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RESEARCH ARTICLE

COMPARATIVE STUDIES ON CRYPTOGENIC CHRONIC LIVER DISEASE SPECIALLY RELATED TO NON-ALCOHOLIC STEATOHEPATITIS (NASH) VERSES OTHER KNOWN CAUSES OF LIVER DISEASES WITH FEATURES OF DE-COMPENSATION - A CASE CONTROL STUDY

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ABSTRACT

Context: The prevalence of cryptogenic cirrhosis ranges from 5% to30% of cirrhotic patients in past series. Several explanations may be offered as possible underlying etiologies include occult alcohol abuse, occult viral (non-B, non-C hepatitis, silent autoimmune hepatitis, or progression of nonalcoholic steatohepatitis (NASH).

Aims: To compare the clinical, biochemical and histologic features between the advanced cryptogenic chronic liver disease and decompensated chronic liver disease with known etiology.

Setting and Design: Hospital based retro-spective study

Materials and Methods: This study was conducted in the Department of Gastroenterological Sciences, CMC, Ludhiana. There were a total of 100 subjects, (50 subjects were cases and 50 were controls). The reports of liver biopsies were examined. All sequential cases of those with histological evidence of Steatohepatitis were chosen and their records examined. This group formed the cases for the study. From the records of the same years a further 50 patients were chosen arbitrarily if they had a known cause of the disease, so a definite disease aetiology the basis of choosing the second 50 (i.e. controls).

Results: In the current study, we found that controls were more likely to have Jaundice, ascites and gastrointestinal bleeding. The cases were more likely to have pedal edema and low albumin that indicates more pronounced parenchymal injury associated in this group. These differences were statistically significant ($p<0.005$).

Conclusion: This comparative study is well co related with decompansated chronic liver disease between the crypto group and known causes of liver disease. In an end stage of both the conditions due to loss of bio-synthetic, and other metabolic function of liver, one can not differentiate these two condition by histologic or calculating MELD , so early stage of liver biopsy is mandate for crypto groups to look for any features of NASH.

INTRODUCTION

Cryptogenic chronic liver disease is defined as chronic liver disease the aetiology of which is unknown or not discernable after exhaustive investigations. The etiology in 5-10 % of cases with cirrhosis, despite reasonably extensive investigations, remains unresolved (Viggiano *et al.,* 1980) and these would qualify for the label. Ever since new causes of parenchymal liver damage were discovered the proportion of patients with Cryptogenic cirrhosis has diminished. The newer causes include Hepatitis (1999) and more recently Non Alcoholic Steatohepatitis or NASH (2001) Even more recently there has been evidence that Non Cirrhotic portal hypertension (NCPF) ends in chronic liver failure and hepatocellular carcinomas (Jacobi *et al*., 2006). It may turn out that this too might be another cause of cryptogenic Cirrhosis. Looking for the aetiology of Chronic Liver Disease or Cirrhosis opens up the possibility of the successful use of therapeutic agents with improvement (Turkiye Klinikleri *et al*., 2003), stabilization or the delay in progression (Khanna *et al*., 2004). Once the stage of Cirrhosis is reached many patients are not intensively studied, except for viral serology, because Cirrhosis is seen as the end game and cursory treatment other than liver transplantation is seen as worthless. With these as the undergirding considerations, this study was undertaken to investigate covert causes of Cryptogenic Chronic Liver disease. This was a retrospective study and as the issue is complex, we concentrated only on two specific areas, Non alcoholic Steatohepatitis as a cause of "cryptogenic chronic liver disease"

The first issue has not been examined in previous reports from India as biopsies are rarely done in those with near end stage disease. The second issue has also not received much attention in India. There are, of course, many other causes of

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"cryptogenic Liver disease" which have not been investigated in this study. We were constrained by other factors from studying causes such as occult HBV infection which may have been another treatable cause of liver disease (Kodali *et al*., 1994). Rarer causes such as Iron storage disorders and auto immune liver disease were also not covered in the current study.

MATERIAL AND METHODS

Study design

This was a retrospective case-control analysis.

Sample size

We studied 100 subjects with 50 subjects in each arm. This was an arbitrary number and was not based on any calculation because there were no previous studies that could be used to determine sample size.

