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Measles, Mumps, Varicella Zoster, Diphtheria and Hepatitis B Surface D

Hanaa M Alam El-Din[1]*, Samah Aly Loutfy[1], Hany Abdel-Rahman[2], Nelly H. Ali Eldin[3], Hanan Ali Ahmed Madani[4] and Mohamed Sedky[5]

[1]*Virology and Immunology Unit, Cancer Biology Department*
[2]*Pediatric Oncology Department*
[3]*Biostatistics & Cancer Epidemiology Department, National Cancer Institute*
[4]*Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Egypt*
[5]*Pediatric Department, National Research Center, Egypt*

Abstract

Background and Aim: This is a preliminary study to evaluate the levels of protective antibodies against some of the vaccine preventable diseases, as a part of the nationwide vaccination program, in Acute Lymphocytic Leukemic children (ALL) and in their non cancer controls of matched age and sex.

Methods: Serum antibody levels of measles, mumps, Varicella zoster, diphtheria, and *hepatitis B* surface antigen were evaluated by ELISA technique in 120 children with ALL as well as in 60 children with no malignancy as a control group.

Results: A protective serum antibody level to measles, mumps, Varicella zoster, diphtheria and hepatitis B were detected in 53%, 14%, 38%, 83% and 72%, respectively of leukemic children irrelevant to phase of treatment compared to 53%, 20%, 40%, 75% and 67%, in the controls.

Seropositivity rate of diphtheria was not found to be related to age in both ALL patients and controls. A significant decline in seropositivity rate to antiHBs with age in both leukemic and their controls was observed (p=0.02, 0.015 respectively).

On multivariate analysis, seropositivity of varicella and mumps was positively dependent on age (P<0.001, 0.03, respectively) and seropositivity of *Hepatitis B* virus significantly decreased with age (P=0.005).

Conclusion: High percentages of acute leukemic patients and their controls were unprotected against measles, mumps and Varicella zoster. Immunogenicity of measles and mumps components in MMR should be re-evaluated. Booster dose of HB vaccine should be given to school aged children. Revaccination must be a task in treating leukemic patients at National Cancer Institute in Egypt.

Keywords: Antibody titre; Measles; Mumps; Varicella zoster; Diphtheria; *Hepatitis B*; Leukemia

Introduction

Today, vaccination still represents a key public health tool for reducing infectious morbidity and mortality all over the world [1]. Immuno-suppression state related to malignancy or its treatment is responsible for reduced serum antibodies levels attained from previous vaccination [2]. This immuno-compromised state renders host unprotected and subsequently predisposes to re-emergence of infections especially in younger patients [3,4]. Measles and Varicella zoster carry the risk of lethal encephalitis and pneumonia among the immune-compromised hosts [5] influenced by age and immunization status at time of diagnosis [6].

It has been suggested that leukaemia itself may affect the antibody levels of vaccination antigens in children with Acute Lymphoblastic Leukaemia (ALL) [7,8]. Although intensified therapy has led to increasing leukaemia survival, it was responsible for transient immunodeficiency in the form of hypogammaglobulinemia [9,10] with subsequent loss of protective antibody levels provided by previous immunization [11].

Up to our knowledge there are no published data in Egypt concerning the level of protective antibody in ALL patients to some vaccine preventable diseases. So this study was done to investigate the antibody status against some of the vaccine preventable diseases including measles, mumps, diphtheria, and *Hepatitis B* virus and also Varicella zoster pathogens among a group of leukemic children at National Cancer Institute, Cairo University and comparing them with a non cancer matched control group. Results might raise the question of revaccinating leukemic children and non cancer controls for some of the vaccines preventable diseases in the nationwide vaccination programme.

Patients and Methods

Patients

This study is a cross sectional one conducted on 120 paediatric leukemic patients diagnosed and treated at the Paediatric Oncology Department, National Cancer Institute (NCI), Cairo University between March 2009 and March 2010. Leukemic children included 40

***Corresponding author:** Hanaa M Alam El-Din, Virology and Immunology Unit, Cancer Biology Department, National Cancer Institute, Fom El-Khalig, Cairo 11796, Egypt, Tel: +20122721081; Email: Halam63@hotmail.com

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newly diagnosed patients, 41 patients under chemotherapy and 39 were under follow up.

Sixty subjects who were free of haematological, immunological, or malignant diseases matched for age and sex were included in the study as controls. They were recruited from general paediatric hospital "Abu el Rish" within the same draining region as National Cancer Institute. The Institutional Review board (IRB) of NCI approved the protocol. Informed written consent was obtained from guardians of all children enrolled in the study. Ages of both study groups ranged between 12 months and 16 years old of both sexes treated from Acute Lymphoblastic Leukaemia (ALL).

