Original Article

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Internal Medicine Section

Aetiology and Clinical Profile of Infectious Causes of Febrile Jaundice at a Tertiary Care Hospital in Eastern Odisha- An Observational Prospective Study

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ABSTRACT

Introduction: Fever with jaundice is one of the most common presentations seen in both outdoor and indoor patients. This manifestation is seen in many individuals infected with hepatotropic viruses (A to E), bacteria, protozoa, fungi, and non hepatotropic viruses. In viral hepatitis due to hepatotropic viruses the patient presents with a short febrile prodrome followed by jaundice, and is often self-limiting without any treatment whereas in patients other than viral hepatitis the patients present with ongoing fever and jaundice and need specific treatment.

Aim: To evaluate clinical profile of patients presenting with febrile jaundice and finding the infections agent responsible for fever with jaundice baring viral hepatitis (A to E).

Materials and Methods: This observational prospective study included 107 patients admitted in the Kalinga Institute of Medical Sciences, from September 2019 to August 2021, who were found to have febrile jaundice after initial evaluation, based on liver function tests and hepatotropic viral markers {hepatitis B surface antigen (HBsAg), Immunoglobulin M antibody against hepatitis C virus (Anti-HCV IgM), Immunoglobulin M antibody against hepatitis A virus (Anti-HAV IgM), Immunoglobulin M antibody against hepatitis E virus (Anti-HEV IgM)}. Routine laboratory parameters, chest radiograph, and electrocardiogram were performed in all cases. Appropriate investigations like specific serological, radiological investigations and cultures were performed to identify the causal pathogen. Statistical analysis of categorical variables was conducted by Statistical Package for Social Sciences (SPSS) 26.0 version.

Results: Out of 107 patients, 25 (23.3%) patients were found to have scrub typhus. Dengue was found in 23 (21.4%) patients (three had dengue associated with scrub typhus). Coronavirus Disease 2019 (COVID-19) was found in 11 patients (10.2%) of study population. Malaria, tuberculosis, *S. typhi*, *K. pneumonia*, *E. coli*, *B. cepacia*, *E. feacalis* were isolated in other individuals. Among these, 41.12% patients had associated transaminitis, whereas, 16 had elevated aspartate transaminase/alanine transaminase (>3 times of ULN). Overall, 18.4% patients had hepatomegaly, and 6.5% were found to have splenomegaly. Eight patients had septic shock, and associated Multiple Organ Dysfunction Syndrome (MODS) was seen in six patients. No definitive aetiology was found in 25 patients.

Conclusion: The study identified a variety of organisms in sera from the patients presenting with febrile jaundice. The most common clinical feature was anorexia followed by headache. The common aetiology for febrile jaundice was viral infections {barring viral hepatitis (A to E)} followed by bacterial Infections.

Keywords: Coronavirus disease 2019, Dengue, Multiple organ dysfunction syndrome, Scrub typhus, Septic shock

INTRODUCTION

Febrile jaundice is a common entity seen in routine practice. Infectious and non infectious conditions are responsible for this. In most cases, patients come with a brief febrile sickness and jaundice. Patients may be fully ignorant that they have a condition known as jaundice, which is observed by family members and physicians. Patients with fever and jaundice or with abnormal liver functions should be subjected to a thorough history, physical examination, and detailed investigations before any treatment is given. This is done to rule out any additional symptoms, such as pain or other systemic manifestations, which might often point to a different diagnosis. If a patient has a persistent fever and jaundice, it is important to screen out various possibilities responsible for this presentation.

Infectious causes can be parasitic (malaria, toxoplasmosis, schistosomiasis) bacterial (typhoid, typhus, borreliosis, leptospirosis), and viral infections (hepatitis, dengue, covid, lassa, ebola, mums, measles, rubella) [1]. Non infectious aetiology mostly includes malignancies, drugs, and connective tissue diseases. Febrile jaundice could be caused by the release of pyrogenic material and haemoglobin into the circulation as a result of haemolysis or cholestasis, along with obstruction in biliary secretion [2-5]. Bilirubin metabolism is divided into three phases: prehepatic, intrahepatic, and posthepatic. Jaundice can occur if any of these phases are disrupted [6].

