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SPECTRUM OF HEPATIC STEATOSIS AT AUTOPSY

Pathology

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ABSTRACT

Objectives: Steatosis is one of the most common histologic findings in the liver at any age and it may or may not be associated with alcohol consumption. We undertook this study to assess:

1. Prevalence of fatty change, significant or otherwise, in liver, at autopsy
2. Risk factors/ causative factors/ associated lesions, if any
3. Severity of fibrosis with steatosis
4. Any associated iron deposition with fatty change

Methods: All liver sections from clinical autopsies (n=308) performed in the year 2011 were screened for fatty change. The cases with fatty change were selected for further analysis. Special stains for collagen (Masson Trichrome) and iron (Prussian blue reaction) were performed on the liver sections showing significant steatosis (> 10%). Fibrosis was graded as pericellular fibrosis (Stage 1), portal fibrosis (Stage 2), bridging fibrosis (Stage 3) and cirrhosis (Stage 4). Clinical and autopsy case records were retrieved for analysis of risk factors, demographic and clinical data.

Results: Approximately 45% of cases showed steatosis of which around 30% showed significant steatosis. Common etiologies found were alcoholism, obesity, tuberculosis, pregnancy, cardiac disorders and diabetes. Significant steatosis was also noted in the pediatric age group where cardiac disorders were the commonest cause. Fibrosis and iron deposition were variable.

Conclusion: Prevalence of significant hepatic steatosis in this study was 30.5%. Among adults, alcoholism was the commonest risk factor. Others were obesity, poor nourishment and diabetes. Among children, cardiac disorders were the commonest risk factor.

KEYWORDS

Autopsy, hepatic steatosis, hepatic fibrosis, iron.

INTRODUCTION

Steatosis is one of the most common histologic findings in the liver at any age and it may or may not be associated with alcohol consumption. Factors known to be associated with steatosis other than alcohol are protein – energy malnutrition, obesity, diabetes mellitus, drugs and toxins, metabolic disorders and infections such as hepatitis C[1]. The steatosis seen in these conditions is often predominantly macrovesicular with or without microvesicular fat. Purely microvesicular steatosis is, however, a more serious condition which can be seen in acute fatty liver of pregnancy, Reye's syndrome, alcoholic foamy degeneration, drug toxicity and others[1]. The mortality rate from natural diseases in alcoholics is higher than that in the general population. Despite the large number of deaths involved, the mechanism of death in many cases of fatty liver death remains a mystery, especially in cases without cirrhosis.

We undertook this study to assess the prevalence of fatty change in liver at autopsy, to study the severity and patterns of steatosis, associated fibrosis and iron deposition, and to detect risk factors and lesions associated with steatosis.

MATERIALS AND METHODS

HE stained standard liver sections of 308 autopsies over a period of 1 year were screened for presence of steatosis. The cases with fatty change were selected for further analysis. Special stains for collagen (Masson Trichrome) and iron (Prussian blue reaction) were performed on the liver sections showing significant steatosis[1-3] (> 10%). Fibrosis was graded[1] as pericellular fibrosis (Stage 1), portal fibrosis (Stage 2), bridging fibrosis (Stage 3) and cirrhosis (Stage 4). Clinical and autopsy case records were retrieved for analysis of risk factors, demographic and clinical data.

RESULTS

Of 308 autopsies studied, significant steatosis, i.e. fatty change involving more than 10% of the liver parenchyma, was seen in 85 cases. Of these, 69 were adults and 16 were children. Steatosis was graded according to Brunt classification[1] [Fig 1, Table 1]. Various risk factors that were present in these patients have been tabulated in Table 2 and 3. Some cases had more than one risk factors. Type of steatosis and zonal distribution in association with different risk factors have been tabulated in tables 4 and 5. On Masson trichrome stain liver fibrosis was seen in total 39 cases of which 26 had fine pericellular fibrosis (Stage 1), 3 had periportal and pericellular fibrosis (Stage 2), 3 had bridging fibrosis (Stage 3) and 7 had cirrhosis (Stage 4). On Prussian blue staining hepatocellular iron deposition was seen in 12 cases. Analysis of causes of death at autopsy of the cases with significant steatosis is given in table 6.