Subjects

This study was conducted in the Department of Gastroenterological Sciences, Christian Medical College, Ludhiana between August 2011 and Sept 2013. There were a total of 100 subjects, 50 subjects were cases and 50 were controls. The reports of liver biopsies obtained in the Department between August 2011 and Sept 2013 were examined. All sequential cases of those with histological evidence of Steatohepatitis were chosen and their records examined. Those patients with other putative causes like Hepatitis B (this included patients who had a positive IgG anticore antibody), Hepatitis C and alcohol were excluded. This group formed the cases for the study. From the records of the same years a further 50 patients were chosen arbitrarily if they had a known cause of the disease. Therefore liver biopsy was the basis of the diagnosis in the first 50 (i.e. cases) and a definite disease aetiology the basis of choosing the second 50 (i.e. controls). The next stage was extracting from the records the clinical features and investigations of this group (both cases and controls) at the time of that admission. The MELD score at the time of presentation was calculated on all subjects. The following steps were undertaken. The clinical findings and investigational reports of the cases were compared with those in the controls to look for any significant differences. The clinical findings on presentation that were recorded for the study were the presence of jaundice, ascites and pedal oedema. Other clinical findings were not included in the comparative analysis. Encephalopathy and spontaneous bacterial peritonitis was recorded if it was the reason for admission.

A past history of either was disregarded. Among the investigations, the indices of liver function, haematological parameters such as haemoglobin and platelets, ESR and Anti nuclear antibody (if available) were compared in the two groups. Further the ratio such as SGOT/SGPT was also compared. Other investigations such as imaging and endoscopy were not included in the study. Based on the histology reports the cases were classified into those with mild, moderate and severe parenchymal disease. A correlation with the MELD score was attempted.

Statistical Methods

Descriptive statistics like mean and SD were presented for normally distributed continuous variables and median with interquartile range for non-normally distributed continuous variables The results between the two groups were compared for statistically significant difference. For the categorical variables chi-square test was used. For continuous variable with normal distribution, t- test was used. For continuous variable with non-normal distribution, Mann-Whitney's U test was used. P value of <0.05 was considered significant. The statistical analysis was done using SPSS software for windows version 16.

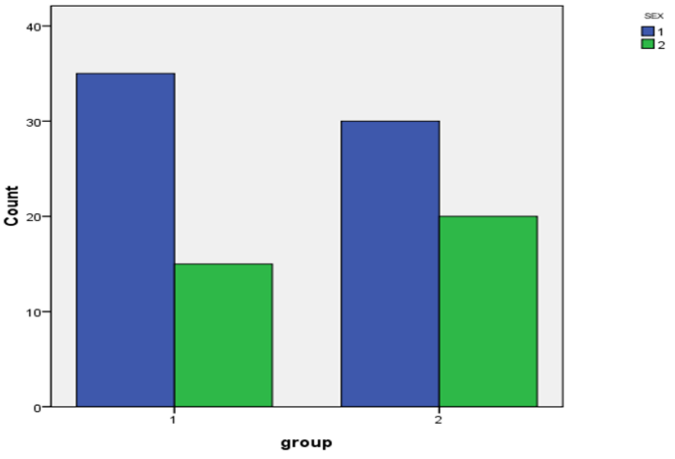
RESULTS

GENDER and AGE: There were 35 males and 15 female in Group-1 and 30 males and 20 females in Group-2. There were no significant differences in these numbers between patients and controls. The ages of the cases of steatohepatitis varied between 7 – 67years with mean ±SD=45.1±10.426.The ages of the control group varied between 14-62 years with mean ± SD =39.49 ± 31.826.

Table 4.

