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Investigating Hepatitis B Immunity In Children with with newly diagnosed Acute Lymphoblastic Leukemia presenting at a Tertiary Cancer Care Centre

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Abstract: Hepatitis B is a dreaded infectious disease and one of the major global public health problems .In India, the prevalence of hepatitis B surface antigen (HBsAg) among the general population ranges from 2% to 8%, placing India in an intermediate HBV endemicity zone. Waning of vaccine induced immunity leaves people at risk of acquiring hepatitis B infection in settings where the prevalence of infection is high .Vaccine-induced seroprotection (AntiHBs) is another useful surrogate of vaccine efficacy.Our purpose in this study was to assess the immunity to Hepatitis B virus in children presenting with newly diagnosed Acute Lymphoblastic Leukemia to the Paediatric Oncology Division of Regional Cancer Centre ,Thiruvanathapuram. Data regarding primary immunization were collected from immunization card. AntiHBsAg titers were estimated in each child at the time of presentation. Patients were classified as immune (antibody levels to hepatitis B surface antigen (anti¬HBs) >100mIU/ml), low immune (anti¬HBs10-100mIU/ml) and not immune (anti¬HBs <10 mIU/ml). Of the 109 children included (median age 5.6 years), 75(68.8%) children had protective antiHBs titres (>10IU/L),34 (31.2%) children had no immunity to hepatitis B despite presumed vaccination as part of the UIP schedule. Of the 75 children with protective antiHBs titres 37 children (49.33%) had low immune antiHBstitres(10-100mIU/ml) and 38 children (50.66%) had immune antiHBstitres > 100 mIu/ml.None of the children had active hepatitis B infection (hepatitis B surface antigen ¬positive)at presentation. A significant number of children lack protective anti HBs titres despite being vaccinated according to Universal Immunization Programme and are at risk of hepatitis B infection. Active surveillance and continued screening for HBV must be done at first presentation for all children and may be continued during treatment if clinically indicated. The use of combined passive-active immunisation should be encouraged, especially in children with haematological malignancies.

Keywords: Hepatitis B, Primary Immunization, Hepatitis B surface antigen, Antibody to hepatitis B, Acute Lymphoblastic Leukemia, Hepatitis B vaccine, Hepatitis B immunoglobulin.

INTRODUCTION

Hepatitis B virus infection (HBV) is a global public health problem. Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350– 400 million people are chronic HBV surface antigen (HBsAg) carriers. The WHO has categorized countries based upon the prevalence of HBsAg into high (more than 8%), intermediate (2 to 8%) and low (less than 2%) endemicity countries. India is an intermediate endemicity country for HBV infection with nearly 3–4% of the population infected by the virus [1].

Hepatitis B viral infection can be a serious problem in patients on anti-cancer treatment for several reasons. Transfusion related, procedure related, and chemotherapy-induced immunosuppression may lead to reactivation and fulminant infection. Reactivation can occur in patients despite previously established HBV immunity [2]. In patients with leukemia, factors like use of steroids and intensive chemotherapy regimens pre-dispose them to HBV reactivation [3]. The HBV reactivation rate in hematological malignancies has been reported to range from 19% to 43% with conventional chemotherapy [4].

Hep B vaccination program was initially launched in 14 metropolitan cities of India in June 2002 and then additional 33 rural districts were included for vaccination in October 2003[5]. In 2011, HepB vaccine became the 7th antigen to be introduced in the Universal Immunization Programme (UIP) across the country. The national policy in India recommends that children receive 3 doses of Hep B vaccine, administered

concurrently with diphtheria, pertussis and tetanus (DPT) and trivalent oral polio vaccine at 6, 10 and 14 weeks. In addition, a birth dose is recommended for all new-borns (within 24 hour of delivery) for all institutional deliveries. According to the World Health Organization (WHO), 86% of babies in India received all three doses of Hepatitis b vaccine.

Objective

To assess immunity to Hepatitis B virus in children presenting with newly diagnosed Acute Lymphoblastic Leukemia to the Paediatric Oncology Division, Regional Cancer Centre, Thiruvanathapuram. A secondary objective was to identify patients at risk of contracting hepatitis B infection through horizontal transmission.

