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RESEARCH ARTICLE

AETIOLOGICAL FACTORS FOR H.C.C- EXPERIENCE AT TERTIARY CARE CENTRE OF NORTHERN INDIA

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Abstract

Hepatocellular Carcinoma (HCC) is one of the most common malignant tumours in the world. It is a heterogeneous group of a tumour which varies in risk factor, genetic and epigenetic alteration event. The mortality rate due to it is increasing with time. The various risk factors include hepatitis B &C viruses, alcohol, metabolic syndrome including diabetes mellitus, chemicals, and inborn and acquired metabolic disease. HCC is closely associated with hepatitis B and C virus because liver injury caused by viral factor affects many cellular processes such as cell signalling, apoptosis, transcription, DNA repair which in turn induce important effects on cell survival, growth, transformation and maintenance. The molecular mechanisms of hepatocellular carcinogenesis vary depending on different factors thus leading to different mechanisms associated with these tumours. Our study shares the experience of various aetiological factorsresponsible for HCC at tertiary care centre of Northern India.

Introduction:-

Liver cancer is one of the leading causes of cancer deaths worldwide. In recent years, the annual death toll with700,000 has been recorded around the globe [1]. Hepatocellular Carcinoma (HCC) represents the major histological subtype of primary liver malignancies, accounting for 70% to 85% of the total liver cancer burden [2]. Most cases of HCC (75% to 90%) develop in cirrhosis resulting from chronic infection by hepatitis B virus and hepatitis C virus, alcoholic injury, and to a lesser extent from genetically determined disorders such as hemochromatosis [3,4]. The risk factors for HCC include chronic HBV (hepatitis B virus) and HCV (hepatitis C virus) infections, autoimmune hepatitis, chronic alcohol use, obesity and diabetes mellitus etc [5]. In last three decades, about 63% increase in totaldeaths has been reported globally because of viral hepatitis. Hepatitis B and C infections accounted for most of themorbidity and mortality since it leads to progressive hepatic damage in patients and ultimately causing cirrhosis andhepatocellular carcinoma [6].In areas of high incidence, HCC has been reported even at two years of age. However, the incidenceincreases with age in all populations and shows a slight decline in the elderly population. HCC shows a strong malepreference. In low incidence regions, it is four times more common in males while in high prevalence areas, it is abouteight times more common. It may be attributed to additional effect of other factors including higherlevels of alcohol intake and smoking coupled with a higher incidence of cirrhosis in males. Animal experiments havesuggested the role of sex hormones and/or hormone receptors. Orchidectomy reduces the carcinogenic effects ofchemicals in male rats to the level found in females. A similar effect has been observed with stilbesterol or oestradiol pellets' implantation but the effect was comparatively less

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[7].In western countries, inborn errors of metabolism and congenital abnormalities have also contributed towards HCCin some cases [8]. The current review describes the various causes of H.C.C seen at our centre.

Observations:-

Total Patients	HBV	HCV	MAFLD	ALD
65	28 (43.07%)	25 (38.46%)	7 (10.76%)	5 (7.69%)

Table 1:- Showing Various Aetiological Factors for H.C.C

The table shows that Hepatitis B virus is most common cause of H.C.C i.e. in total pool of 65 patients, 28 (43.07%) followed by HCV infection 25 patients (38.46%), MASH group 7 patients (10.76%) and alcohol group of 5 patients (7.69%).

AGE (YRS)	HBV (N-28)	HCV (N=25)	MAFLD (N=7)	ALD (N=5)
10-19	0	1	0	0
20-29	2	0	0	0
30-39	3	0	0	0
40-49	2	1	0	2
50-59	6	8	4	2
60-69	11	6	3	1
70-79	4	8	0	0
80-89	0	1	0	0

Table 2:- Showing Age Distribution in Various Aetiological Factors for H.C.C.

The above table has clearly highlighted the fact irrespective of aetiology, H.C.C is commonly seen in older age group. In Hepatitis B group, out of 28 patients, 21 patients (75%) were above 50 yrs of age. The two patients who belonged to third decade were non cirrhotic and were having chronic hepatitis B with high viral load and directly developed multifocal H.C.C without going into cirrhotic stage. In Hepatitis C group, out of 25 patients, 23 patients (92%) were above 50 yrs of age. All the 25 patients in this group were cirrhotic. In MASH group, all the 7 patients (100%) were above 50 yrs of age and all were cirrhotic. In alcohol group, out of 5 patients, 3 patients (60%) were above 50 yrs of age and all were cirrhotic.

Epidemiology	HBV (N-28)	HCV (N=25)	MAFLD (N=7)	ALD (N=5)
Sex (Male)	26	21	3	5
Sex (Female)	2	4	4	0
Rural	23	22	3	3
Urban	5	3	4	2
Diabetes	1	3	4	0
Smoking	10	14	2	5
Alcohol	10	14	2	5
Coinfection	HCV-2	HBV-1	0	0
Cirrhosis	26	25	7	5

Table 3:- Showing Epidemiological factor Distribution in Various Aetiological Factors for H.C.C.