ALL Patients were subjected to a battery of investigations for diagnostic purposes and specific investigations. They were treated according to the Total Therapy Study XV protocol adopted from St. Jude Children Research Hospital [12].

All patients and controls had been previously vaccinated according to the Egyptian national compulsory vaccination program at ages 2, 4, 6 and 18 months to Diphtheria, and *hepatitis B* virus surface antigen and at age 12 months to measles. Varicella zoster vaccine is not included in the Egyptian vaccination program and it is given on facultative bases. Measles vaccine has been included since 1977, *Hepatitis B* (HB) vaccine has been added to vaccination schema since 1992 using recombinant variant and booster dose for MMR was introduced at 15 month and 6 years since 1991 [13].

Laboratory methods

Five ml venous blood was withdrawn from each subject under study and sera were separated in aliquots and stored at -20˚C till examined.

Antibody levels against measles, mumps, Varicella zoster, diphtheria and *hepatitis B* surface antigen were measured in each subject by ELISA test.

Determination of measles, mumps, Varicella zoster antibodies

Qualitative and semi quantitative determination of IgG-class antibodies to Measles, Mumps and Varicella zoster was performed by DRG ELISA Kit (Marburg, Germany) according to the manufacturer's instructions. Negative, cut-off and positive controls were run in each assay. The antibody level was expressed as DRG Units (DU) according to the following equation:

$$\frac{\text{Patient absorbance value x 10}}{\text{CO (cut off)}} = (\text{DRG Units} = \text{DU})$$

The cut off value of the test was 10 DU. The individual is considered negative if antibody level is < 9DU and positive when antibody titre is >11DU [14].

Determination of diphtheria antibody

Quantitative determination of IgG antibodies against Diphtheria toxoid in serum was performed using RIDASCEEN ELISA assay kit (K3821) (Darmstadt, Germany) according to manufacturer's instructions. Negative, standard, and positive controls were run in each assay. The antibody level was expressed as IU/ml according to the enclosed table of values. The results were interpreted as follows: <0.1 IU/ml indicates individual's basic immunization who need a vaccine; 0.1-0.9 IU/ml indicates individual who need a booster inoculation; 1-1.4 IU/ml needs to be checked up after 5 years; 1.5-2 IU/ml to be checked after 7 years and >2 IU/ml to be checked after 10 years [15].

Determination of antibody against *Hepatitis B* virus surface antigen

Quantitative determination of anti HBs in serum was carried out by DiaSorin ELISA kit (Saluggia, Italy) according to manufacturer's instructions. Negative control, calibrators from 1 to 4 were included in each assay. The antibody level was expressed as IU/ml and was obtained directly from the calibration curve. The results were interpreted as in table 1.

Statistical analysis

SPSS (Chicago, IL, USA) version 12.0 was used for data management. Median and ranges described quantitative data. Chi-square and Fisher exact tested proportion independence. Factors which thought influencing seropositivity (as detected or not detected) included study groups (4 groups as 3 ALL groups and one control), gender and age categories were the predictor variables in multivariate logistic regression analysis. Seropositivity was tested for the 5 vaccine preventable diseases independently. Odds ratio with 95% confidence interval expressed the likelihood of seropositivty adjusted for age, gender and phase of treatment. P value is significant at 0.05 level.

Results

Median ages of leukemic children were 6.5 (1-12) years for newly diagnosed, 7(1-15) years for those under chemotherapy and 8 (3-13) years for cases during follow up. Median age of non malignant control group was 6 (1.9-15) years. Male to female ratio was 1:1.66 and 1:1.2 in ALL patients and control group, respectively.

Anti-HBs concentration after basic immunization	Recommended time for revaccination
below 10 IU/L	Immediately
10-100 IU/L	after 3-6 months
100-1,000 IU/L	after one year
1,000-10,000 IU/L	after 3.5 year
Above 10,000 IU/L	after 7 years

Antibody level of 10 IU/L was the clinically recognized immunity threshold (minimal protective level) according to the recommendations of the CDC Immunization Practices Advisory Committee (MMWR, 40 RR13:1-25, 1991) [16].

Table 1: The level of anti-HBS and recommended time for revaccination.

