **=statistically highly significant, NS = not significant

Table 3: Comparison of results of liver function tests in Type-I reaction vs control

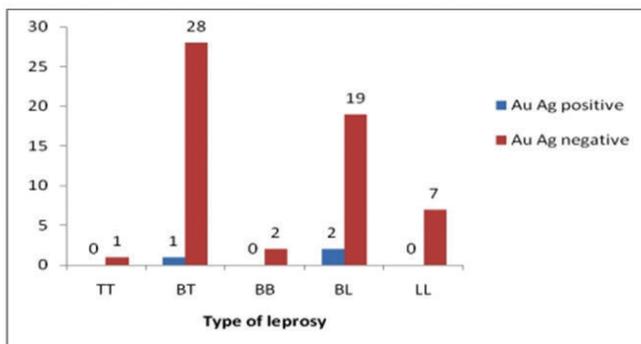
Variable	Type I reaction (n=6)		control (n=30)		"t" - value	"p" - value
	Mean	Sd	Mean	sd		
Total Proteins	5.86	0.53	6.57	0.96	-1.70923	0.048261*
Serum Albumin	2.97	0.27	3.49	0.47	-2.55088	0.007708**
Serum globulin	2.88	0.29	3.15	0.57	-1.09949	0.139639
Serum bilirubin	0.72	0.12	0.64	0.12	1.448712	0.078289
SGPT	21.12	13.14	16.2	5.62	1.440372	0.079454
SGOT	16.67	2.42	13.5	4.18	1.747661	0.044775*
Serum alk. phosphatase	8.17	2.79	6.47	1.60	1.99449	0.027083*
Serum cholesterol	198.67	81.42	216.4	34.59	-0.84038	0.203285

* = statistically significant, ** = statistically highly significant, NS = not significant

Table 4: Comparison of results of liver function tests in Type II reaction vs control

Variable	Type II reaction (n=5)		control (n=30)		“t” - value	“p” - value
	Mean	Sd	Mean	sd		
Total Proteins	6.26	0.36	6.57	0.96	0.693055	0.246562
Serum Albumin	3.17	0.27	3.49	0.47	1.439241	0.079751
Serum globulin	3.19	0.18	3.15	0.57	-0.15112	0.440402
Serum bilirubin	1.14	1.16	0.64	0.12	-2.22219	0.016619*
SGPT	42.2	29.24	16.2	5.62	-4.27864	0.000007**
SGOT	20.6	10.92	13.5	4.18	-2.52255	0.008327**
Serum alk. phosphatase	7.60	2.61	6.47	1.60	-1.27632	0.105377
Serum cholesterol	174.6	14.83	216.4	34.59	2.584527	0.007181**

* = statistically significant ** = statistically highly significant NS = not significant



$\chi^2 = 1.57, d.f = 4, p = 0.813$ (Not significant)

Figure 4: Incidence of Australia Antigen (Au Ag)

DISCUSSION

In this study sixty cases of freshly diagnosed patients of leprosy were included. The ratio of male to female patients was 2.33:1 which corresponds to normally found 2:1 ratio of male leprosy patients to female leprosy patients in our population. Out of 60 cases, 42 were male patients and 18 were female patients. Majority of the patients were belonging to age group of 20 to 40 years. The youngest patient was 16 years old while the oldest was 75 years. (Fig 1)

The two groups studied include 30 paucibacillary leprosy patients in first group and 30 multibacillary leprosy patients in the second group. In the 30 cases of paucibacillary leprosy 29 were borderline tuberculoid (BT) and 1 was of tuberculoid tuberculoid (TT) leprosy. In second group of 30 cases of multibacillary patients, 2 were borderline borderline (BB), 21 were borderline lepromatous (BL), 7 were lepromatous lepromatous (LL) patients. This shows statistically highly significance. (Fig 2)