The above table has clearly highlighted the fact that H.C.C is commonly seen males except MASH group. In Hepatitis B group, out of 28 patients, 26 patients (92.85%) were males, in HCV group, out of 25 patients, 21 (84%) were males. In Mash group, out of 7 patients, 3 (42.85%) were males whereas in alcohol group all 5 patients (100%) were male. H.C.C is commonly seen in rural area except MASH group. In Hepatitis B group, out of 28 patients, 23 patients (82.14%), in HCV group, out of 25 patients, 22 (88%) belonged to rural area. In Mash group, out of 7 patients, 3 (42.85%) and in alcohol group, out of 5 patients, 3 (60%) belonged to rural area. As expected, Diabetes mellitus was seen more commonly in MASH group i.e. in 4 patients (57.14) whereas it was seen in 1 (3.5%) patient of HBV, 3 (12%) of HCV and none was found diabetic in alcoholic group. Out of 28 patients of HBV, 10 (35.71%) were both alcoholic & smoker, whereas in HCV group of 25 patients, it was seen in14 patients (56%). In MASH group of 7 patients, it was seen in 2 (40%) patients and 100% in alcoholic group. In HBV group of 28 patients, 2 (7.1%) patients were found to be co-infected with HCV whereas in 25 patients of HCV, only 1(4%) patient was found to be HBV co-infected. In MASH and alcohol group none was having HBV or HCV infection. In all four groups, none patient was infected with HIV.

Parameters	HBV (N=28)	HCV (N=25)	MAFLD (N=7)	ALD(N=5)
AST	32-470	18-172	52-104	49- 204
ALT	20-496	22-256	42-98	47- 180
S.Bilirubin	0.4- 2.2	0.5-6	1.8-3.4	1.9-8.2
S.Albumin	2,1-4.3	2.2-4.6	2.4-3.9	2.3-3.7
INR	0.94-1.6	0.91-1.92	1.01-1.73	1.2-2.23
Platelet Count	0.80-3.6L	0.60 – 2.5 L	0.76-1.48 L	0.67-1.35 L
S. Creatinine	0.5-1.7	0.8-1.22	1- 1.44	1.2-1.8
Fibroscan	6-67 Kpa	13-75 Kpa	19-74	23-75
Viral Load	101-107	101-107	Nil	Nil

Table 4:- Showing Parameters Distribution in Various Aetiological Factors for H.C.C.

In HBV group AST level varied from 32-470 IU (mean 101), whereas in HCV, MASH and alcohol group range was 18-172 IU (mean 88), 52-104 IU (mean 70), 49-204 IU (mean 100) respectively. In HBV group ALT level varied from 20-196 IU (mean 90), whereas in HCV, MASH and alcohol group range was 22-256 IU (mean 98), 42-98 IU (mean 67), 47-180 IU (mean 101) respectively. In HBV group serum bilirubin level varied from 0.4-2.2 (1.13) mg/dl, whereas in HCV, MASH and alcohol group range was 0.5-6 (mean 1.75), 1.8-3.4 (mean 1.55), 1.9-8.2 mg/dl (mean 3.8) respectively.In HBV group serum albumin level varied from 2.1-4.3 (mean 3.52), whereas in HCV, MASH and alcohol group range was 2.2-4.6 (mean 2.6), 2.4-3.9 (mean 2.9), 2.3-3.7 (mean 2.7) respectively.In HBV group INR level varied from 0,94-1.6 (mean 1.18), whereas in HCV, MASH and alcohol group range was 0.91-1.92 (mean 1.18), 1.01-1.73 (mean 1.28), 1.2-2.33 IU (mean 1.48) respectively.In HBV platelet level varied from 0.80-3.6 lakhs/mm3 (mean 1.93), whereas in HCV, MASH and alcohol group range was 0.6-2.5 lakhs/mm3 (mean 1.14), 0.76-1.48 lakhs/mm3(mean 90), 0.67-1.35 lakhs/mm3(mean 88) respectively. In HBV group serum creatinine level varied from 0.5-1.7 (mean 0.95), whereas in HCV, MASH and alcohol group range was 0.8-1.22 (mean 0.98), 1-1.44 (mean 1.1), 1.2-1.8 (mean 1.3) respectively.In HBV group Fibroscan score varied from 6-67 Kpa (mean 37), whereas in HCV, MASH and alcohol group range was 13-75 Kpa (mean 38.01.), 19-74 Kpa (mean 39), 23-75 (mean 42) respectively. The HBV & HCV viral load ranged between 101-107 IU/ml (mean 105). Out of total 28 patients HBV, 26 were on monotherapy and 2 were on dual therapy. Out of 25 patients of HCV, only 10 (40%) patients achieved sustained virological response (SVR).