Variables	New cases N=40	Chemotherapy cases N=41	Follow up cases N=39	Total N=120
Age Years (Median, range)	6.5 (1-12)	7 (1-15)	8 (3-13)	7 (1-15)
Sex				
Male	26	26	23	75
Female	14	15	16	45
M:F ratio	1:1.85	1:1.7	1: 1.4	1:1.66
CBC (Median, range)				
Hb (g/dl)	10.2 (4-14.8)	11.1 (7-14)	12.4 (6.5-14.9)	11.3 (4-14.9)
TLC (x10^9/l)	4.3(0.23-204)	3.8 (2.9-9.2)	7 (2.74-26.7)	5.5 (0.23-204)
ANC (x10^9/l)	1.9(0-16.3)	1.4(0.05-5.9)	2.8(0.80-6.9)	2.4(0-16.3)
Lym (x10^9/l)	1.6(0-8.8)	1.4(1-4.3)	2(0.89-19)	1.7(0-19)
Mono (x10^9/l)	0.5(0-1.4)	0.3(0.04-1.8)	0.7(0.2-1.8)	0.6(0-1.8)
Plt (x10^9/l)	84(8-495)	242(32-3350)	323(42-550)	250(8-3350)

CBC: Complete Blood Count; Hb: Hemoglobin Concentration; TLC: Total leukocytic Count; ANC: Absolute Neutrophilic Count; Lym: Lymphocytes; Mono: Monocyte; Plt: Platelet Count

Table 2: Demographics and Laboratory findings of the pediatric ALL.

Clinical and laboratory findings of leukemic children at different phases of chemotherapy are shown in table 2.

A protective serum antibody level to measles, mumps, Varicella zoster, diphtheria and *hepatitis B* were detected in 53%, 14%, 38%, 83% and 72%, respectively of ALL children irrelevant to phase of treatment compared to 53%, 20%, 40%, 75% and 67%, in the control group with no significant difference in any. Detailed results of antibody positivity in both study groups are shown in table 3.

Further insight in serpositivity rate was done by stratifying children into three age categories: below age of 6 years, between6 and10 years, and those above 10 years.

According to age, minor differences in measles seropositivity rate were found in ALL and control group, yet not significant (Table 4).

For mumps, minor fluctuation in seropositivity by age was found in ALL patients with no significance, though a significant increased from 7% to 38% in control group was found in those aged below 6 years and those between 6-10 years respectively (Table 4).

As regards seropositivity rate to varicella zoster, it was significantly changed with age in both leukemic children (14% in patients aged below 6 years versus 55% in those above 10 years, p=0.001) and control children (18% in those aged below 6 years versus 73% in children above 10 years, p=0.005) (Table 4).

On the contrary, seropositivity rate to anti-HBs was significantly declined with age in both leukemic children (86% in patients aged below 6 years vs 60% in those above 10 years, p=0.02) and control children (85% in those below 6 years vs 36% in children above 10 years, respectively, p= 0.015) (Table 4).

Seropositivity rate of diphtheria was not found to be related to age in both leukemic and control children. Out of 99 (83%) seropositive ALL patients for diphtheria, more than half of them 76% (75/99) had low protective titre of antibody (0.1-0.9 IU/ml). Further analysis of low protective rate of antibody titre with age in ALL patients showed a significant gradual decrease in low antibody titre ranging from 91% (20/22) in patients aged below 6 years, 76% (45/59) in those aged 6-10 years and 56% (10/18) in those aged above 10 years (p=0.03). On the contrary, gradual increase in low protective level of antibody with age was found in control group though not significant (58% (14/24) in children below 6 years, 64% (9/14) in 6-10 years and 100% (7/7) in children above 10 years, p=0.11) (data are not presented in table).

As regards anti-HBs, out of 86 (72%) seropositive ALL patients, and out of 40 (67%) seropositive control children, more than half of them had low protective level of antibody (10-100 IU/L), 55/86 (64%) and 25/40 (63%) for ALL and control group, respectively.

Further analysis concerning low protective level of HBs antibody according to age, showed that among ALL serpositive patients, gradual increase in low protective level of anti HBs (>10-100 IU/L) was observed, ranging from 48% (12/25) in patients aged below 6 years, 69% (34/49) in those aged 6-10 years and 75% (9/12) in those above 10 years, though this difference was not significant (p=0.13). In contrast, among seropositive control children a gradual decrease in low protective titre of anti-HBs was found in children aged below 6 years 72% (16/22), 57% (8/14) in those between 6-10 years and 25% (1/4) in those above 10 years, but yet again this was not statistically significant (p= 0.17) (data are not presented in table).

