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PATHOLOGICAL FINDINGS OF LIVER IN AUTOPSY CASES OF CIRRHOSIS- 6 YEAR STUDY

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ABSTRACT
Liver is vulnerable to a wide variety of metabolic, toxic, microbial and circulatory insults. Liver diseases and cirrhosis contribute to 23.59% of mortality in world and ranks 27th as major cause of death in world. In India, it is 2.74 % of all the causes of death. The exact prevalence of cirrhosis is not known because the disease is often silent. Nearly 30% to 40% of cases are discovered at autopsy, indicating that in substantial proportion of people, the disease goes undetected during life. The leading cause of liver disease in India is excess alcohol consumption. The other causes of liver disease and liver cirrhosis are Hepatitis B and C infections, which silently damage the liver over a period of years. There is also an emerging disease of the liver called NASH (or fatty liver), mainly due to 'westernization' of our diet and a sedentary lifestyle, and associated disorders like obesity, diabetes and high triglyceride levels. Alcohol consumption is estimated to cause from 20% to 50% of cirrhosis of the liver, making it one of the commonest causes of cirrhosis. The word cirrhosis comes from the Greek word kirrhos, which means orange yellow. Laennec gave cirrhosis its name kirrhos in 1819 in a brief footnote to his treatise De l'auscultation mediate.

INTRODUCTION

The definition of cirrhosis remains morphological, described by a working party for the World Health Organization (WHO) in 1978 as: "a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules". The most common complications are: gastrointestinal hemorrhage, ascites, encephalopathy, bacterial infections, renal failure, hepatocellular carcinoma and hepatic failure. Quite rightly liver is, called as "The custodian of milieu interior" so an autopsy study is useful to monitor the cause of death and to plan medical strategy.

AIMS AND OBJECTIVES: 1. to classify liver cirrhosis on morphological basis. 2. to establish etiology of cirrhosis if possible. 3. to study the gross morphological changes in cirrhosis. 4. to study histopathology of liver in cirrhosis.

MATERIAL AND METHOD

This was a descriptive cross sectional retrospective (2008-2011) and prospective (2012-2013) study carried out at Lokmanya Tilak Memorial Municipal General Hospital which is a tertiary care hospital in the Department of Pathology. All Cases diagnosed as cirrhosis, which were noted on autopsy records and which were confirmed by histology were included in this study. Out of the total 824 Liver Pathology Cases the 118 number of cases were selected for the study. In prospective study, after selection of cases as per inclusion and exclusion criteria, the liver specimen was examined grossly and

microscopically. Special stains were used wherever necessary.

Data entry and Statistical Analysis: Data entry and analysis was done in Microsoft Office Excel 2007. Master Chart was prepared in Excel.

OBSERVATION AND RESULT: A total of 118 patients of cirrhosis were studied. The results obtained are analysed as follows