Gender	Male	Female	Total
Group-1(cases)	35(70%)	15(30%)	50(100%)
Group-2(control)	30(60%)	20(40%)	50(100%)

GENDER



Clinical findings

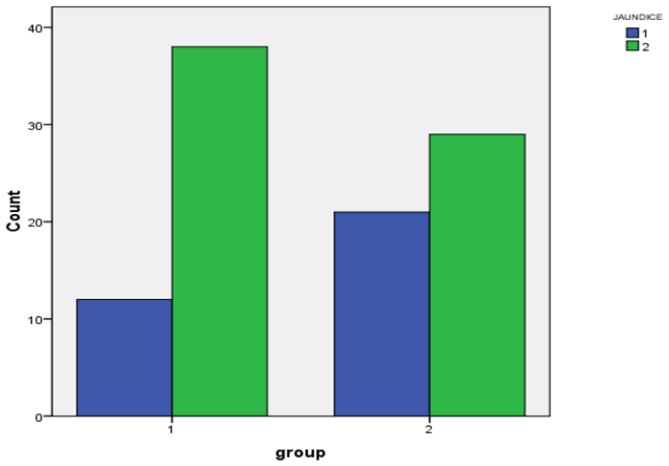
JAUNDICE

12(24%) patients in gr-1 and 21(42%) patients in Gr-2 were jaundiced, so jaundice is more common in the control group as compared to cases, which is statistically significant (P<0.05).

Table 5.

Jaundice	yes	No	Total
Group-1(cases)	12(24%)	38(76%)	50(100%)
Group-2(control)	21(42%)	29(58%)	50(100%)

JAUNDICE



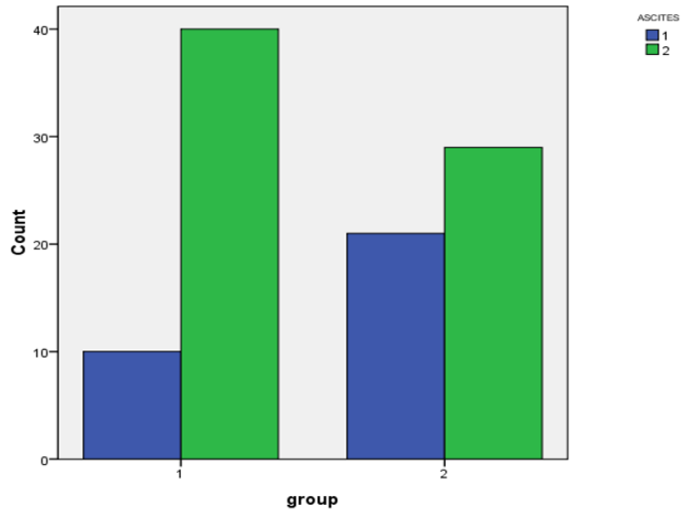
ASCITES

10(20%) patients in Group-1 and 21 (42%) patients in Groups-2 had ascites. Ascites is more common in the control group and this finding is statistically significant (P<0.05).

Table 6.

Ascites	yes	No	Total
Group-1(cases)	10(20%)	40(80%)	50(100%)
Group-2(control)	21(42%)	29(58%)	50 (100%)

ASCITES



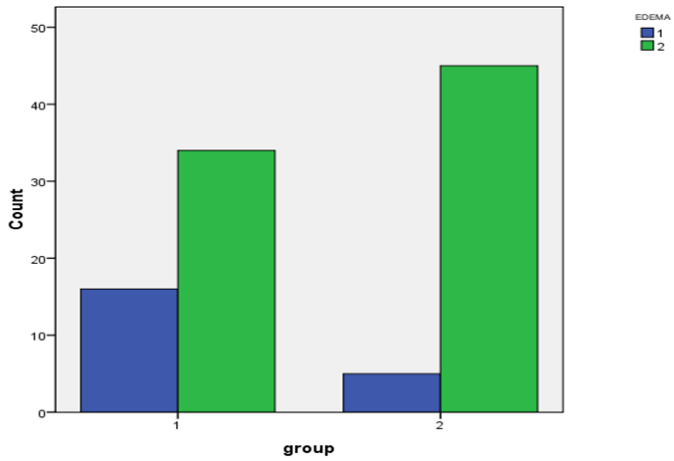
EDEMA

16(32%) patients from gr-1 and 5(10%) patients from gr-2 had bilateral pedal edema and this difference is statistically significant (P<0.05).

Table 7.