Studies have found that viral hepatitis (A to E) is the most common infection causing febrile jaundice [7-9]. But the present study was undertaken with the objective to exclusively evaluate infections causing febrile jaundice, barring viral hepatitis, in hospitalised patients and to analyse their clinical features. Identifying the aetiological organism needs a comprehensive and planned analysis by taking aid of clinical features and needed investigations which helps in reducing the financial burden to patient. These cases need specified armamentarium, such as, Reverse Transcription-Polymerase Chain Reaction (RT-PCR) analysis for evaluating viral organisms and various serological markers specific to the infectious agent, which are scarce in primary and secondary centres. Besides this many patients infected with viruses may get recovered and discharged within a week or few more days before the aetiology is identified. The study also aims to help clinicians in better assessment of such patients, and help in epidemiologic surveillance.

MATERIALS AND METHODS

An observational prospective study was carried out in the Department of General Medicine at Kalinga Institute of Medical Science, Bhubaneswar, Odisha during September 2019 to August 2021. The ethical approval was obtained from Institutional Ethical Committee (KIMS/IEC/121/2019) before sample collection. The desired minimum sample size of 101 was calculated based on the prevalence (2.76 per 1000 population) and at 95% CI [10].

Inclusion criteria: A total of 107 hospital-admitted patients of age more than 18 years with fever and clinical jaundice or serum bilirubin greater than 1.5 mg/dL with or without Aspartate Transaminase (AST) and Alanine Transaminase (ALT) elevation were included in the study.

Exclusion criteria: Patients with only viral hepatitis (Ato E) and non infectious causes of febrile jaundice were excluded from the study.

Study Procedure

Demographic profile: Demographic features like age, sex, onset and duration of fever of all 107 patients were recorded.

Clinical parameters: Clinical signs and symptoms like fever, icterus, rashes, headache, myalgia, shortness of breath, pain abdomen, seizures, vomiting, altered bowel habits, altered mental status and focal neurological deficit were noted with a history of present and past illness like diabetes, hypertension, tuberculosis, immunodeficient states, family history, drug and food allergies and any prior antibiotic treatment.

Sample collection and pathogen identification for febrile jaundice: Serum samples were collected for clinical investigations such as complete blood count, peripheral blood smear, urine routine examination and microscopy, Typhidot-IgM, malarial parasite immunochromatographic test, Scrub typhus- IgM, Dengue-NS1 antigen and IgM, Leptospira- Microscopic Agglutination Test (MAT), blood culture, specific viral markers. Appropriate laboratory technique was used to identify each pathogen. Chest X-ray (posteroanterior view), ultrasound imaging of liver and spleen, bone marrow examination in suspected haemophagocytic lymphohistiocytosis cases were obtained in all the cases. Fundoscopy was done in needed cases who presented with headache, altered sensorium and signs of meningeal irritation and the findings were noted. Lumbar puncture was done only after excluding the contraindications in needed cases. Tests of liver function, Hepatitis B surface Antigen (HBsAg), IgM anti-HCV, IgM Anti-HAV, Anti-HEV IgM were done to rule out viral hepatitis, and to determine the serum bilirubin levels of patients. Evidence of infection, aetiology, clinical features, and outcome of febrile jaundice were analysed in 107 patients.

STATISTICAL ANALYSIS

Statistical analysis of categorical variables was conducted by Statistical Package for Social Sciences (SPSS) 26.0 version. All the data are presented in the form of mean, standard deviation and percentage. One sample T-test was implemented to calculate the p-value. A p-value <0.05 was obtained which is considered to be statistically significant.

RESULTS

All the admitted patients were in the range of 18-87 years with mean age of 47.03±17.38 years. Maximum patients 38 (35.5%) belonged to the age group of 41-60 years [Table/Fig-1], overall, 82.3% were males. Pain abdomen was the most common symptom which was seen in 21.4% of the study population. Associated myalgia was seen in 23.3%, whereas Icterus was seen in 12.1% [Table/Fig-2]. Overall, 18.4% of the population presented with hepatomegaly, 6.5% presented with splenomegaly, and hepatosplenomegaly was seen in 3.7% and encephalopathy was seen in 5.6% patients. Other than hepatitis A to E, infectious agents like viral, bacterial, fungal organisms, parasites were identified in the study population. Predominance pathogens identified were scrub typhus 25 (23.3%), dengue 23 (21.4%), Coronavirus Disease 2019 (COVID-19) 11 (10.2%). Other organisms such as malaria, tuberculosis, Salmonella, *E. coli* and Varicella were also detected [Table/Fig-3].

