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Clinical Study of Acute Viral Hepatitis withSpecial Reference to Complementary andAlternative Medicine Induced Liver Injury

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ABSTRACT:
Background:Acute viral hepatitis continues to be a major public health problem in the world, especially in India. Complementary and alternative medicine(CAM) has gained much popularity and is preferentially used for various chronic diseases worldwide. Although CAM is generally thought to be safer than conventional drugs, many reports suggest hepatotoxicity and other adverse effects of herbal products. This study evaluates the clinical profile of the patients with acute viral hepatitis and its complications and clinical profile of patients of acute viral hepatitis taking "Complementary and Alternative Medicine".
Materials and Methods:A hospital based observational study was conducted on 130 patients who presented with serologically confirmed acute viral hepatitis with a history of intake of complementary and alternative medicine. Each patient underwent a detailed clinical and biochemical assessment. The data collected were tabulated and summarized as frequency and percentages.
Results:In our study most common clinical symptom in patients with Acute Viral Hepatitis were anorexia (79.23%) followed by yellowish discoloration of eyes (77.69%), nausea (75.38%), and malaise (73.07%). 33.8% patient had a history of taking Complementary and Alternative Medicine for the treatment of Acute Viral Hepatitis. 31.82% patients had Serum Bilirubin level was >20.1 mg/dl. Maximum number of patients10(22.73%) with a history of CAM intake for AVH had an ALT level in the range of 1501-2000 IU/L. Hepatitis A was responsible for a majority of acute viral hepatitis with cholestasis being the most common complication. 9.09% of patients with CAM intake developed acute liver failure.
Conclusion:Complementary and alternative medicine intake is a popular method of treatment for jaundice and commonly used in form of herbal medications. CAM use in acute viral hepatitis is associated with increased incidence of cholestasis and precipitating factor for acute liver failure.
Key Word: herbal medications, hepatotoxicity, jaundice, acute liver failure, complementary and alternative medicine, acute viral hepatitis

I. INTRODUCTION

Globally, acute viral hepatitis is a serious public health issue, particularly in emerging nations like India. One of the five viral agents—hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), HBV associated delta agent (HDV), and hepatitis E—causes nearly all episodes of acute viral hepatitis (HEV). With the exception of hepatitis B, which is a DNA virus, all of these human hepatitis viruses are RNA viruses.Acute hepatitis is a general diagnosis referring to any of a wide variety of conditions causing acute inflammation or injury to hepatocytes, resulting in elevation of liver biochemical lab tests[1].
Acute viral hepatitis can be defined clinically as an acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis(e.g., fever, headache, malaise, anorexia, nausea, vomiting,diarrhoea, abdominal pain or dark urine).**AND** a) jaundice or elevated total bilirubin levels ≥ 3.0 mg/dL, **OR** b) elevated serum alanine aminotransferase (ALT) levels >200 IU/L, **AND** c) the absence of a more likely diagnosis. (Centres for Disease Control and Prevention USA 2019).

Hepatitis is classified as acute if it resolves in less than six months, and if abnormal findings last over six months, it is classified as chronic hepatitis[2]. Natural childhood illnesses have declined as a result of advancements in sanitation, hygiene, and socioeconomic situations. As a result, there is a rise in the number of susceptible people

and a corresponding rise in the proportion of clinical disease, particularly acute viral hepatitis A. Hence, adult acute viral hepatitis A may be prevented to a great extent by hepatitis A immunisation.

Complementary and alternative medicine (CAM) has gained much popularity and is preferentially used for various chronic diseases, worldwide [3]. Compared to a single chemically-characterized drug, complementary and alternative medicine is a mixture of phytochemical constituents present in the herbal extracts [4]. In CAM/drug-induced liver injury, over or misdiagnosis is a common phenomenon [5]. The notion that these compounds are natural and safe and hence have no side effects has contributed to their popularity and widespread use.In a large cohort of patients with cirrhosis, Philips et al in 2019 [6] retrospectively studied complementary and alternative medicine-related health seeking behaviour and attempted to identify those who developed possible CAM-induced liver injury related acute on chronic liver failure. In a study of Drug-Induced LiverInjury at a Tertiary Hospital in India the most commonly implicated drugs were antitubercular therapy (ATT)(49%), antiepileptic drugs (12%),complementary and alternative medicine (CAM) in 10%,antiretroviral drugs (9%) and non-steroidal anti-inflammatory drugs (6%) [7].