Out of these 60 patients, 11 patients were undergoing lepra reaction– 6 undergoing type I and 5 undergoing type II lepra

reaction. In type I reaction, 4 were BT and 2 were BL leprosy cases. In type II (erythema nodosum leprosum) reaction, 5 cases of BL leprosy were studied. Here not any difference observed between type I and type II reaction in both groups of leprosy. (Fig 3)

LIVER FUNCTION TESTS IN LEPROSY

Plasma proteins (Total serum proteins, Albumin and Globulins):

In this study, total serum proteins with standard deviation (sd) of 0.44 in paucibacillary leprosy patients as compared to 0.96 in control group giving statistically highly significant ‘p’ value. In multibacillary group serum total proteins with sd 0.56 which was very near to that in control group with sd 0.96 with statistically non significant p value. Thus we found that total serum proteins in normal range in multibacillary leprosy patients but significantly decreased in paucibacillary.

In our study serum albumin and globulin levels in paucibacillary leprosy patients were 3.154 gm% and 2.857 gm% respectively which were 3.49 gm% and 3.15gm% respectively in healthy control group. However, the mean serum albumin and globulin levels in multibacillary leprosy patients were 3.01 gm% and 3.18gm% respectively indicating that in paucibacillary serum albumin and globulin decrease is highly significant statistically. But in multibacillary leprosy there is highly significant decrease in albumin level but not significant with globulin. (Table 1 & 2)

Gupta et al¹¹ recorded fall in total proteins in lepromatous type however we recorded significant fall in total proteins in paucibacillary leprosy but not in multibacillary type. M Swathi¹² found the lowering of A/G ratio in leprosy cases which was statistically significant when compared to controls. But Shivde and Junnarkar et al⁷ and Nigam et al⁶ found normal or raised total proteins. Increase in total proteins,

lowered serum albumin and raised globulin values were recorded by Kinnier and Davison¹³ and Gharpuray et al¹⁴. Gupta and Gupta¹⁵ states that decrease in total proteins and albumin are due to chronic destructive nature of the disease and liver involvement. It is well known that albumin synthesis takes place in hepatic cells whereas in globulin synthesis, both plasma cells and lymphocytes participate. Therefore one or more factor like decreased albumin synthesis due to hepatic dysfunction. However significant decrease in serum globulin is not detected due to stimulation of reticuloendothelial system leading to globulin synthesis.

In our study with type I reaction patients total serum proteins and albumin was significantly decreased but that of globulin is not statistically significant as compared to control. In type II reaction patients statistically significant changes were not observed in all three levels. In contrast to our observations, Patnaik J.K. et al¹⁶ observed altered albumin to globulin ratio in patients with lepra reaction. Similar findings observed by Ischikara's¹⁷ in erythema nodosum leprosum (type II) are interesting. During the acute attack, globulins (particularly gamma) levels were very high and they came down after acute antibody phenomenon. Type I reaction is because of change in cell mediated immunological status hence there is hardly any change in humoral immunity so immunoglobulin production is not increased. In erythema nodosum leprosum, there is rapid destruction of lepra bacilli and antigenic load is more in circulation. This leads to antibody production and formation of immune complexes; this explains slight increase in globulin level in type II reaction as compared to type I reaction in our study.

Serum Enzyme Estimations in Leprosy (SGPT, SGOT):

In the present study SGOT was significantly raised in paucibacillary as well as in multibacillary leprosy patients but there were not statistically significant alterations in SGPT levels. (Table 1&2) There was highly significant rise in the levels of SGPT in type II reaction patients as compared to type I reaction patients. In all the forms of leprosy including lepra reactions significant increased levels of SGOT were noted. (Table 3 &4)

Teresa et.al¹⁸ reported that there is raised SGOT and SGPT in lepromatous leprosy which correlates with our study. Nigam et al⁶ found increase in values of SGOT and SGPT in all types of leprosy. Gharpuray et al¹⁴ found increase in SGPT levels in 7 out of 20 tuberculoid cases, 7 out of 10 lepromatous cases and normal value in 8 dimorphous cases. Mohanty et al¹⁹ found increase in levels of both SGPT and SGOT in 14 out of 24 lepromatous patients and 5 out of 8 patients with lepra reaction.