Edema	Yes	No	Total
Group-1(cases)	16(32%)	34(68%)	50(100%)
Group-2(control)	05(10%)	45(90%)	50(100%)

EDEMA



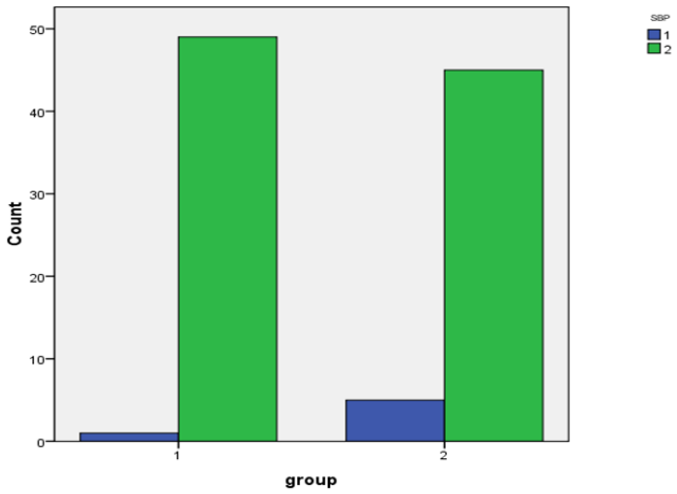
COMPLICATIONS

Spontaneous bacterial peritonitis: 1(2%) patient from Gr-1 and 5(10%) patients from Gr-2 had SBP. The control group had a higher incidence of SBP, but this did not reach statistical significance.

Table 8.

SBP	Yes	No	Total
Group-1(cases)	1(2%)	49(98%)	50(100%)
Group-2(control)	5(10%)	45(90%)	50(100%)

SBP



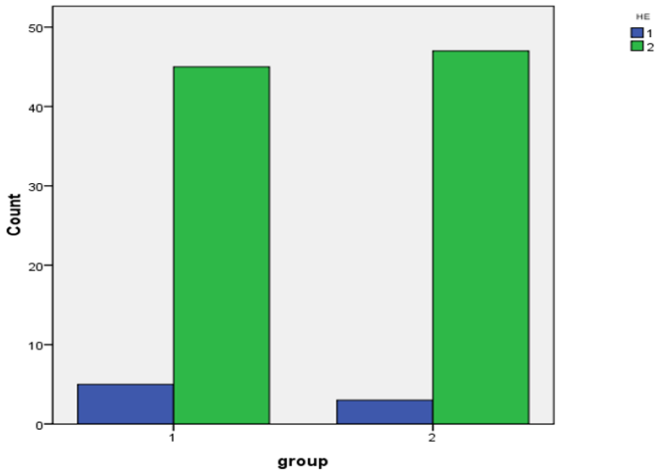
HEPATIC ENCEPHALOPATHY

5(10%) patients in gr-1 and 3(06%) patients from gr-2 had hepatic encephalopathy. Here, the incidence of hepatic encephalopathy was more in the cases, but again this was not statistically significant.

Table 9.

HE	Yes	No	Total
Group-1(cases)	05(10%)	45(90%)	50(100%)
Group-2(control)	03(06%)	44(94%)	50(100%)

Hepatic Encephalopathy



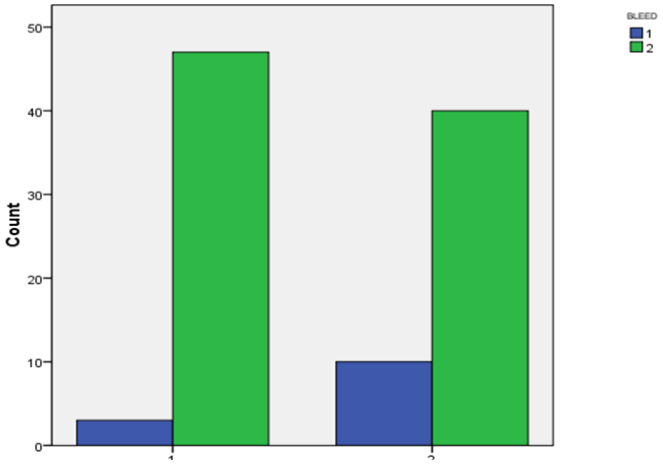
BLEED

3(6%) patients in Gr-1 and 10(20%) patients from Gr-2 had upper g.i. bleed, control group more variceal bleed as compared to cases, which is significant statistically(P<0.05).