II. MATERIALS AND METHODS

This study was carried out in the Department of Medicine in a tertiary care hospital of Assam, for a period of one year from 1st June 2019 to 31st May 2020. This study was approved by the Institutional Ethics Committee of Gauhati Medical College and Hospital, Guwahati. The procedures followed were in accordance with the responsible committee's ethical standards based on the Good Clinical Practice guidelines.

Objectives:1) To evaluate the clinical profile of the patients with Acute Viral Hepatitis attending the outpatient clinic and in-patient at Gauhati Medical College and Hospital.

2) To study the complications ofAcute Viral Hepatitis in thisgroup of patients.

3) To study the clinical profile of patients of Acute Viral Hepatitis taking "Complementary and alternative medicine."

Study Population: The study population included the patients who were serologically detected with acute viral hepatitis and a history of intake of Complementary and alternative medicine attending the OPD or were admitted in department of medicine of a tertiary care hospital in Assam, India.

Sample Size: 130 patients.

Inclusion criteria:

1) All patients with clinical and biochemical profile suggestive of acute hepatitis with at least one positive serological viral marker.

2)Patients with positive history of intake of complementary and alternative medicine including herbal medications.

3)Age of more than 12 years.

4)Patients willing to take part in the study.

Exclusion Criteria:

1) Intake of any Hepatotoxic allopathic medication (Drug induced Hepatitis)

2) Cholestatic jaundice of pregnancy.

3) Congestive Hepatopathy.

4) Cirrhosis of liver.

5) Past history of jaundice.

Procedure and Methodology:

Each patient underwent a complete clinical examination as well as a detailed history detailing their current symptoms and any potential risk factors for viral hepatitis. Complete blood count, liver function test, PT with INR, serum ammonia, serum amylase, serum lipase, and rapid malaria test were done. To rule out an extrahepatic source of cholestasis, ultrasonography of the entire abdomen was performed. The diagnosis was confirmed using serological viral markers. The presence of "Anti Hepatitis A virus IgM (IgM Anti HAV) by Enzyme linked immunosorbent assay (HAVAB M, Abbott Laboratories Chicago IL)" was used to confirm a diagnosis of hepatitis A.Acute hepatitis B was diagnosed by the presence of antibody against Hepatitis B core antigen (Anti HBclgM) by Enzyme immune assay and a positive Hepatitis B surface Antigen (HBsAg) by immune assay. Hepatitis E was diagnosed by the presence of Anti Hepatitis E virus IgM (IgM Anti HAV) by enzyme immunoassay (Abbot Laboration III USA).

III. RESULTS

A total number of 130 cases were included in the study, who presented with features of acute viral hepatitis. A detailed history regarding presenting symptoms and possible risk factors for acquiring viral hepatitis was taken and a thorough clinical and biochemical examination was done.

The three most common clinical manifestations of Acute Viral Hepatitis were anorexia (79.23%), yellowish discoloration of the eyes (77.69%) and nausea (75.38%). Other common symptoms were headache, myalgia, arthralgia, itching, weight loss, and abdominal

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discomfort. Rare presenting complaints included photophobia and bleeding manifestations. (Table 1)

Features	No of Cases	Percentage
Anorexia	103	79.23%
Yellowish discolouration of eyes	101	77.69%
Nausea	98	75.38%
Malaise	95	73.07%
Fever	92	70.76%
Yellowish discolouration of urine	91	70.00%
Headache	80	61.53%
Vomiting	76	58.46%
Myalgia	73	56.15%
Itching	55	42.30%
Clay Coloured Stool	51	39.23%
Weight Loss	46	35.38%
Abdominal Discomfort	42	32.30%
Diarrhoea/Constipation	35	26.92%
Cough/Coryza	21	16.15%
Arthralgia	16	12.3%
Skin Rash	8	6.15%
Photophobia	3	2.30%
Bleeding Manifestations	2	1.53%

TABLE 1: Clinical Presentation in Acute Viral Hepatitis.

It was seen that out of 130 patients with acute viral hepatitis, 44(34%) patients had a history of CAM intake(figure 1).