Balkrishnan²⁰ found more increase in patients with lepra reaction than lepromatous patients. Levels of SGPT were 34 and 30 IU/L and of SGOT were 52 and 32 IU/L respectively

which correspond to our study. Kinnier and Davison¹³ and Shivde and Junnarkar⁷ observed a rise in serum transaminase activity in leprosy patients especially in lepromatous group which corresponds to our study.

The transaminases, serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) are present in substantial amount in liver and other sites like skeletal and cardiac muscle, pancreas and kidney. Normally they are just detectable in plasma. SGPT estimation is more sensitive than SGOT estimation. Estimation of these enzymes in leprosy is of particular importance since involvement of liver and skeletal muscle is frequently encountered in good number of leprosy cases mainly of lepromatous leprosy.^{6, 19}

In different studies it is stated that slightly increase in these enzyme levels is due to skeletal muscle involvement in lepromatous leprosy. Nigam et al⁶ quoted this increase may be due to hepatic dysfunction and muscular involvement. Mohanty et al's¹⁹ impression was that increase indicates subclinical involvement. Balkrishnan²⁰ concluded that the increase in values in reaction may be due to breakdown of liver tissue in reaction. Shivde and Junnarkar⁷ quoted that rise in SGPT in lepromatous leprosy indicated a toxic effect of leprosy bacilli to hepatic cells. The values were especially high in those cases with portal cirrhosis and in those harboring miliary lepromas in the liver.

Alkaline Phosphatase:

In our study, significant rise in serum alkaline phosphatase was seen only in type I reaction patients, however normal levels were recorded in both the forms of leprosy and in patients with type II reaction.

Kappor²¹ and Mukharjee²² found increased levels in lepra reactions than lepromatous cases which correlates with our findings. Balkrishnan²⁰ and Nigam et al⁶ found increased values more commonly in lepromatous type. According to Dhople and magar²³ values of serum alkaline phosphatase are normal in early cases and increase with severity of disease. They found more values in tuberculoid type than lepromatous type which correlates with our study. Ischihara¹⁷ also found increased value in all types of leprosy. This increase in levels of serum alkaline phosphatase may indicate subclinical hepatic involvement and it higher values in reaction may be due to destruction of liver tissue during reaction.

Serum Bilirubin

In the present study, serum bilirubin levels were significantly raised in type II reaction but no significant rise was noted in paucibacillary, multibacillary and in type I reaction patients.

Dhople A. M. and Balkrishnan S.²⁴ observed increased values of serum bilirubin levels in advanced stages of lepromatous leprosy. Nigam et al⁶ also observed hyperbilirubi-

naemia chiefly in lepromatous leprosy. Dhopale A.M. and Balkrishnan²⁴ stated that the term bilirubin is generally employed to designate the several forms of iron free pigment present in the blood which are ultimately derived from the breakdown of hemoglobin. It is important to bear in the mind that bilirubin level in the blood is probably maintained at normal by different excretory mechanisms. The blood is cleared of bilirubin so long as sufficient normal functioning of hepatic tissue remains.

Serum Cholesterol

In our study of paucibacillary patients as well as multibacillary patients shows significant decrease in serum cholesterol value and highly significant decrease in type II reaction but not significant in type I reaction .

Our findings correspond to the findings of following studies. Robins et al⁸ and Gupta et.al²⁵ (2002). They found low serum cholesterol values in patients of leprosy as compared to the normal controls, whereas Dhopale A.M. and Balkrishnan²⁴ observed lowering of serum cholesterol levels in lepromatous leprosy. Dhopale and Magar²³ observed that reduction of serum cholesterol levels was proportional to the severity of the disease. However K.C. Nayak et al²⁶ in their study observed normal values for serum cholesterol in all groups of leprosy patients.

