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RESEARCH ARTICLE

CHANGE IN IMMUNOLOGICAL MEMORY OF HEPATITIS B VACCINE AFTER CHEMOTHERAPY; A REAL PROBLEM IN PEDIATRIC CANCER PATIENTS.

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Abstract

Background:-Children with cancer are at risk of Hepatitis B virus infections as a result of recurrent blood transfusions and also due to suppressed immune system. The national immunization program plays an important role in decreasing hepatitis B infection in children with cancer; however, the efficacy of the immunization strategies is questionable. We aimed at evaluating the acquired immunity from previous hepatitis B vaccination in cancer patients after recovery of their immune system.

Patients and Methods:- Case control study was conducted on 22 patients with cancer(13 males,9 females, mean age 7.2±3.14 years) who completed their standard chemotherapy at least 6 months prior to the study. Twenty two age and sex matched healthy children were enrolled as a control group. HBsAb and HBcAb concentrations were determined in the studied subject's serum by ELISA.

Results:- The frequency of non immune subjects in children with cancer was significantly higher than those in healthy children (P-value=0.001), where anti-HBs antibody titer was more than 10 mIU/ml in 54.5% of patients and less than 10 mIU/ml in 45.5% of patients. While in healthy controls, 90.9% had antibody titer more than10 mIU/ml and 9.1% had antibody titer less than 10mIU/ml. No significant relation was found between loss of immunity against HBV and age of patient, type of cancer and duration of chemotherapy.

Conclusion:-Children with cancer are at increased risk for HBV infection. HBV revaccination should be considered at least six month post chemotherapy.

Introduction:-

Children with cancer are at risk of severe infections especially who have not completed their primary immunizations[1]. Immune competence decreases not only due to chemotherapy-induced neutropenia, but also due to the reduction of serum antibody titers gained from previous immunizations[2].The damage to the immune system varies with the age of the patient, the type of cancer, and the intensity of the chemotherapy used to treat it [3].There is a reduction of vaccine-antigen specific antibody concentration after completion of chemotherapy with or without radiotherapy. The immune system recovers to normal three to six months aftercompletion of chemotherapy [4].Therefore children with cancer after finishing chemotherapy may become susceptible to infectious diseases [5].

Hepatitis B virus (HBV) infection in cancer patients occurs as a result of recurrent blood transfusions and also due to suppressed immune system. There are few studies inrevaccination of children after intensive chemotherapy. Most of them were established based on the data from limited published studies and specific cancers [6].The national

immunization program plays an important role in deceasing subsequent hepatitis B infection in children with cancer [7]. However, the efficacy of the immunization strategies employed is questionable 8]. In this study we evaluate change of acquired immunity in previously vaccinated children with cancer after recovery of their immune system by assessing antibody titer for hepatitis B vaccine.

Subject and methods:-

Case control study was conducted on 22 patients with cancer (13 male and 9 female) with mean age 7.2±3.14 year who were registered in and followed up at pediatric oncology unit of Zagazig university hospital, Zagazig , Egypt during period from January 2014to January 2015. The patients had been treated successfully for hematological malignancy and solid tumors using standard chemotherapy protocols. All the patients were selected at least six months after completion of chemotherapy treatment. In this study also 22 age and sex matched healthy children were enrolled as control. Healthy children didn't show any systemic, immunodeficiency or metabolic diseases according to their histories. According to type of cancer, patients enrolled were as follow: ten patients with Acute Lymphocyte Leukemia, six patients with Non- Hodgkin lymphoma, two patients with Neuroblastoma, one patient with wilm's tumor, one patient with yolk sac tumor and one patient with rabdomyosarcoma. Acute lymphocyte leukemia was classified as hematologic malignancy and the rest of cancers were considered as non hematologic malignancy. Inclusions criteria were Patients who achieved complete remission confirmed by a bone marrow examination at least one month after the end of chemotherapy and complete neutrophil recovery, All patients and healthy children had received HBV vaccination according to World Health Organization(WHO) schedule of vaccination in Egypt which include three doses of hepatitis B vaccine at two, four and six month of age.