Table 10.

Bleed	Yes	No	Total
Group-1(cases)	03(06%)	47(94%)	50(100%)
Group-2(control)	10(20%)	40(80%)	50(100%)

Gastrointestinal bleed



Composite Table 5-10

Indices	Cases(n=50)	Control (n=50)	Significant
Jaundice	12(24%)	21(42%)	*
Ascites	10(20%)	21(42%)	*
Edema	16(32%)	05(10%)	*
SBP	01(2%)	05(10%)	-
HE	05(10%)	03(06%)	-
Bleed	03(06%)	10(20%)	*

* → statistically Significant (p<0.05)

SBP= Spontaneous Bacterial Peritonitis,
HE = Hepatic Encephalopathy

Investigations and laboratory parameters

These laboratory investigations (Ref. Table -11) did not show any Significant differences between cases and control except ESR (<0.05).

T – test

Table 11.

Group Statistics

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
ALB	1	50	3.392	.8121	.1149
	2	50	3.256	.8553	.1210
GLO	1	50	4.496	.9337	.1320
	2	50	4.272	.8347	.1180
PT	1	50	14.514	4.9422	.6989
	2	50	15.436	4.3863	.6203
APTT	1	50	36.132	14.2593	2.0166
	2	50	36.418	9.4658	1.3387
HB	1	50	10.710	2.5453	.3600
	2	50	11.138	2.5136	.3555
TC	1	50	5588.00	3241.670	458.441
	2	50	6850.00	4321.623	611.170

ALB= Albumin,
GLO=Globulin,
PT=Prothrombin time,
HB= Hemoglobin
aPTT= activated partial thromboplatin time,
TC= Total count.

Table 12.

Independent Samples Test

		t-test for Equality of Means						
		t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
ALB	Equal variances assumed	.815	98	.417	.136	.1668	-.1950	.4670
	Equal variances not assumed	.815	97.738	.417	.136	.1668	-.1950	.4670
GLO	Equal variances assumed	1.265	98	.209	.224	.1771	-.1275	.5755
	Equal variances not assumed	1.265	96.794	.209	.224	.1771	-.1275	.5755
PT	Equal variances assumed	-.987	98	.326	-.922	.9345	-2.7765	.9325
	Equal variances not assumed	-.987	96.637	.326	-.922	.9345	-2.7768	.9328
APTT	Equal variances assumed	-.118	98	.906	-.286	2.4204	-5.0893	4.5173
	Equal variances not assumed	-.118	85.163	.906	-.286	2.4204	-5.0984	4.5264
HB	Equal variances assumed	-.846	98	.400	-.428	.5059	-1.4319	.5759
	Equal variances not assumed	-.846	97.985	.400	-.428	.5059	-1.4319	.5759
TC	Equal variances assumed	-1.652	98	.102	-1262.00	764.004	-2778.135	254.135
	Equal variances not assumed	-1.652	90.881	.102	-1262.00	764.004	-2779.620	255.620

Mann-Whitney Test

Table 13.

Ranks

	GROUP	N	Mean Rank	Sum of Ranks
MELD	1	50	49.81	2490.50
	2	50	51.19	2559.50
	Total	100		
TB	1	50	47.41	2370.50
	2	50	53.59	2679.50
	Total	100		
DB	1	50	49.90	2495.00
	2	50	51.10	2555.00
	Total	100		
SGOT	1	50	48.43	2421.50
	2	50	52.57	2628.50
	Total	100		
SGPT	1	50	48.15	2407.50
	2	50	52.85	2642.50
	Total	100		
ALP	1	50	54.30	2715.00
	2	50	46.70	2335.00
	Total	100		
PLATELETHB	1	50	48.01	2400.50
	2	50	52.99	2649.50
	Total	100		
TC	1	50	45.86	2293.00
	2	50	55.14	2757.00
	Total	100		
ESR	1	50	56.95	2847.50
	2	50	44.05	2202.50
	Total	100		
SGOT/SGPT	1	50	52.87	2643.50
	2	50	48.13	2406.50
	Total	100		

MELD= model for end-stage liver disease, TB= Total bilirubin, DB= Direct bilirubin ALP= Alkaline phosphatase

Table 14.