METHODS

Children (less than 14 year's age) with newly diagnosed Acute Lymphoblastic Leukemia who were treated in the Paediatric Oncology Division Regional Cancer Centre, Thiruvanathapuram between January 2016 to August 2016 were evaluated. Data regarding primary immunization were collected from immunization card. Demographic data (age and gender) of each patient was documented at presentation. Serological screening for hepatitis B, C and HIV is routinely done for all new patients at presentation to the unit. Screening for HBV includes serological testing for HBs Ag and anti-HBs antibodies to hepatitis B. Anti HBs Ag titers were done at presentation using Enzyme Linked Fluoroscent Assay method using VIDAS (Bio-Merieux).Anti-HBs levels of >100 mIU/ml were defined as complete protection against hepatitis B infection, levels of 10 - 100 mIU/ml as partial protection and levels of <10 mIU/ml as no protection. Antibody levels of >100 mIU/ml are recommended for ensuring protection against hepatitis B infection in immune-compromised patients[9-12].Data were analysed with SSPS version 21.

RESULTS

A total of 109 children who presented to our unit between 1 January 2016 and 31 August were included. The median age of the study group was 5.5 years (range 11months - 13 years). There were 60 boys and 49 girls in the study group. (M:F=1.2:1).89(82%) children had B cell immunophenotype, 18 (16%) had T cell immunophenotype and 2 children had Mixed phenotype acute Leukemia. Of the 109 children enrolled in the study, 77.6%(n=85) had taken the complete primary immunization schedule for Hepatitis B (Birth dose followed by three doses at 6,10,14 weeks respectively).18.4%(n=20) had not completed the full schedule and 4%(n=4) were not aware of their immunization status .(Figure 1).Active hepatitis B infection (HBsAg) was not detected in any of the patients during screening at the time of presentation to the unit. 75(68.8%) children had protective antiHBs titres (>10IU/L), 34 (31.2%) children had no immunity to hepatitis B despite presumed vaccination as part of the UIP schedule. Of the 75 children with protective antiHBs titres 37 children (49.33%) had low immune antiHBstitres(10-100mIU/ml) and 38 children (50.66%) had immune antiHBstitres > 100 mIu/ml. (Figure 2).