The immunization data of all participants was verified on their vaccination cards, a document that is compulsory for all children in Egypt. Informed consent was obtained from all participant or their guardians to collect 3 ml of their peripheral blood samples.

The serum samples were stored in -70 C until being analyzed by using enzyme linked immunosorbent assay (ELISA) anti-HBsAg IgG antibody was measured according to the kit instructions. The antibody concentrations were calculated using standard curves. Titers equal or more than 10 mIU/ml for each patients and healthy children were defined as protective titer and titer less than 10 mIU/ml were considered as non- immune subject to HBV infection [9]. Also anti-HBc IgG antibody was measured using colloidal gold enhanced immunoassay according to kit instructions .Anti-HBc IgG antibodiesdone to distinguish between immunity acquired from previous immunization and immunity acquired from current or resolved HBV infection.

- If the anti-HBc-Total test is negative, the patient has no evidence of current or remote HBV infection.
- If the anti-HBc-Total test is positive, this is compatible with current or resolved HBV infection[10].

Data abstraction form was designed to capture the appropriate information, collected data included:Full history taking focusing on age, sex, residence, full clinical information, transfusion data,history of hepatitis B infection with emphasis on the signs of hepatitis as jaundice, hepatomegaly, pallor, loss of appetite, dark urine .

Statistical Analysis:-

In this case control study Continuous variables were expressed as the mean ± 1 SD (range) and the categorical variables were expressed as a number(percentage). Continuous variables were checked for normality by using Shapiro-Wilk test. Independent samples Student's t-test was used to compare two groups of normally distributed data. Percent of categorical variables were compared using the Pearson's Chi-square test. All tests were two sided. $p< 0.05$ was considered statistically significant. All data were analyzed using Statistical Package for Social Science for windows version 18.0 (SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA).

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 as revised in 2008 and was approved by our local ethics committee.Informed consent was obtained from all individualsparticipating in the study or their guardians.

Results:-

A total of forty four children were included in the study twenty two cases and twenty two controls with a mean age of 7,2±3.14 and 8.11±3.83 respectively, and a range of 2-14 years. They were 13 males and 9 females with no significant difference as regard their residence. (Table 1)According to type of cancer, patients enrolled were classified as follow: ten patients with Acute Lymphocyte Leukemia, six patients with Non- Hodgkin lymphoma, two patients with Neuroblastoma, one patient with wilm's tumor, one patient with yolk sac tumor and one patient with rabdomyosarcoma, Table 1.

The frequency of non immune subjects in children with cancer was significantly higher than those in healthy children (P-value=0.007),where anti-HBs antibody titer was more than 10 mIU/ ml in 54.5% of patients and less than 10 mIU/ ml in 45.5% of patients. While in healthy controls, 90.9% had antibody titer more than10 10 mIU/ ml and 9.1% had antibody titer less than 10 mIU/ ml. Also anti-HBcAb was positive in 4.5% of patients and negative in 95.5% of patients while it was negative in all healthy controls with no significant difference, Table 1.

Table 1:- Demographic and clinical data of studied groups.

Demographic and clinical data	Cases (N=22)			Control (N=22)			p-value
Age (years)							
Mean ± SD	7.20	±	3.14	8.11	±	3.83	0.393*
(Range)	(3	-	14)	(2	-	14)	
Sex							
Male	13 (59.1%)			13 (59.1%)			1.000§
Female	9 (40.9%)			9 (40.9%)			
Residence							
Urban	9 (40.9%)			9 (40.9%)			1.000§
Rural	13 (59.1%)			13 (59.1%)			
Type of cancer							
ALL	10 (45.5%)						
NHL	6 (27.2%)						
Wilma's tumor	2 (9.1%)						
Neuroblastoma	2 (9.1%)						
Yolk sac tumor	1 (4.5%)						
Rhabdomyosarcoma	1 (4.5%)						
HBs Ab							
Negative	10 (45.5%)			2 (9.1%)			0.007§
Positive	12 (54.5%)			20 (90.9%)			
HBcAb							
Negative	21 (94.5%)			22 (100%)			1.000§
Positive	1 (4.5%)			0 (0%)			
Immunity							
Not immune	10 (45.5%)			2 (9.1%)			0.007§
Immune	12 (54.5%)			20 (90.9%)			

N=Total number of patients in each group; Quantitative data were expressed as the mean ± SD; Qualitative data were expressed as a number (percentage); *Independent samples Student's t-test; §Chi-square test; $p < 0.05$ is significant.