Test Statistics

	MELD	TB	DB	SGOT	SGPT
Mann-Whitney U	1215.500	1095.500	1220.000	1146.500	1132.500
Wilcoxon W	2490.500	2370.500	2495.000	2421.500	2407.500
Z	-.238	-1.066	-.208	-.714	-.810
Asymp. Sig. (2-tailed)	.811	.286	.835	.475	.418

Table 15.

Test Statistics[a]

	ALP	PLATELETHB	TC	ESR	SGOT/SGPT
Mann-Whitney U	960.000	1125.500	1018.000	927.500	1131.500
Wilcoxon W	3335.000	2400.500	2293.000	2202.500	2406.500
Z	-1.310	-.858	-1.600	-2.239	-.817
Asymp. Sig. (2-tailed)	.190	.391	.110	.025	.414

a. Grouping Variable: GROUP

For all non normally distributed data a Mann whitney test was done for the above investigation and laboratory parameters including MELD scores to see if there is any statistically significant difference between the groups and was found to be significant only ESR at P<0.05.

Model for End-stage Liver Disease (MELD)

There was no difference in the MELD score between the cases and controls.

Table 16.

	MELD
Mann-Whitney U	1215.502
Wilcoxon W	490.500
Z	-.238
Assymp. Sig.(2-tale)	.811

(Also ref. to Table-14)

Below is the frequency data (ref. Table-17)

MELD score frequency data (cases and control):

Table 17.

MELD Score	Cases (No. of patients)	Controls (No. of patients)
1-5	12	15
6-10	19	15
11-15	16	14
16-22	03	06
	Total =50	Total =50

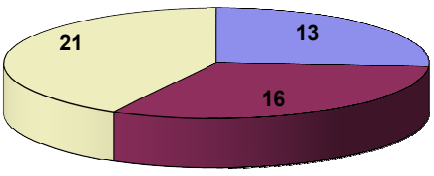
Comparison of MELD score in relation to histological liver injury

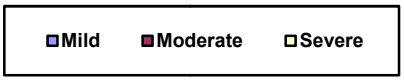
When the MELD score was below 6, there were very few cases with severe injury. When MELD scores were above 6, the histological damage was much more but did not show a progressive increase thereafter (ref. Table-18).

Table 18.

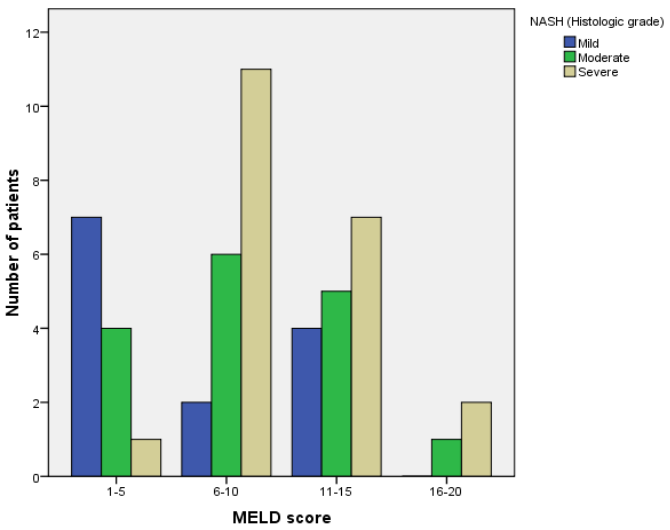
	MELD SCORES			
NASH	1-5	6-10	11-15	16-20
Mild	07(58.34%)	02(10.53%)	04(25.00%)	00(0.00%)
Moderate	04(33.34%)	06(31.58%)	05(31.58%)	01(33.33%)
Severe	01(08.34%)	11(57.89%)	07(43.75%)	02(66.33%)

Distribution of histological severity of the disease according to the MELD score





Graph: Comparision of histologic grades (NASH) with MELD score.