Discussion:-

Hepatocellular carcinoma (HCC) is a highly prevalent cancer globally, occupying the sixth place and was the third leading cause of cancer death worldwide in 2020 [9]. The prevailing aetiology varies by country. Viral hepatitis and alcohol consumption are the most important risk factors for the development of HCC [10]. In countries where vaccination against hepatitis B virus (HBV) is widely available, alcohol-related HCC can be more prevalent [11]. In the last decades, non-alcoholic fatty liver disease (NAFLD), now called as MAFLD has become a more prevalent risk factor for HCC due to the rise of obesity and metabolic syndrome in this country [12]. Early detection of HCC is likely beneficial, and prognosis can be calculated using tumour characteristics, clinical parameters, or both. HCC accounts for 70% of primary liver cancers and is the sixth most common cancer worldwide [9-11,13]. It is the third leading cause of cancer-related deaths in the world [10-12]. It is more common in men and the average age at diagnosis is 50 – 70 years [10-11] which is in alignment with our study group of 65 patients, in which 55 patients(84.61%) were males and 48 patients (73.84%) were above fifty years of age. The reason behind this can be that HBV & HCV infection itself is more commonly in men and moreover alcoholic liver disease (ALD) is more commonly seen in males. Only MAFLD related is equally or more commonly in females and all these findings matched with our study. Africa and Asia account for 80% of all HCC cases, with Asia bearing approximately 72.5%. This is thought to be due to their high rates of HBV infection, as well as high rates of aflatoxin exposure [10,11,14]. Limited access to HBV screen-ing, vaccination, and treatment also plays a role [15]. The incidence of HCC in patients with chronic HBV infection is 44%, and in HCV infection, 21%. Patients with high alcohol consumption have up to 26% risk of developing HCC. Other risk factors include non-alcoholic liver disease, tobacco smoking, aflatoxin-contaminated food intake, diabetes, and obesity [9, 16,17]. Our study also highlighted the same fact that HBV is most common aetiological risk factor for H.C.C. followed by HCV infection. The prevalence of H.C.C. is less in ALD because many patients succumb to their illness after decompensation and before developing H.C.C.In all the groups except MAFLD related, there was rural predominance, strikingly in HBV & HCV group because these two diseases occur more commonly in rural areas due to lack of proper safe needle practices because of lack of trained health professionals in rural areas. The prevalence of diabetes mellitus was maximally seen in

MAFLD group, it being a major risk factor for the same and was followed by HCV group, the association of diabetes mellitus and HCV has already been reported in many studies. The history of alcohol and smoking was seen in all patients of ALD, followed by HCV and HBV group. It has already been proven by many studies that alcohol and smoking are independent risk factors for H.C.C and in association with other risk factors like HBV, HCV, MASH & alcohol, increases the risk of developing H.C.C and finding in our study are in alignment of the same. As, it is well known all aetiological factors for H.C.C. except HBV & HCV in selected cases have to progress through cirrhotic stage before developing H.C.C. In our study group also, all patients in HCV, MAFLD and ALD group were cirrhotic and only two patients in HBV group were young non-cirrhotic and were in chronic hepatitis stage with high viral load, transaminases level and Fibroscan scores. The co-infection with HBV & HCV increases risk of H.C.C. and in our study group also, two HBV patients were co-infected with HBV and one patient in HCV group was having HBV co-infection. Out of 28 patients in HBV group, 26 were on monotherapy and two were on dual therapy. In 25 patients of HCV, all were treated with antiviral treatment but only 15 patients (60%) achieved sustained virological response (SVR). We know that SVR is 90-93% in non-cirrhotic and decreases to 80-90% in cirrhotic and in our study group all were cirrhotic. The AST & ALT elevation were seen maximally in HBV group and minimal in MASH group. In HBV group, many patients may have developed acute flare leading to significant rise in transaminases. The serum bilirubin was maximally seen in alcoholic group and minimal in HBV group which is easily understandable because many alcoholics have severe alcoholic hepatitis leading to substantial rise in serum bilirubin levels. The serum albumin level & platelet counts were maximally reduced and INR & serum creatinine rise was maximally seen in alcoholic group. The reason is that alcoholics are usually diagnosed in later stage of chronic liver disease (CLD), as majority of them are adamant of not taking timely medical help and even after being diagnosed as CLD, half of them have recidivism. Fibroscan score was maximally increased in ALD & HCV group. The mean viral load in both HBV & HCV group was one lakh I.U. /ml but in few cases in both groups H.C.C. developed with low viral loads which is further area of research.

Conclusion:-

HCC is the sixth most common cancer worldwide and it is the third leading cause of cancer-related mortality. The risk factors for HCC can be classified as infectious or behavioural and survival rates vary between them. Currently, viral hepatitis,MAFLD and alcohol use are the most important risk factors for HCC. HBV and HCV are the major risk factors for virus-induced HCC development through direct or indirect mechanisms but good thing is that there is provision of free treatment for both of them under National viral hepatitis control (NVHCP) in India. Thus, need of time is integrated approach of both prevention and treatment for them which require widespread screening of high-risk groups for early detection and timely treatment by dedicated team. There should be large scale campaign for making understand society against ill effects of alcohol and taming the arms of metabolic syndrome like obesity, diabetes mellitus and dyslipidaemia. Thus, by applying above manoeuvres, we can effectively curtail the incidence and prevalence of H.C.C.

Conflict Of Interest-

The authors declare that there was no conflict of interest during this research study.

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