Table 1: Number of cases with steatosis

Total no of cases studied	308
Cases with fatty change	138 (44.8%)
Cases with significant FC (> 10%)	85 (27.6%)
Amount of fat	
1 to 5 %	44 (14%)
(non-significant)	
5 to 10 %	9 (2.9%)
(non-significant)	
10 to 33 %	28 (9.1%)
(Grade 1)	
33 to 66 %	21 (6.8%)
(Grade 2)	
> 66 %	36 (11.7%)
(Grade 3)	

Table 2: Risk factors associated with significant steatosis (overlapping in some cases)

RISK FACTORS	Children	Adults	Total
Alcohol	0	16	16
Overweight or obese	2	30	32
Undernourished or cachectic	1	12	13
DM	0	8	8
Cardiac disorder	10	10	20
Pregnancy	0	11	11
TB with liver involvement	1	2	3
TB without liver involvement	0	9	9
Cachexia with malignancy	0	2	2
SLE	0	3	3
HIV	0	2	2
Methotrexate toxicity	0	1	1
Metabolic disorder (glutaric aciduria)	1	0	1
Miscellaneous (smoking)	0	3	3

Table 3: Risk factors of severe (Grade 3) steatosis (>66% fatty change)

Risk factor	No. of cases
Over-nourished	16
Under-nourished	6
Alcohol	9
Cardiac	7
TB	6
AFLP	2
DM	1
SLE	1
Methotrexate toxicity	1
Metabolic (glutaric aciduria)	1

Table 4: Type of fatty change (macrovesicular or microvesicular) seen in various risk factors of significant steatosis

RISK FACTORS	Adults		Children	
	Macovesicular or mixed fat	Pure microvesicular fat	Macovesicular or mixed fat	Pure microvesicular fat
Alcohol	15	1		
DM	8			
Cardiac disorder	8	2	10	
Pregnancy	9	2		
TB with liver involvement	2		1	
TB with liver involvement	7	1		
Cachexia with malignancy	2			
SLE	3			
Methotrexate toxity	1			
Metabolic disorder (glutaric aciduria)	0		1	
Miscellaneous (Smoking)	2	1		
HIV	2			
NOURISHMENT				
Obese	5			
Overweight	24	2	1	
Average	25	2	13	
Undernourished	7	2		
Cachectic	2		1	1

Table 5: Zonal distribution of significant steatosis with various risk factors

A]

Zonal distribution of fat	Alcohol	Overnourished	Cardiac	DM	Total
Centrilobular	8	14	13	4	39
Panlobular	1	3	2	0	6
Periportal	2	6	5	2	15
Random	5	1	0	2	8
Total	16	24	20	8	68

B]

Zonal distribution of fat	TB	Undernourished	Cachexia with Malignancy	Total
Periportal	9	6	1	16
Panlobular	2	3	0	5
Centrilobular	0	2	1	3
Total	11	11	2	24

C]

Zonal distribution of fat	AFLP	Methotrexate poisoning	Metabolic (glutaric aciduria)	Total
Panlobular	2	1	1	4
Centrilobular	0	0	0	0
Periportal	0	0	0	0
Total	2	1	1	4

Table 6: Analysis of causes of death (broad categories) of cases with significant steatosis.

Cause of death	No. of cases
Total no. of cases	85
Complications of cirrhosis	4
AFLP	2
Cardiac failure	22
Acute pancreatitis	11
Tuberculosis	11
Respiratory failure	4
Renal failure	3
CNS (Meningitis)	1
GI (Peritonitis following perforated peptic/ intestinal ulcers)	6
Septicemia	4
Disseminated Intravascular Coaguloathy	2
Acute Febrile Illness	5
Malignancy	2
Other systemic causes	5
Unexplained	3

DISCUSSION

The prevalence of significant fatty change at autopsy in this study is 27.6% which is similar to the 20 to 50 % prevalence noted by other investigators.[4, 5] Amongst the 69 adults with significant steatosis, the commonest causative or risk factors were over-nourishment (30 cases; 41.1%), chronic alcoholism (16; 21.9%), poor nourishment (12; 16.4%), tuberculosis with or without involvement of the liver (11; 15.1%), cardiac disorders (10; 13.7%) and diabetes mellitus (8; 11%). Also, there was a lot of overlap amongst the risk factors. 27 patients (37%) were averagely nourished. In an analysis of 270 patients with fatty liver by Leevy, the commonest causes were alcoholism (43.3%), diabetes (6.3%), heart disease (4.07%) and obesity (2.6%).[6] In a study of 195 adult patients with significant steatosis at autopsy by Amrapurkar et al, the common risk factors found were alcohol (38.5 %), tuberculosis (25.6 %), obesity (5.1%), diabetes (5.1%), hypertension (5.1%) and cardiac disorders (5.1%).[7]

11 of the 42 adult females with significant steatosis were either pregnant or in the immediate postpartum phase (<1 week). Five of them had tuberculosis, three of whom were undernourished. Three others were overweight of whom one had developed acute fatty liver of pregnancy and another had hepatic veno-occlusive disease. Of the three averagely nourished women, one had dengue hemorrhagic fever and another one had acute fatty liver of pregnancy.

Amongst the 16 children with significant steatosis, the commonest risk factor was presence of underlying congenital heart disease (10 cases). Other factors were over-nourishment (1) or undernourishment (2), tuberculosis (1) and metabolic disorder (1).