Variables	n, %
Age (years)	
18-20	5 (4.7%)
21-40	28 (28%)
41-60	38 (35.5%)
≥61	36 (33.6%)
Mean±SD	47.03±17.383
Range	18-87
Gender	
Male	84 (82.3%)
Female	23 (17.7%)

[Table/Fig-1]: Demographic features of patients.

Symptoms	Number	Signs	Number
Fever	107 (100%)	Icterus	13 (12.14%)
Anorexia	45 (42.05%)	Hepatomegaly	20 (18.4%)
Pain abdomen	23 (21.49%)	Splenomegaly	7 (6.54%)
Headache	38 (35.51%)	Hepatosplenomegaly	4 (3.7%)
Myalgia	25 (23.36%)	Altered sensorium	6 (5.607%)
Rashes	9 (8.41%)		
Breathing difficulty	7 (6.54%)		

[Table/Fig-2]: Clinical features of the population.

Aetiology	n (%)
Viral infections (n=42)	
Dengue	23 (21.4%)
SARS-CoV-2	11 (10.2%)
Varicella	3 (2.8%)
HIV with *Streptococcus mitis*	1 (0.9%)
Hepatitis A with others	2 (1.8%)
Hepatitis E with others	1 (0.9%)
Hepatitis B with others	1 (0.9%)
Bacterial infections (n=41)	
Scrub typhus	25 (23.3%)
Tuberculosis	4 (3.7%)
Salmonella	3 (2.8%)
E. coli	3 (2.8%)
Klebsiella	2 (1.8%)
Leptospira	1 (0.9%)
Enterobacterace clocae	1 (0.9%)
Enterobacterace faecium	1 (0.9%)
Streptococcus mitis	1 (0.9%)
Others (n=32)	
Malaria	6 (5.6%)
Candida	1 (0.9%)
Unknown	25 (23.3%)

[Table/Fig-3]: Various aetiologies responsible for febrile jaundice.

Among the study sample, the majority of the patients had a viral aetiology (n=42), followed by bacterial aetiology (n=41). Among the viral aetiology, dengue was the most common viral organism responsible for febrile jaundice. There were few patients infected with hepatotropic viruses, while few had associated infections which include malaria and scrub typhus. Similarly, few patients infected with scrub typhus had co-infection with malaria and dengue [Table/Fig-3].

Thrombocytopaenia was one of the major findings with majority of the cases infected with viruses. It was observed in 29 patients. Mean serum bilirubin value was 4.44±5.77 mg/dL. Associated transaminitis (AST or ALT elevation) was seen in 44 (41.12%), and among these 44, 16 patients had elevated level above three times the upper limit of normal value. The mean Aspartate Aminotransferase (AST) was 342.28±863.5, with the highest value 7550 and the lowest of 26. The mean Alanine Transaminase (ALT) was 237.7±552.812 with the highest 4258 and the lowest 19 [Table/Fig-4]. Deranged Prothrombin Time and International Normalised Ratio (PT INR) and hypoalbuminaemia was found in four and three patients, respectively, among the study population. Total four patients died- three with COVID-19, and one succumbed to dengue.

Laboratory parameters	Reference range	Mean value	Highest value observed	Lowest value observed
Serum bilirubin (mg/dL)	0.2-1.2	4.44±5.77	37.09	1.76
AST (U/L)	0-40	342.28±863.500	7550	26
ALT (U/L)	5-40	237.7±552.812	4258	19
Platelet count (lakh/mcL)	1.5-5	1.94	5.64	12000
PT INR	0.8-1.1	0.93	1.7	0.7
Serum albumin (g/dL)	3.4-5.5	4.72	6.1	1.8

[Table/Fig-4]: Table describing various investigations performed in patients and the values observed.
AST: Aspartate transaminase; ALT: Alanine transaminase; PT INR: Prothrombin time and international normalised ratio

DISCUSSION

In febrile jaundice, jaundice is the initial symptom followed by fever. Infectious and non infectious conditions such as hepatotoxic drugs are responsible for this presentation. In this study, viral aetiology was the most common cause of febrile jaundice, though hepatotropic viruses were excluded in this study. This was followed by bacteria and parasites. Dengue virus was responsible to cause febrile jaundice due to hepatopathy in (20.2%) of the cases. Similar studies found that dengue is responsible for transaminitis and elevated bilirubin due to inflammatory process in the liver parenchyma [11-13].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was also responsible for the presentation of febrile jaundice in 10%. Majority of this group initially presented with fever followed by jaundice. Studies found that COVID-19 infection is associated with hepatopathy, leading to elevated bilirubin and transaminases. The virus binds to the target hepatocytes through Angiotensin-Converting Enzyme 2 (ACE2). Because ACE2 is expressed abundantly in the liver hepatocytes and in biliary epithelial cells, the liver is a potential target for direct infection. Hypoxic hepatitis as a result of anoxia seen in severe SARS-CoV-2 infected individuals augments hepatopathy [14-15]. Previous studies are tabulated [Table/Fig-5] [7,11-13,15-17].