The year wise and sex distribution of cases of cirrhosis is shown in the *Table 1* above which shows a decreasing number of autopsy and decreasing trend of incidence of cirrhosis on autopsy from 2008 to 2013 in men and a slight increase in incidence of cirrhosis in women. Maximum numbers of cases were in the age group (*Table 2*) of 31-40 years (25.4%). The youngest case of cirrhosis was of 1 year of age and oldest case was of 90 years of age.84 patients (71%) were males and 34 patients (29%) were females, when expressed in the ratio the male to female ratio is 2:1(*Table 3*). 97 patients (83.2%) had alcohol associated cirrhosis, 2 patients (1.6%) had viral associated cirrhosis like Hepatitis B, Hepatitis C each. Three patients(2.4%)had Wilson's disease,one patient each of hemochromatosis secondary to thalessemia sickle cell anemia, post necrotic cirrhosis, cirrhosis secondary to storage disorder and NASH.10 patients (8%) had cryptogenic cirrhosis(*Table 4*), 97 patients (82%) were having positive history of alcoholism, remaining 21 patients(18%) were non alcoholic. The youngest case with history of alcoholism was 18 years and eldest was 90 years (*Table 5*). The weight of liver (*GRAPH 1)* between 1200-1300 grams was taken as normal, which seen in 65 cases (55.1%). According to above criteria weight <1200 grams was considered as shrunken in 20 cases (16.9%) and weight >1300 grams was considered enlarged in 33 cases (28%). In the present study mean weight of liver was 1360grams. Other gross finding like colour was studied. Yellow was most common colour (*Table 6*) (57.6%). Nodularity *(Table 7)* was the other gross finding seen. Out of which micronodularity was seen in 48 cases and macro nodularity was seen in 39 cases and remaining 31 cases showed mixed features. Out of 118 cases of cirrhosis the most common microscopic finding (*Table 8*) was loss of lobular architecture of liver in 114(96.6%)cases. 93% (110)of cases showed fibrosis of which portal to portal , portal to central and both were 8%,38% and 50% respectively. 43 cases(36%) showed inflammatory infiltrate. Bile duct proliferation was seen in 51.6% cases. Hepatocytes changes like ballooning, steatosis, necrosis and cholestasis in 0.8%, 67% and 9.3% respectively. Of the 80 cases of steatosis most common type of steatosis was macro vesicular type in 83% cases. 2 cases (1.6%) showed hemosiderin deposition. 2cases showed features of malignancy. 12 cases (10%) of cirrhosis showed associated TB granuloma. Out of 97 patients of alcohol induced cirrhosis, 48.4% showed micronodular cirrhosis, 29.8% showed mixed cirrhosis,19.5% showed macronodularcirrhosis, of these cases 43 cases (44.3%)of micronodular cirrhosis 4 cases had features of alcohol induced hepatitis ,and early cirrhosis . Three cases showed fatty change and necrosis. Two cases of alcohol induced cirrhosis had associated findings of hepatocellular carcinoma.

DISTRIBUTION OF CASES ACCORDING TO ETIOLOGY OF CIRRHOSIS:

DISCUSSION

The day has not arrived when predictive value of liver disease can be given like many laboratory tests. Autopsy studies provide us with useful baseline data to start a step towards achieving good morphological accuracy. The present study compromised of 118 cases of cirrhosis detected from the period January 2008 to December 2013. 3960 autopsies done during this period were scrutinized and 824 cases had liver pathology. Out of the 824 cases 118 had cirrhosis as the liver pathology, which makes incidence of cirrhosis at autopsy as 14.3% of all liver pathology, which shows a decreasing incidence of cirrhosis which may be due decrease in autopsy rate over the years, the reasons for the continuing decline are complex and include attitudes toward autopsies of hospital administrative staff, medical staff, and family members and also because of increase in diagnosis by liver biopsy and introduction of antifibrotic therapy. The result shows a decreasing trend as evident by the Table 1 showing year and sex distribution of cirrhosis on autopsy. The findings are comparable to study conducted by MS Bal et al in which the incidence of cirrhosis was 14%.

AGE AND SEX DISTRIBUTION OF CIRRHOSIS:

Out 118 cases 48.1% cases were in the age group 31-50 years, and mean age of cirrhosis was 43.67 years. It is occurred a decade earlier than the study by MS Bal et al. in which 42.8% cases of cirrhosis were in age group 41-50 years. It is also similar to study conducted by R Manjunath et al. were mean age was 48.6 years and most common age group affected was 40-70 years. Many other studies by Tarun Kumar et al., Nandkumar et al. and Chakrabati et al. also the most common age group affected were 41-60 years.There was male preponderance seen in our study. The male to female ratio was 2:1. In study conducted by MS Bal et al. there was only single female case of cirrhosis. Male predominance was also seen in study by **R** Manjunath et al. were only 16% of cases were females. In other studies like also males were more affected.

Though identification of cirrhosis at autopsy is easy but etiologic characterisation may be difficult. The

results of various causes illustrated earlier results identified alcoholic as the most common cause.

In a study conducted by Deepak Kumar et al in Delhi it was found that that there is decline in prevalence of HBV infection as a cause of chronic liver disease in the past five years. In the present study decreased incidence of HBV associated chronic liver disease can be attributed to this. So according to the above a mentioned result there is a need to create more awareness among general population regarding adverse effect of alcohol consumption.