Results of regression analysis in table 5, confirmed what have been found in univariate analysis in table 4. Whereas like hood of seropositivity increases with age to VZV, like hood of seropositivity for HB vaccine decreases with age regardless of gender, disease or phase of treatment.

Severe neutropenia (ANC <500 cumm) and lymphopenia (Absolute Lymphocytes <1000 cumm) were found in 15% and 20% of leukemic patients, respectively. Lack of protective antibodies against measles, mumps, varicella, diphtheria and *hepatitis B*, was observed in 44%, 89%, 66%, 16% and 11%, in severely neutropenic patients respectively, which was comparable to that in severely lymphopenic patients (42%, 87%, 62%, 13% and 9% respectively) with no statistical difference.

Group Total	Measles N(%)	Mumps N(%)	VZV N(%)	Diphtheria N(%)	AntiHBs N(%)
New cases (n=40) Positive Ab	**23(58)**	**5(13)**	**13(33)**	**34(85)**	**33(83)**
Chemotherapy: (n=41) Positive Ab	**21(51)**	**7(17)**	**16(39)**	**37(90)**	**27(66)**
Follow up (n=39) Positive Ab	**19(49)**	**5(13)**	**16(41)**	**28(72)**	**26(67)**
Total: n=120 Positive Ab	**63(53)**	**17(14)**	**45(38)**	**99(83)**	**86(72)**
controls: n=60 Positive Ab	**32(53)**	**12(20)**	**24(40)**	**45(75)**	**40(67)**

Table 3: Prevalence of antibodies against measles, mumps, Varicella zoster, Diphtheria and hepatitis B surface antigen among all studied groups.

Group	Measles N(%)	Mumps N(%)	VZV N(%)	Diphtheria N(%)	AntiHBs N(%)
ALL: n=120					
<6Y(29)	18(62)	3(10)	4(14)	22(76)	25(86)
>6-10Y(71)	32(45)	13(18)	30(42)	59(83)	49(69)
>10Y(20)	13(65)	1(5)	11(55)	18(90)	12(60)
P value	0.46	0.12	**0.001**	0.17	**0.02**
Controls: n=60					
<6Y(28)	14(50)	2(7)	5(18)	24(86)	22(85)
>6-10Y(21)	13(62)	8(38)	11(52)	14(67)	14(66)
>10Y(11)	5(45)	2(18)	8(73)	7(64)	4(36)
P value	0.618	**0.029**	0.005	0.170	**0.015**

Table 4: Antibody positivity of studied vaccines stratified according to age.

Vaccine Age (years)	B	SE	OR (95%CI)	P value
Measles				
>10 (Ref.)	-	-	-	0.59
<6	-0.07	0.46	0.94(0.38-2.30)	0.89
6-10	-0.355	0.42	0.70(0.31-1.61)	0.40
Mumps				
>10 (Ref.)	-	-	-	**0.03**
<6	-0.25	0.78	0.78(0.17-3.60)	0.751
6-10	1.09	0.67	2.98(0.80-11.1)	0.104
VZV				
>10 (Ref.)	-	-	-	**<0.001**
<6	-2.17	0.53	0.12(0.04-0.33)	**<0.001**
6-10	-0.60	0.43	0.55(0.24-1.28)	0.16
Diphtheria				
>10 (Ref.)	-	-	-	0.93
<6	-0.029	0.58	0.97(0.310-3.05)	0.96
>6-10	-0.163	0.54	0.85(0.29-2.43)	0.76
Hepatitis B				
>10 (Ref.)	-	-	-	**0.005**
<6	1.75	0.54	5.7(1.99-16.48)	**0.001**
6-10	0.737	0.44	2.09(0.89-4.91)	0.09

B = regression coefficient; SE = Standard Error/ likelihood of seropositivity; CI = Confidence Interval

Table 5: Results of multivariate logistic regression analysis for age as predicting the likelihood of seropositivity adjusted for gender and state of the child (normal, new case, under chemotherapy or in maintenance phase).