Author name	Place of study	Mean age/gender distribution/ sample size	Most common signs/symptoms (top 3)	Most common aetiology- Bacterial/viral/ others
Vasanthan K et al., [7]	Chennai, India	Male: 70 Female: 16	Most common sign: Hepatomegaly	Malaria
Yudhishdran J et al., [11]	South Asia	Mean age: 38 years Gender: Female Total sample size: 2	Most common symptom: Myalgia	Dengue virus
Lee LK et al., [12]	Singapore	Male: 493 Female: 197		Dengue virus
Samanta J et al., [13]		Pooled analysis	Most common symptom: Pain abdomen	Dengue virus
Paliogiannis P and Zinellu A, [15]			Most common symptom: Shortness of breath	COVID-19
Mokta J et al., [16]	Southeast Asia	Mean age: 38.76±12.89 Gender: Female: 110 Male: 60	Most common symptom: Headache Most common sign: Tachypnea	Scrub typhus
Zhang Y et al., [17]	Sierra Leone	Sample size: 96	Most common symptom: Loss of appetite Most common sign: Hepatomegaly	Cytomegalovirus

[Table/Fig-5]: Various studies related to febrile jaundice and their findings [7,11, 12,13,15-17].

Bacterial infection also caused febrile jaundice in the present study population. In majority of the patients, the causal bacterial organism responsible for infection was scrub typhus. The mechanism of hepatic impairment caused by scrub typhus is unknown so far. It might be direct invasion of *Orientia tsutsugamushi* and that cellular immunity may be attributed to pathogenesis of hepatic injury [16]. Biochemical analysis shows elevation in transaminases apart from elevated bilirubin. Associated thrombocytopaenia was seen in majority of patients infected with dengue and scrub typhus. This is similar to the findings of Souza L et al., [18]. In the present study, mortality rate was high in COVID-19 infection with sepsis and MODS, followed by dengue infection. Jäger B et al., also found that hypoxic hepatopathy in COVID-19 which leads to jaundice and other complications and even mortality [19].

Limitation(s)

As it was hospital-based, the incidence of febrile jaundice might have been under-estimated. Patients with both jaundice and raised transaminases were included, however, raised bilirubin and transaminases can reflect pathology in other organs, potentially confounding the results. Anti-HAV IgM, conventionally considered the gold standard for the diagnosis of acute HAV, and it persists for 3 months to 5 years. Though patients with viral hepatitis A were excluded in this study, an important diagnostic problem for identification of Hepatitis A is that, HAV IgM can result from non specific polyclonal activation of memory cells and positive results not reflecting acute HAV infection may be more common than previously appreciated. It can be challenging to explain and interpret apparent mixed infections, having clinically similar symptoms particularly when the basis for interpretation of these infections is made according to serology. The apparent mixed infections with hepatitis A may lead to false positive reports of acute hepatitis A given the challenges in diagnosing this condition. Some patients who are infected with both leptospirosis and typhus and some being infected with dengue and typhus as well, having antibody persistence are examples of serial infections which are mostly seen in tropics and endemic regions confined to those infections. These type of mixed infections could be genuine mixed infections though some may represent false positivity. To elucidate the relative prevalence of these theories in the tropics, more investigation is needed utilising culture reports, genetic assays and antigen tests [8]. Also, paediatric population was not included in this study which may have a modest impact on the results.

CONCLUSION(S)

The incidence of possible bacterial, viral, and other infections and complications caused by the pathogens causing febrile jaundice is shown in this study. This study also outlines the endemic infections responsible for febrile jaundice, providing a baseline for physicians for better evaluation and management as well as assisting in epidemiological surveillance. Early evaluation and identification of the causative organism, as well as treatment, has a significant impact in the ultimate outcome and aids in the prevention of complications, as well as the reduction of mortality and morbidity.

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