A single case of biliary cirrhosis(0.8%),in which we came across a case of biliary cirrhosis secondary to exta hepatic biliary atresia in a 12 month old male, which was a operated case of extra hepatic biliary atresia. The histopathology of the liver showed cholestasis, portal fibrosis, and ductular proliferation, expansion of the portal areas due to fibrosis nodular transformation is evident as a prelude to the development of secondary biliary cirrhosis.

3 cases (2.4%) of cirrhosis were secondary to Wilson's disease. The average age of onset of Wilson's disease is 11.5 years and die before age of 30 years as quoted by Ronald F. Pfeiffer in his article on Wilson's disease, there is progressive copper accumulation ultimately compromising hepatic function, the hepatic storage capacity is also eventually exceeded and unbound copper spills out of the liver and is deposited in other organs and tissues like heart, kidney, pancreas, brain etc where it also provokes damage and dysfunction.In our study the average age were 15 years which is earlier than the average age for cirrhosis in rest of cases, the liver sections from cases of Wilson's showed ballooning and feathery degeneration of hepatocytes, cholestasis, fibrous band showed lympho-plasmacyticinfiltrate and bile duct proliferation. Special stain for copper like Orcein showed reddish brown cytoplasmic granules.

There were two cases (1.6%) of hemochromatosis secondary to thalessemia and sickle cell anaemia, on autopsy liver was shrunken in size and it showed bridging fibrosis vague nodules and brown pigment in hepatocytes more in periportal areas. The special stain for hemosiderin, Prussian blue reaction was positive showed iron deposition in periportal hepatocytes and bile duct epithelium, kupffer cells absence of iron in septate which are seen in cases of secondary hemochromatosis. In both the conditions cirrhosis was secondary to hemochromatosis because of iron overload due to repeated blood transfusions for haemolytic anaemia.

Other causes included a case of NASH, post necrotic cirrhosis, and fatty acid oxidation. Obesity, diabetes, hyperlipidemia and female sex are important risk factors for NASH as mentioned by K Das, in our study it was in a 65 years old female known diabetic and hypertensive, admitted for acute coronary insufficiency. No liver function tests were done in this case. The liver showed extensive fatty change and fibrotic band extending between the portal tract giving rise to ill formed nodules. Nadkumaret al. reported 5% of cirrhosis secondary to NASH. While the post necrotic cirrhosis was seen in 0.8% patientin present study, Medha Y Raoet al. reported 4.6% of postnecrotic cirrhosis. The case storage disorder induced cirrhosis was of defect in fatty acid oxidation in a 3year old male with complaints of developmental delay, the MRI of this case showed fatty change in neck muscles, ante-mortem liver biopsy showed diffuse macro vesicular steatosis with mixed inflammatory infiltrates and portal to portal bridging fibrosis, post mortem section from liver showed altered liver architecture with thin fibrous septa forming nodules infiltrated by mononuclear infiltrate and bile duct proliferation and macro vesicular steatosis. Enzyme levels of carnititne and other biochemical tests were not done. Special stain of Glycogen like PAS and PAS with diastase is negative.

Cryptogenic cirrhosis contributed only 8% of total cases a series of discoveries in the laboratory and a few clinical observations, have established the aetiology of cirrhosis in the vast majority of patients, and the diagnosis of cryptogenic cirrhosis is infrequent, comparison is tabulated shows markedly reduced incidence of cryptogenic cirrhosis as it contributed 61.9% of cirrhosis in study by R. N. M. MacSween and A. R. Scott in 1969. Histologically these cases showed thick fibrous bands encircled hepatocytes nodules with pseudoacinar transformation. These hepatocytes showed not much fatty change and few showed cholestasis. This could be the end stage of many disorders like metabolic defects or infective etiology, thus was labelled as cryptogenic as no other history and investigations were available to classify these cases.