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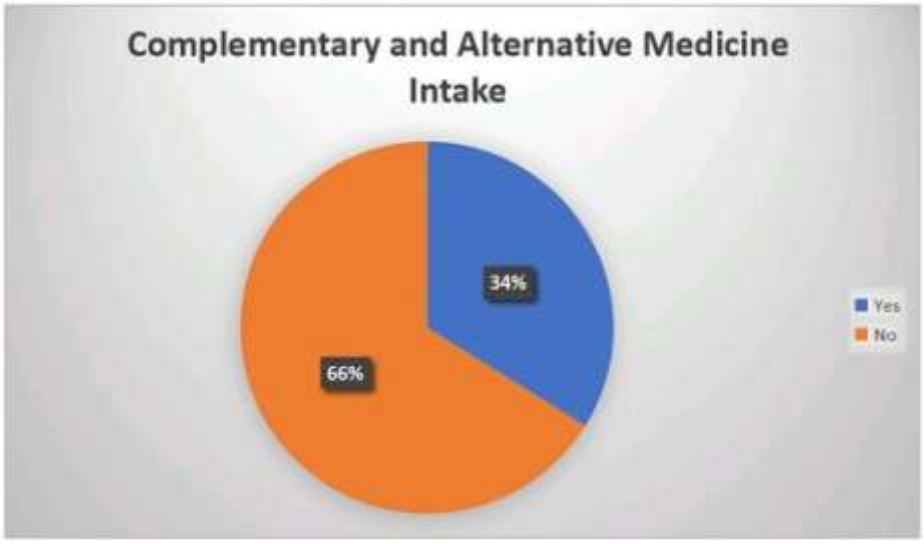

FIGURE 1: Complementary and Alternative Medicine Intake In Acute Viral Hepatitis

In our study majority of the patients of AVH with CAM intake had serum bilirubin >20.1 mg/dl(31.82%)(Figure2).

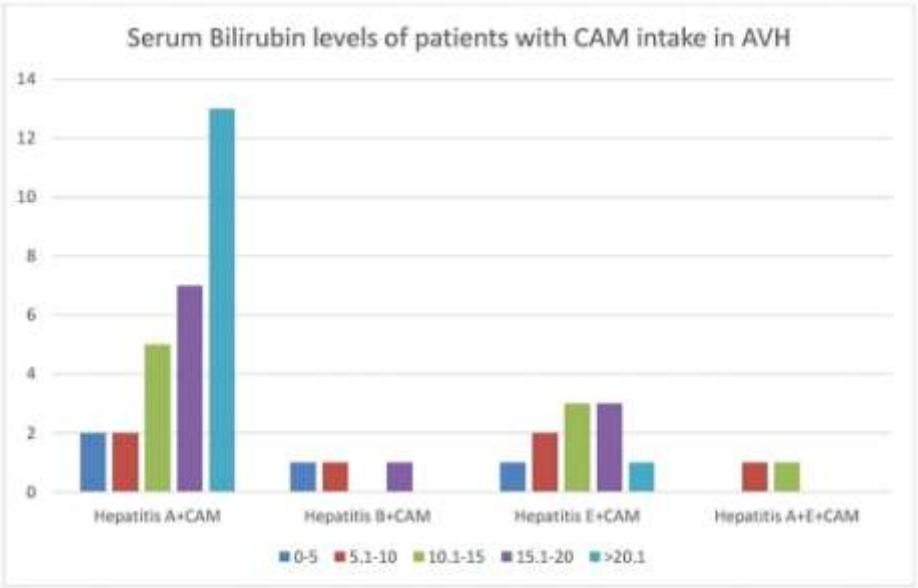

FIGURE 2: Serum Bilirubin level of patients with CAM intake in AVH

Our study shows that in patients with CAM intake in AVH most of the patients 10(22.73%) had ALT level in the range of 1501-2000 IU/L(Table 2).

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ALT in U/L (Range) Normal(21-72U/L)	Hepatitis A+CAM	Hepatitis B+CAM	Hepatitis E+CAM	Hepatitis A+E+CAM	Total No of Cases (%)
1-500	3	0	2	0	5(11.36%)
501-1000	5	2	2	0	9(20.45%)
1001-1500	6	1	1	0	8(18.19%)
1501-2000	8	0	2	0	10(22.73%)
2001-2500	3	0	1	1	5(11.37%)
2501-3000	2	0	0	0	2(4.55%)
3001-3500	0	0	0	1	1(2.27%)
3501-4000	0	0	1	0	1(2.27%)
4001-4500	0	0	1	0	1(2.27%)
4501-5000	1	0	0	0	1(2.27%)
5001-5500	1	0	0	0	1(2.27%)
Total	29	3	10	2	44(100%)

TABLE 2: ALT levels of patients with CAM intake in AVH

Most of the patients with Acute Viral Hepatitis with or without complications recovered fully. The patients who developed acute liver failure had a recovery rate of 33.33%(Table 3).