Majority of the steatosis in both adults and children was macrovesicular or mixed. Only one child who had protein-energy malnutrition and 6 adults had pure microvesicular steatosis. Of the six adults, two had acute fatty liver of pregnancy, one was a chronic alcoholic, one had tuberculosis and two had cardiac disease.

Steatosis due to alcohol, NAFLD (associated with obesity, diabetes) and cardiac diseases is believed to be predominantly centrilobular in location, progressively extending to the rest of the lobe. This was seen in most of the cases in our study, except for 7 alcoholics, 7 overnourished patients, 5 with cardiac diseases and 4 with diabetes mellitus in whom the fat was located in the periportal region or was randomly distributed. Steatosis due to cachexia and debilitating conditions such as tuberculosis and malignancy is believed to periportal in location. This was seen in most of our cases, except in 2 under-nourished patients and in 1 case of malignancy in which the fat was located in centrilobular zone. All the cases of acute fatty liver of pregnancy (2), drug induced liver injury (1) and metabolic disorder (1) in this study had panlobular steatosis.

On studying the causes of deaths in cases (85) with significant steatosis, it was observed that 4 cases died due to complications of cirrhosis alone. Two women died of acute fatty liver of pregnancy. In 76 cases, diseases of other organs led to death, majority of these died of cardiac diseases (22). The next common cause of death was acute pancreatitis (11) followed by disseminated tuberculosis (11).

In 3 cases, clinical history, investigations and morphology of organs at autopsy did not reveal any specific pathology, other than significant fatty change, that could have led to death. One of them was a young man (22 years old), chronic alcoholic, with jaundice and abdominal pain. On ante mortem investigations, his prothrombin time, INR and serum fibrinogen were found to be deranged with increase in fibrin degradation products. Investigations for dengue, malaria, leptospirosis, and hepatitis A, B, C and E were all negative. Autopsy revealed liver infarct, ischemic lesions in bowel and fatty liver. On microscopy the liver showed 90 – 95% microvesicular steatosis without any inflammation or fibrosis. No other pathology was found in other organs and no cause for the coagulopathy was found.

Another case of a 52 year old overweight woman on replacement therapy for hypothyroidism developed severe abdominal pain and vomiting. She was icteric, with elevated serum transaminases and bilirubin. In this patient, too, prothrombin time and INR were elevated with a low platelet count. Investigations for dengue, malaria, leptospirosis, and hepatitis A, B, C and E were all negative. She died within 4 hours of ward stay. Autopsy revealed enlarged fatty liver which on microscopy showed 70% macrovesicular steatosis, predominantly in periportal and midzonal locations without any inflammation or fibrosis. None of the other organs showed any pathology. This led us to believe that fatty liver itself may have led to DIC in the above two patients, causing liver infarct in the first.

The third case, a 37 year old man, chronic alcoholic, presented with disorientation. Injection thiamine was administered. However, he died within 5 hours of ward stay. At autopsy, the liver was found to have 75 – 80% steatosis, predominantly macrovesicular located mainly in the centrilobular and midzonal areas. There was no inflammation or fibrosis. None of the other organs showed any significant pathology. Therefore, it can be inferred that steatosis, even in the absence of cirrhosis, was probably responsible for death in this case. In an autopsy study of 397 sudden non-traumatic deaths by Kuller, it was found that 111 showed only fatty liver at autopsy with no other significant pathologic finding.[8] These were defined as fatty liver deaths. He postulated that pathologists are reluctant to use fatty liver as the diagnosis if other, even meager, pathologic changes such as mild coronary arteriosclerosis are present. However, we have to recognize and accept fatty liver deaths. Randall proposed various mechanisms of fatty liver death. These included hypoglycemia, fat embolism, hypomagnesemia, ethanol withdrawal syndrome and ethanol induced neurotransmitter changes.[9]

CONCLUSION

The prevalence of significant hepatic steatosis (>10%) at autopsy was 27.6%. The common causes among adults were malnourishment (over-nourishment – 41.1% and undernourishment – 16.4%), chronic alcoholism (21.9%), tuberculosis (15.1%), cardiac disorders (13.7%) and diabetes (11%). Congenital heart disease (62.5%) was the commonest cause in children. Protein-energy malnutrition and tuberculosis are important causes of steatosis in the non-obese, non-alcoholic population.

Steatosis due to alcohol, overnourishment, diabetes and cardiac diseases, in majority of the cases, was predominantly centrilobular in location, with or without involvement of the rest of the lobe. Steatosis due to cachexia and debilitating conditions such as tuberculosis and malignancy was predominantly periportal in most of the cases.

In majority of the cases, cause of death could be ascertained at autopsy. However, in three cases, fatty liver itself probably led to death as no other antecedent cause of death was found despite complete autopsy. The etiology of fatty liver death is most likely multifactorial and may well touch upon some of the theories proposed by Randall.[9]

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