ALCOHOLISM AND SEX PREDILECTION IN CASES OF ALCOHOLIC CIRRHOSIS

As present study comprised of large number of cases of alcoholic cirrhosis the alcoholism history was studied in more detail. Studies show that the amount of alcohol consumed and the duration of that consumption are closely associated with cirrhosis. 97 cases were having history of alcoholism. Of those, 95% were male. Similar results were seen in study by Terada et al. where 92% alcoholics were male and 8% were female. In study by Gronbaeket al. the alcoholic male contributed to cirrhosis was 72%. Women are less likely to be suspected of alcohol abuse, even if they develop withdrawal symptoms in hospital. There are several reasons like social stigma a woman is less likely to admit to alcohol abuse. Any given level of alcohol consumption, women have a higher likelihood of developing cirrhosis than men. This phenomenon is poorly understood, but several possible explanations have been offered. One is that levels of alcohol dehydrogenase may be lower in the stomachs of

females than in males, which would result in higher blood alcohol content for females than for males who consume equivalent amounts of alcohol according to Frezzaet al. Because damage to the liver is a function of blood alcohol levels and exposure time, factors that lead to higher blood alcohol concentrations could at least partially explain females' higher risk for alcohol related cirrhosis. Another possible explanation is that estrogen may increase the susceptibility of the liver to alcohol related damage Ikejima et al. and Colantoni et al. Behavioural factors, including drinking patterns and diet, also may contribute to females' higher risk of cirrhosis.

MORPHOLOGICAL FINDINGS

Gross findings : According to Gall EA gross examination of liver is important to classify cirrhosis. In the present study mean weight of liver was 1360grams suggesting that there was hepatomegaly, it was shrunken (<1200 grams) in 20 cases (16.9%), enlarged in 33 cases (28%) and normal in 65 cases (55.1%). In study conducted by Agrawal P, Vaiphei K from PGIMER, 2014 the liver was studied on similar criteria and was found that in majority of cases the liver (288 cases 74%) was also enlarged and 90 cases (23%) were shrunken while only in 12 cases it was normal in weight.

Nodularity: Among the systems of morphological categories currently in use, the division of cirrhosis into micronodular, macronodular and mixed forms is preferred. It can be applied macroscopically and microscopically. 79In present study liver on gross examination showed micronodularity (<0.3cm) in 48 cases (40.6%) and micronodularity (>0.3cm) in 39 cases (33.0%). Mixed nodularity was seen in remaining 31cases (26.2%). Among the alcoholics, 48.4% showed micro nodular cirrhosis, 29.8% showed mixed cirrhosis, 19.5% showed macro nodular cirrhosis, similar results were observed in study done by Agrawal P, Vaiphei K were micronodularity was in 49% and macro nodularity was in 26% cases. Other etiological causes of cirrhosis contributed quite less in number, type of cirrhosis is like biliary cirrhosis showed micronodularity, similar to study by Aishima S et al in 2006, in which out of 26 cases of biliary cirrhosis 12 had micro nodular cirrhosis. Macro nodular cirrhosis was seen in varied aetiology like secondary to virus(2 cases), hemochromatosis (2 cases), Wilson's disease (3 cases), post necrotic (1 case), storage disorder like defect in fatty acid oxidation (1 case) and cryptogenic cirrhosis (8 cases). All these cases macro nodularity was secondary to hepatic necrosis caused by either virus, iron over load, copper deposition, enzyme deficiency leading to fatty acid accumulation. Other gross finding like colour of liver was observed. It serves as an indication of underlying pathology, like yellow discolouration indicates fatty liver, greenish discolouration indicates bile stasis. In cases of hemochromatosis liver is brown in colour. In present study yellow was most common colour (57.6%). Green colouration (bile stasis) was seen in 55 of cases. In study conducted by MS Balet al, most common colour observed was yellow in 31% cases and consistency was soft and on cut surface was greasy.**Error! Bookmark not defined.**

MICROSCOPIC FINDINGS IN CIRRHOSIS

The microscopic evaluation of cirrhosis is essential to identify the underlying aetiology and mechanism of fibrosis leading to cirrhosis, as it is the end result of variety of liver pathology, criteria indicating cirrhosis in decreasing order are nodules surrounded by septate with or without portal and central canal, hepatic vein tributaries in contact with fibrous septa, connective tissue septa linking central with portal canals, irregularity of architecture. In present study microscopy of all cases revealed loss of architecture in 96% cases prominently in cases of alcoholic cirrhosis , equivalent results were seen in Spahr et al (n=163).