No significant relation was found between loss of immunity against HBV and age of patient, type of cancer and duration of chemotherapy, Table 2.

Table 2:- Relation between immune status and demographicdata ,type of cancer and duration of chemotherapy in cases**.**

Demographic and clinical data	Total	Cases (N=22)						
		Non immune (N=10)			Immune (N=12)			p-value
Age (years)								
Mean ± SD		7.40	±	3.72	7.04	±	2.83	0.799*
(Range)		(	-	)	(	-	)	
Type of cancer								
ALL	10	6 (60%)			4 (40%)			0.391§
Other cancers	12	4 (33.3%)			8 (66.7%)			
Duration of chemotherapy								
2 years	9	6 (66.7%)			3 (33.3%)			0.192§
3 years	13	4 (30.8%)			9 (69.2%)			

N=Total number of patients in each group; Quantitative data were expressed as the mean ± SD; Qualitative data were expressed as a number (percentage); *Independent samples Student's t-test; §Chi-square test; $p< 0.05$ is significant.

Discussion:-

Children with cancer are prone to lose the antibody protection previously acquired by vaccination. The reasons for this loss, although not fully understood, seem to be related to the intensity of treatment, individual sensitivity to chemotherapy and time interval required for the recovery of B lymphocytes[11].

Risk for developing chronic hepatitis in children with cancer may be related to multiple blood transfusions and immunosuppression secondary to chemotherapy and radiotherapy[12].

In our study we found that the immunity acquired from hepatitis B vaccine in case group was less than in control one as P value is 0.001 and the loss of protective antibody serum titers was recorded in 45.5% of patients compared with 9.1% of healthy children.

In agreement with our results**,** Zignol et al reported that immunity against hepatitis B virus was most significantly affected by chemotherapy and the loss of protective antibody serum titers was recorded in 52% of patients who were evaluated before and afterchemotherapy[13]**.**

Similarly**,** Shams et al reported that 62.5% of children with positive Anti-HBs titers lost their immunity at a mean age of 15.9±10 and a range from 6-21month after chemotherapy [14].And about 29% of the patients did not have protective antibody level in their serum after finishing chemotherapy [14].

Contrarily, Fioredda et al from Italy reported that protective antibody titers were present in 81%of children with ALL after a median time of 12 months post chemotherapy and he did not recommend further antibody determination and revaccination in those children [15].

Also we agreed with the study of Cheng et al who reported that reduction of protective serum antibody for Hepatitis B virus was affected by immunosuppressive effects of cytotoxic therapy more than diphtheria, tetanus, and pertussis, and also reported that chemotherapy and cytotoxic drugs are toxic for lymphocytes which produce antibody [16]..

In our result we found that 60% of ALL cases lost their protective antibody titre.

This was in agreement with Serap et al who was investigate antibody titers in a heterogeneous group of cancer patients including those with leukemia, lymphoma, and solid tumors and reported that the loss of antibody titers after therapy was determined to be the highest in patients with leukemia 63.6% compared to other types of cancer [17].

In the current study we found that there was no significant relation between the immunity statusacquiredfrom hepatitis B vaccine and the duration of chemotherapybut it may be due to small sample size of our study. In contrast, Serap et al explained that the more time of exposure to chemotherapy the more decreasing in immunity status.Their study was conducted over a relatively large sample size (159 pediatric cancer patients) [17].

Conclusion:-

Children with cancer who received chemotherapy are at increased risk for decreased immunological memory of previously given HB vaccines .So HBV revaccination should be considered at least six month post-intensive chemotherapy. Actually, larger studies still needed to confirm our finding and to detect the possible causes of decreased antibody titer against HB vaccine after receiving chemotherapy.

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