Categories	Total No of Patients	No of Cholestasis Cases	No of Acute Liver Failure cases	No of Acute Pancreatitis cases
Hepatitis A	61	19(31.14%)	1(1.11%)	2(3.27%)
Hepatitis A+CAM Intake	29	18(62.08%)	2(6.89%)	1(3.44%)
Hepatitis B	5	0(0%)	1(12.50%)	0(0%)
Hepatitis B+CAM Intake	3	1(33.33%)	0(0%)	0(0%)
Hepatitis E	16	4(25%)	0(0%)	0(0%)
Hepatitis E+CAM Intake	10	3(30%)	1(10%)	0(0%)
Hepatitis A+E	4	3(75%)	0(0%)	0(0%)

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Hepatitis A+E+CAM Intake	2	1(50%)	1(50%)	0(0%)
Total	130	49	6	3

TABLE 3: CAM intake and complications in Acute Viral Hepatitis

IV. DISCUSSION

In our study, the most common clinical symptoms in patients with Acute Viral Hepatitis were anorexia (79.23%), yellowish discoloration of eyes (77.69%), nausea (75.38%), malaise (73.07%), fever (70.76%), yellowish discoloration of urine (70.0%). A few patients also reported headaches, arthralgia, itching, fever, weight loss, and abdominal discomfort. Whereas skin rash, photophobia, and bleeding diathesis were rarely found. Desai et al in 2020 [8] in their study found that the most common presenting symptom was yellowish discoloration of urine (84.2%) followed by yellowish discoloration of the sclera (81.2%) followed by anorexia (65.7%). In a study done by Shah et al in 2014 [9] the most common symptoms observed were jaundice(86.10%) followed by anorexia (76.50%), dark-coloured urine (73%), fever with chills (66.1%), and abdominalpain (36.3%).

In our study, it was found that 33.8% of patients had an intake of Complementary and Alternative Medicine for the treatment of Acute Viral Hepatitis which is found to be similar to a study by Leah M Ferrucci et al in 2010 [10] who found that (27.3%) of the patients used CAM therapies for their chronic liver disease. Patients in our study used CAM in the form of leaves of Phyllantusniruri, aloe vera extract, and guava leaves which were found to be similar with regard to CAM intake formulation in the study of herbal medication-induced liver injury done by Philips et al in 2019 [11].

In our study out of 130 patients, 49 patients (37.69%) with Acute Viral Hepatitis had features of cholestasis.

Similar results were obtained by Khuroo et al in 1994 [12] (25% incidence of cholestatic hepatitis in Hepatitis E) and Perez et al in 1992 [13] (20% incidence of cholestatic hepatitis among Acute viral hepatitis). In our study, we found that out of 130 patients who presented with AVH 3(2.30%) patients had Pancreatitis, and all of them recovered. All the 3 cases were associated with HAV infection. Jain et al in 2007 [14] in their study of 124 patients with acute viral hepatitis found that 7(5.65%) patients had pancreatitis which recovered with conservative management. S.K Sarin et al in 1999 [15] in their study reported six cases of nonfulminant viral hepatitis complicated by acute pancreatitis, including the first documented case of hepatitis E virus (HEV) associated acute pancreatitis.

Maximum patients had Serum Bilirubin levels >20.1 mg/dl in 31.82 % of cases. In a study by Philips et al in 2019 [6] he found Mean+SD serum bilirubin in the range of 11.2 ± 6.7 mg/dl in patients with CAM-induced liver injury.

Our study showed a maximum number of patients 10(22.73%) with a history of CAM intake in patients ofAVH had an ALT level in the range of 1501-2000 IU/L. In a case report by Hyo Jin Kim et al in 2015 [16] on a 55-year-old who had an intake of herbal extract, the patient's liver function test results showed significantly elevated aspartate aminotransferase (AST) (958 IU/L) and alanine aminotransferase (ALT) (1000 IU/L) levels.

In our study out of 44 cases of AVH 34(79%) had history of intake of CAM who developed features of cholestasis which can be compared to the study done by Philips et al in 2019 [11] who showed that (67%) of the patients who took CAM in the form of Ayurvedic formulations developed cholestasis. Out of 44 patients who took CAM, 4(9.09%) patients developed acute liver failure. Acharya et al 1996 [17] in a study conducted in India, comprising 430 patients with acute liver failure, demonstrated that 4.5% (19/430) of the cases were related to drugs. Estes et al 2003 [18] showed in a series of 20 patients with acute liver failure referred to liver transplantation, (35%) of cases had no identified cause other than herbal supplement use.

V. CONCLUSIONS

Complementary and alternative medicine intake is a popular method of treatment for jaundice as seen in our study and is mostly used in the form of herbal medications. Our study shows that Complementary and alternative medicine use in acute viral hepatitis present with an increased incidence of cholestasis as well as a precipitating factor for acute liver failure consistent with increased serum bilirubin levels and serum ALT levels.

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