Portal triaditis i.e. inflammatory infiltrate which is a indicator of underlying activity of regeneration and repair was seen in 37 % cases, similarly 46% cases in study by Agrawal P, Vaiphei K showed this feature. Depending on which type of fibrosis is prominent in initial stages it is possible to know the underlying cause of cirrhosis. In post necrotic central vein to portal areas is seen with displaced, disarranged central vein and portal tracts. Creeping fibrosis/bridging or fibrillar tongues interconnect and cause both circumscription and segmentation of hepatic lobules. In present study bridging fibrosis was seen in 107 cases, portal to portal was seen in 7.6% cases which is characteristic of biliary cirrhosis, portal to central in 35% cases and both in 47 % cases, which suggests nutritional cause (alcohol) in pathogenesis of cirrhosis as it is a centrolobular process of collagen deposition. While in Agrawal P, Vaiphei K study portoportal was seen in 58% and portocentral in 47 % cases.

Large steatosis droplet is one of criteria in diagnosis of alcoholic cirrhosis with Mallory Denk bodies, pericellular fibrosis, hypo cellular central or portal bridges. In present study steatosis was seen in 68% cases, equivalent results (63.8%) were seen in Spahr et al

Bile duct reaction/proliferations the marker of regeneration in liver, more prominent in case of biliary cirrhosis secondary to EHBA. It is seen in 61 % cases in present study. The results varied in other studied were in Spahr et al it was 37 % and in Agrawal P, Vaiphei K it was only 12 %.

Necrosis was present in 9% of cases and Cholestasis which is also a feature of biliary cirrhosis, occurs because of bile duct destruction or obstruction. In present study it was seen in 2.5% cases,in Agrawal P,

Vaiphei K study these parameters were also observed less namely 16% and 10 % respectively.

Hemosiderin deposition in hepatocytes which simulates fibro-genesis, most iron overload cirrhosis show little inflammation, diagnosis is possible ante-mortem when iron deposition precedes fibrosis, post-mortem hemosiderin deposition is also seen in alcoholic cases. In present study hemosiderin deposition was seen in two cases of hemochromatosis secondary to thalessemia and sickle cell anaemia. Likewise it was seen in 15% cases of Agrawal P, Vaiphei K study.

The frequent association of hepatocellular carcinoma with cirrhosis.In present study HCC was seen in 2 cases, both were of alcoholic cirrhosis with macro nodularity. The study by Kew MC demonstrated HCC to be more in macro nodular cirrhosis and was secondary to alcohol, Hepatitis B virus.

CONCLUSION

There has been a massive increase in alcoholism in India contributing to an increase in chronic liver disease including cirrhosis. This leads to an immunodeficient state and along with malnutrition which is commonly present in such patients, may increase the risk of tuberculosis.12 cases (10%) were associated with tuberculous granuloma, while no such findings were seen in Agrawal P, Vaiphei K study. While it has been emphasized by Lin YT et al that cirrhotic patients have a greater risk of TB than non-cirrhotic patients, particularly those with alcoholism and hepatitis C infection, while in their study of 2.32% developed tuberculosis.