DISCUSSION

There have been some studies on Cryptogenic liver disease, Cirrhosis is usually accepted as ''cryptogenic'' only after an extensive evaluation has excluded recognizable etiologies. The prevalence of cryptogenic cirrhosis ranges from 5% to30% of cirrhotic patients in past series. (Ludwig *et al.,* 1980; Jacobi *et al.,*2006) Several explanations may be offered as possible underlying etiologies include occult alcohol abuse, occult viral (non-B, non-C hepatitis, silent autoimmune hepatitis, or progression of nonalcoholic steatohepatitis (Turkiye Klinikleri, 2003; Khanna and Kumar, 2004). The prevalence of clinically silent autoimmune hepatitis is not known; however, asymptomatic patients with autoimmune hepatitis and previously unrecognized cirrhosis have been described (Sheth *et al.,* 1997; Kodali *et al.,* 1994; Saunders *et al.,* 1981). Non-B, non-C hepatitis is thought to account for about 15% of post transfusion hepatitis and may exist in a silent form for years. Obesity and non–insulindependent diabetes mellitus are the two most common conditions associated with NASH, (Powell *et al.,* 1990; Hay *et al.,* 1989; Sheth *et al.,* 1997) which is frequently asymptomatic and which can progress silently to cirrhosis with loss of definitive histological features (Department of GI Surgery and Liver Transplantation, 2005). Nonalcoholic steatohepatitis (NASH) is the term used to describe the distinct clinical entity in which patients lack a history of significant alcohol consumption (≤40gm/d) but have liver biopsyfindings indistinguishable from alcoholic steatohepatitis (Nippon Rinsho, 2006; Alter *et al.,* 1990). Other terms that have infrequently been used to describe this condition include pseudoalcoholic hepatitis, alcohol-like hepatitis, fatty liver hepatitis, steatonecrosis, and diabetic hepatitis.

NASH is also considered to be a subset of nonalcoholic fatty liver disease (NAFLD). Diagnosis of NASH was based on the following criteria: (i) intake of less than 20 g of ethanol per day, (ii) biopsy proven steatohepatitis; steatosis, inflammatory infiltrates, and ballooning degeneration with or without Mallory bodies or pericellular/perivenular fibrosis, (iii) appropriate exclusion of other liver diseases The detection of NASH is usually delayed, since there are no serum Surrogate markers for NASH, and a definitive diagnosis requires a liver biopsy (Alter *et al.,* 1990). The detection of NASH is usually delayed, since there are no serum surrogate markers for NASH, and a definitive diagnosis requires a liver biopsy (Koretz *et al.,* 1993; Galambos, 1972; Marbet *et al.,* 1987). Studies of nonalcoholic fatty liver disease have come to conflicting conclusions about the course of the disease. It can be argued that the disparate results are largely the result of nonuniform definitions. When histologic features such as hepatocyte ballooning, necrosis, and Mallory hyaline are seen, nonalcoholic fatty liver disease has been shown to be associated with an aggressive outcome. Steatosis alone, in contrast, appears to be benign (Marbet *et al.,* 1987; Lee, 1989). The current understanding of nonalcoholic fatty liver disease, the limited treatments available (Galambos, 1972; Marbet *et al.,* 1987; Lee, 1989; Powell *et al.,* 1990; Baldridge *et al.,* 1995).

Our study used cases and controls with similar MELD scores, gender ratios and age ranges. Therefore these are fairly well matched cases and controls. In this study of chronic liver disease with steatohepatitis, we found that group-2 (diseased controls) were more likely to have Jaundice, ascites and gastrointestinal bleeding. The cases were more likely to have pedal edema and low albumin that indicates more pronounced parenchymal injury associated in control group. These differences were statistically significant ($p<0.005$). All investigational parameters between the two groups were not significantly different except for the ESR. MELD score showed no correlation with histological findings in the Steatohepatitis cases it was observed that with MELD scores below 6 there were few patients with severe histological damage, that is why lower the MELD score (< 6) both case and control groups are less likely to develop feared complications. When the MELD score was below 6, there were very few cases with severe injury. When MELD scores were above 6, the histological damage was much more (Table 18).