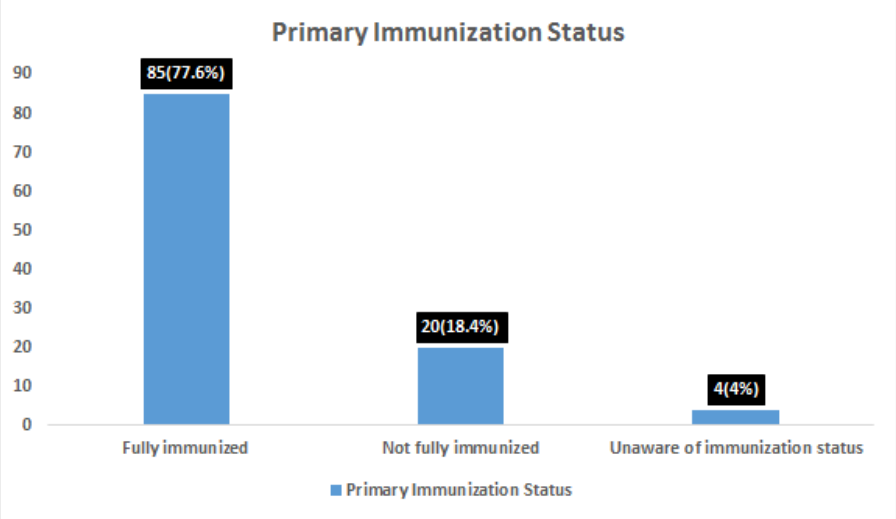

Fig-1: Primary Immunization Status of children

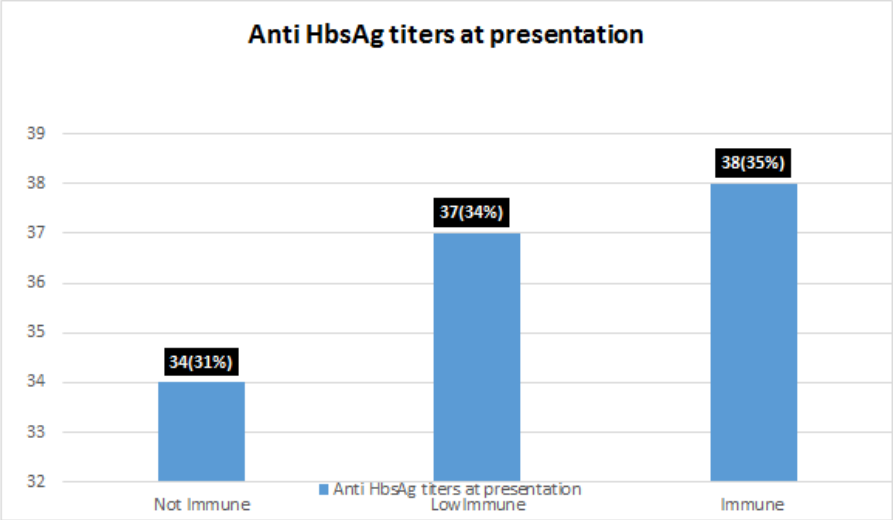

Fig-2: AntiHbsAg titers at presentation of children in the study group

DISCUSSION

Acute Lymphoblastic Leukemia (ALL) is the most common malignant disease in children. The more intensive treatment and risk stratification adopted over the last decade have resulted in an improvement in the survival rate, which, in many cases, reaches 90%.Both the illness and treatment affect the immune system. Immune competence decreases not only due to chemotherapy-induced neutropenia, but also due to the loss of protective serum antibody titers gained from previous immunizations. Children are at a high risk for developing hepatitis B virus (HBV) infection from immunosuppression secondary to chemotherapy and multiple blood transfusions. Most of the children infected with HBV develop chronic hepatitis. The increasing potential for the cure of childhood Acute Lymphoblastic leukemia emphasizes the need for a method of reducing hepatitis B and its sequelae in these children.

None of the patients in this study had active hepatitis B infection at initial screening which reflects the protective effect of the immunization received as part of the Universal Immunization Programme. In a recent evaluation of the hepatitis B universal infant immunization program in Gambia, 94% vaccine effectiveness was observed in fully vaccinated infants. The study concluded that complete infant HBV vaccination protects strongly against chronic HBV infection but less strongly against ever having HBV infection [6]. Waning of vaccine induced immunity leaves people at risk of acquiring hepatitis B infection in settings where the prevalence of infection is high. According to Jacob Puliyel *et al*. an Indian study, at 6 years of age, protective levels of anti-HBs antibody (>10 mlU/mL) were present only in about 59% of those immunized. By 11 years, only 13% had protective levels. Our study with a median age of 5.5 years among Acute lymphoblastic Leukemia children, had 68.8% children with protective anti HBs titres (>10IU/L) at presentation, similar to studies described among immunocompetent children[7].

Latest ASCO guidelines recommends screening of all leukemia patients for HBs Ag, anti-HBc, and anti-HBs antibodies prior to treatment initiation [8].A feasible option in India for better management of paediatric patients with ALL would be to screen the patients for occult HBV infection prior to institution of therapy and appropriately cover with anti-viral drugs and/or immunization. In our study initial screening was done only with HBs Ag, and anti-HBs antibodies which was a limitation of this study.

The effectiveness of the HBV vaccine is assessed by measuring antibody levels to HBsAg (anti-HBs) levels in the serum. Nearly 50 % of children in this study had sub-optimal anti-HBs titres of <100 mIU/ml. Anti-Hbs >10 mIU/l were defined as protective in healthy, immune-competent children, there is no consensus about what level of antibodies against HBV is protective in immune-compromised patients [9-12]. The defects in immunological functioning caused by intensive chemotherapy may adversely affect the immune memory so that it may not be protective in childhood cancer patients[13].

Routine vaccination under national schedule plays an important role in decreasing subsequent infection in children with ALL. Active immunisation against HBV has been shown to be effective in patients with cancer[14]. For seronegative children who develop malignancies, an accelerated, double dose (40 mcg) schedule of vaccination has been shown to induce protective antibody titres. Combined passive-active immunisation offered better protection against nosocomial HBV infection than active immunisation alone [15,16]. The cost implication of offering solely passive prophylaxis during intensive chemotherapy of patients with leukaemia led to discontinuation of this

protocol and a recommendation for simultaneous passive and active immunoprophylaxis from the start of such therapy. Usage of passive immunization (hepatitis B immunoglobulin) during the intensive phase of chemotherapy, followed by active immunization during the maintenance phase has also been shown to induce protective antibody titers in nearly 88% of patients[17].

CONCLUSION

A significant number of children with newly diagnosed ALL lack protective anti HBs titres despite being vaccinated according to Universal Immunization Programme and are at risk of hepatitis B infection. Active surveillance and continued screening for HBV must be done at first presentation for all patients and during treatment if clinically indicated. The use of combined passive-active immunisation should be encouraged, especially in children with haematological malignancies.

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