Table 1. Total number of autopsies

Total number of autopsies done during Jan 2008 till December 2013	3960
Total number of autopsies with liver pathology	824
Total number of autopsies with cirrhosis as liver pathology	118

Table 2. Year wise presentation of cirrhosis at autopsy

Year	Total no. of autopsy	Autopsies with liver pathology	Autopsy with cirrhosis	Percentage of cirrhosis(%)
2008	1248	309	28	11.8
2009	1025	178	21	12.7
2010	456	79	10	21.1
2011	390	90	19	23.6
2012	414	89	21	23.6
2013	427	79	19	24.0
Total	3960	824	118	14.3

Table 3. Etiological Comparison of Cirrhosis with other studies

Study	Number of cases	Alcohol Induced	Viral	Biliary/ Autoimmune	Wilson's	Hemochromatosis	Nash	Post Necrotic	Cryptogenic	Others
R. Manjunathet al. KIMS Hospital,2014	50	80%	16%						4%	
Goncalves PL et al. 2014	262	40.5%	26.7%						10.6%	3.8%
Medha Y Raoet al., MS Ramaiah Medical College, Bangalore,2008	43	58.1%	18.6%					4.6%	18.6%	
Nandakumaret al. 2003	46	65%	25%				5%		5%	
Terada et al. 1992	209	12.4%	80.3%	5.1%	0.4%	1.4%				0.4%
Present study	118	83.2%	1.6%	0.8%	2.4%	1.6%	0.8%	0.8%	8%	0.8%

Table 4. Age Distribution of Cirrhosis

Age	No. of Cases	Percentage
0-10	6	5.1%

11-20	5	4.2%
21-30	13	11.3%
31-40	**30**	**25.4%**
41-50	**28**	**23.7%**
51-60	20	16.9%
61-70	11	9.3%
71-80	4	3.3%
81-90	1	0.8%
Total	118	100%

Table 5. Sex Distribution of cirrhosis

Males	84	71%
Females	34	29%
Total	118	100%

Table 6. Distribution of Cirrhosis According To Etiology

Causes	**No. of Cases**	**Percentage**
Alcoholic Cirrhosis	97	83.2%
Viral- HBV HCV	1 1	0.8% 0.8%
Biliary Cirrhosis	1	0.8%
Wilson's Disease	3	2.4%
Hemochromaosis Secondary To Thalessemia Sickle anemia	 1 1	 0.8% 0.8%
NASH	1	0.8%
Post Necrotic	1	0.8%
Cryptogenic	10	8%
Storage Disorder	1	0.8%
Total	118	100%

Table 7. Sex Distribution of cirrhotic cases with history of alcoholism

History of alcoholism (M+F)	93 +4
No history of alcoholism(M+F)	15+6
Total	118

Table 8. Colour of Liver in Cirrhosis

Colour	**No. of Cases**	**Percentage %**
Yellow	64	57.6
Yellow brown	28	23.7
Greyish	9	7.6
Whitish	8	6.8
Greenish	6	5.1
Total	118	100

Table 9. Distribution of Cirrhosis According To Nodule Size

Etiologically	**Micronodular<0.3 CM**	**Macronodular>0.3 CM**	**Mixed**
Alcohol induced cirrhosis(n=97)	47	21	29
Virus induced cirrhosis (n=2)		2	
Wilson's disease (n=3)		3	
Biliary cirrhosis(n=1)	1		

Hemochromatosis (n=2)		2	
NASH (n=1)		1	
Post necrotic (n=1)		1	
Cryptogenic (n=10)		8	2
Storage disorder (n=1)		1	

Table 10. Microscopic findings of Liver in cirrhosis

Features	No. of Cases with these features	Percentage (%)
Loss of architecture	114	96.6
Fibrosis Incomplete fibrosis Bridging fibrosis-Portal-portal Portal –central Both	 3 9 42 56	2.5 7.6 35.6 47.5
Inflammatory infiltrate-portal triadities Chronic-lymphocytic Lymphoplasmacytic Lymphoid aggregates	 39 3 2	33.1 2.5 1.7
Bile duct proliferations	61	51.7
Hepatocytes Ballooning Micro vesicular steatosis Macro vesicular steatosis Both	 1 11 67 2	0.8 9.3 56.8 1.7
Necrosis Sub massive Centrilobular	11 1 10	9.3 0.8 8.5
Cholestasis	3	2.5
Hemosiderin deposition	2	1.7
Sinusoidal congestion Dilatation	61 3	51.7 2.5
Malignancy	2	1.7
Metastasis	-	
Tuberculosis- granuloma	12	10.2

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS
All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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