Robins et al⁸ found no cause for low serum cholesterol values in leprosy patient. However Dhopale A. M. and S. Balkrishnan²⁴ stated that changes in serum cholesterol in leprosy patients are more in keeping with the usual cholesterol metabolism and excretion; and suggests that low serum cholesterol levels in lepromatous leprosy is due to the hepatic involvement. CM Nwosu and SNN Nwosu²⁷ observed higher cholesterol level in lepromatous leprosy and also mentioned that patient have serum cholesterol levels in abnormal range this may predisposed to enhanced atherogenesis and increased cardiovascular morbidity.

Australia Antigen (Au Ag)

In the present study only one patient from borderline tuberculoid and 2 patients from borderline lepromatous leprosy were positive of Australia antigen. Thus incidence of Australia antigen in the present study is 5%.our study data correlate with observations of SK Sinha et.al²⁸. Tin et al ²⁹ in their study observed positivity for Australia Antigen only in 2 patients in study group of 75. Blumberg et al³⁰ in 1967 found that there is increased positivity for AuAg and in 1970 they found 6.2 % incidence in lepromatous and 2.5 % in tuberculoid leprosy in South India. Datta R. N. et al³¹ demonstrated high incidence of HbsAg in 8.1 % with no clinical manifestation of hepatitis but it was not found in tuberculoid leprosy cases. Nuti et al³⁵ had found very high incidence of 24.4% in lepromatous leprosy (175 cases) and 11.5 % in tuberculoid leprosy (87 cases). Chakravarti et al³² had given incidence of

HbsAg in lepromatous as 3.8% (234 cases) and in tuberculoid as 2.5% (431 cases). Kelkar et al³³ found increased incidence in tuberculoid (6.3%) than lepromatous (5%) leprosy. Various other authors have given incidence upto 4%, slightly more in lepromatous than in tuberculoid leprosy.

Datta R. N. et al³¹ described this positivity of HbsAg to poverty and hot climate. He also suggested that the increased incidences of positive AuAg in lepromatous leprosy as compared with tuberculoid leprosy may be due to decreased cell mediated immunity in patients of lepromatous leprosy. According to Kelkar et al³³ this association of Australia antigen was merely reflection of opportunity for infection and stay in hospital. Because of decrease in cell mediated immunity in patients with lepromatous leprosy, they are unable to get rid of hepatitis – B virus once it gets entry in the body.

K. C. Nayak et al²⁶ in study of 50 patients of various subtypes of leprosy and 25 healthy control, for detection of Australia antigen concluded that incidence of Australia antigen in both groups were zero. No relationship was established between hepatic lesion, Australia antigen and liver function test. They could not find any relationship between leprosy and HbsAg. These authors proposed genetic hypothesis that patients who are homozygous for a gene designated ‘AU’ are more susceptible to chronic infections with AU (I) virus, than individuals with alternate phenotypes as a consequent detectable Australia antigen in their blood. In their study patient represented as identical socio-economical group of population. The chance of infective organism in a community living in a residential home is always more which might be the reason for the higher incidence of HbsAg in lepromatous cases in Blumberg’s study.³⁰

Genetic hypothesis states that presence of Australia antigen is determined by gene which is autosomal recessive. The individual homozygous for the gene may have detectable Australia antigen. Bearers of this gene may be more susceptible to certain illness like leukaemia, viral hepatitis, lepromatous leprosy etc. If this hypothesis is correct, then the population having both the gene and mycobacterium leprae are more likely to have impairment of their immunological mechanisms and so are more likely to have lepromatous leprosy than tuberculoid leprosy.

CONCLUSION

In concluding, we found that liver is significantly affected in both the types of leprosy (Paucibacillary and Multibacillary) and in lepra reactions (Type I and Type II). AS the drugs used in the treatment of leprosy are known to be hepatotoxic, assessment of liver functions is useful to measure the severity of affection of the liver in leprosy and for monitoring the patients on antileprosy treatment.

ACKNOWLEDGEMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Sources of Funding: None

Conflict of Interest: None

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