Conclusion

This study used cases and controls with similar MELD scores, gender ratios and age ranges. Therefore these are fairly well matched cases and controls. In this study of chronic liver disease with steatohepatitis, we found that group-2 (controls) were more likely to have Jaundice, ascites and gastrointestinal bleeding. The cases were more likely to have pedal edema. These differences were statistically significant. All investigational parameters between the two groups were not significantly different except for the ESR. MELD score showed no correlation with histological findings in the Steatohepatitis cases it was observed that with MELD scores below 6 there were few patients with severe histological damage. However the damage did not proportionately increase MELD above 6. In an end stage of both the conditions due to loss of bio-synthetic and other metabolic function of liver, one can not differentiate these two condition by histologic or calculating MELD, so early stage of liver biopsy is mandate for crypto groups to look for any features of NASH.

REFERENCES

Alter MJ, Hadler SC, Judson FN, Mares A, Alexander JW, Hu PY, Miller JK, *et al.* Risk factors for acute non-A, non-B

hepatitis in the United States and association with hepatitis C virus infection. *JAMA* 1990; 264:2231-2235.

Baldridge AD, Perez-Atayde AR, Graeme-Higgins L, Lavine JE. Idiopathic steatohepatitis in childhood: a multicenter retrospective study. *J Pediatr.,* 1995;127:700-704.

Department of GI Surgery and Liver Transplantation, AIIMS , New Delhi, and *Department of GI Surgery and Liver Transplantation, Sir Ganga Ram Hospital, New Delhi - 2005 Vol 24 November - December 241

Galambos, JT. Natural history of alcoholic hepatitis III. Histological changes. Gastroenterology 1972; 63:1026.

Hay JE, Czaja AJ, Rakela J, Ludwig J. The nature of unexplained chronic aminotransferase elevations of a mild to moderate degree in asymptomatic patients. HEPATOLOGY 1989; 9:193-197.

Inugasa A, Tsunamoto K, Furukawa N, Sawada T, Kusunoki T, Shimada N. Faliver and its fibrous changes found in simple obesity of children. *J Pediatr Gastroenterol Nutr.*, 1984;3:408-414.

Jacobi, D., de Muret, A., Asbertle, B. and Perarnan, T.A. 2006. TIPS for treatment of portal hypertension secondary to noncirrhotic perisinusoidal hepatic fibrosis and Hcc. *Eur J Gastrohepatol*., 18:549–51.

Khanna S. and Kumar A. 2004. Management of HBV infection in decompensated liver disease. Hep B Annual 1:153-98

Kodali VP, Gordon SC, Silverman AL, McCray DG. Cryptogenic liver disease in the United States: further evidence for non-A, non-B, non-C hepatitis. *Am J Gastroenterol*., 1994;89:1836-1839.

Koretz RL, Abbey H, Coleman E, Gitnick G. Non-A, non-B posttransfusion hepatitis. *Ann Intern Med*., 1993;119:110-115.

Lee RG *Hum Pathology,* 1989 Jun; 20(6):594-8.

Marbet UA; Bianchi L; Meury U; Stalder GA J Hepatol 1987 Jun; 4(3):364-72

Nippon Rinsho, Hashimoto-E department of Internal Medicine and Gastroenterology, Tokyo Women's Medical University 2006 Jun;64(6):1025-32.

Nonalcoholic steatohepatitis, Mayo Clinic experiences with a hitherto unnamed disease Ludwig J; Viggiano TR; McGill DB; Oh *BJMayo Clin Proc*., 1980 Jul; 55(7): 434-8.

Nonalcoholic steatohepatitis Sheth SG; Gordon FD; Chopra S Ann Intern Med 1997 Jan 15;126(2):137-45.

Powell EE, GrahamW, Cooklsey E, Hanson R, Searle J, Halliday J, Powel L. The natural history of non-alcoholic steatohepatitis: a follow-up Study of forty-two patients for up to 21 years. HEPATOLOGY 1990;11:74-80.

Powell EE; Cooksley WG; Hanson R; Searle J; Halliday JW; Powell LW Hepatology 1990 Jan;11(1):74-80.

Saunders JB, Walters JR, Davies AP, Paton A. A twenty year prospective study of cirrhosis. *Br Med J*., 1981;282:263-266.

Sheth SG, Gordon FD, Chopra S. Nonalcoholic steatohepatitis. Ann Intern Med 1997;126:137-145.

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