Discussion

The current study demonstrated that the nationwide vaccination program against measles was not satisfactory as seropositivity rate of measles in our control children was only 62% and 45% in those at school age (6-10years) and in children above 10 years, respectively, compared to that in Thai children which was 76% and 73% in those aged 1-7years and 8-14 years respectively [16]. This figure was also comparable to that found in turkey, where they demonstrated that seropositivity rate of measles was 72% in children aged 4-5years [17]. In Egypt, Darwish et al. [18] reported clinical infections with measles in 51% of vaccinated children below 3 years. Tidjani et al. [19] explained that the high incidence of measles in developing countries stems from 2 major factors: inadequate vaccination coverage and breaks in cold chain during handling of the vaccine. The low seropositivity rate of measles antibody in both our ALL children and control group (53%) compared to other studies [19,20] could be explained by the poor compliances to immunization schedule, or due to vaccine failure [3], presence of neutralizing antibody [3], rapid waning of immunity after vaccination [16], or potency problem with measles component of MMR vaccine used in Egyptian compulsory vaccination program [16]. Such low seroprotective rate of measles antibody and that reported previously in Egypt may raise the necessity of a booster dose to be given during second to third year of life in all Egyptian children.

In the present study, seropositivity rate against mumps, irrespective of age, was 14% in ALL children and 20% in control group was found to be much less than that reported in Western countries where 97% of leukemic patients had antibody against mumps [20] and that reported in Turkey [21] and Madrid [22], where seropositivity rate was 88.8% in children aged 13-16 years and 80% in 6-7 years vaccinated children, respectively. Such low seropositivity against mumps in our controls may reflect poor immunogenicity of this component of the MMR vaccine given to Egyptian children [23]. Therefore, revaccination against mumps should be given to seronegative children to limit spreading of mumps virus in the community. Previously, an Egyptian report appreciated mumps revaccination at 2 years as the lowest seroimmunity was found between 1 and 2 years [24]. In addition, we recommend future follow up studies to investigate waning of antibody titer after the end of chemotherapy to investigate seroconversion rate at different follow up times.

Seroprevalence to VZV antibodies varies from region to region, but immunity is acquired later in life in more temperate areas of the world. Seroprotective rate against VZV was reported in 50%–60% of 5 years European children with more than 90% being seropositive by the age of 10 years [25]. Reports from Asia, specifically from Tharan, showed that VZV seropositivity was reported in 25.3% and 73.5% of 1-5 and 11-15 years children, respectively [26]. This figure is close to what has been found in the current study, where the rate of VZV seropositivity was 18% in controls below 6 years and was 73% in those above 10 years indicating that the rate of VZV seropositivity was positively related to age. The same figure was found in our leukemic children where seropositivity of VZV increased with age from 14% in patients below 6 years to 55% in those >10 years, p=0.001. This is an indicator of infection with the wild type VZV among Egyptian population with its serious consequences which may lead to hospitalization with severe condition in healthy normal individuals and causes fatal encephalitis, severe pneumonia in immune-compromised patients. Therefore, VZV vaccine is extremely advocated in control children and VZV IgG may be given to leukemic children below 6 years until being vaccinated at the end of treatment.

The present study showed that, seropositivity rate of diphtheria in ALL patients aged below 6 years was lower than those aged 6-10 years or above 10 years (76% vs 83% or 90%, respectively) yet with no significance, p = 0.17. Furthermore, among seropositive ALL patients, low protective antibody against diphtheria (0.1-0.9 IU/ml) was significantly associated with young age group (91% in patients below 6 years), p=0.03 and a booster dose is necessary according to kit instructions. This was in agreement with Torben et al. [27] report which showed that young ALL patients (3–10 years) had significantly lower anti-diphtheria levels before vaccination than older patients (above 10 years). This could be explained by double hit of immunosuppression due to young age and underlying disease resulting in increased susceptibility to infection with diphtheria [27].

In the present study, seroprotective rate against diphtheria in control children was relatively well (83%). This was satisfactory compared to a Turkish study which found that seroprevalence of diphtheria antibody in healthy children was 77.9%. Also they did not report a relation between seropositivity and age [28]. Moreover, our results showed waning of immunity with age as evidenced by increasing low protective antibody level (58% in controls below 6 years vs 100% in those above 10 years) with no significance (p=0.11), which might be due to the small numbers in the study group.

In the current study, seropositivity of anti-HBs in both leukemic patients and control children significantly decreased with age both on the univariate and multivariate levels. The likelihood of being seroprotected if < 6 years is 5.7 (2 – 16.5) times compared to those above 10 years. The present results are supported by a study from Taiwan, where anti-HBs seropositive rate decreased to 50% within 15 years after vaccination [26]. On further analysis, our results showed that among seropositive ALL patients , low protective anti-HBs antibody (10-100 IU/L) was more associated with older age group (above 10 years) and those patients need a booster dose within 3-6 months according to the instructions of the kit. Therefore, the necessity and the age for boost among anti-HBs negative adolescents should be further evaluated [29].

The younger the patient is, the longer the immunosuppression lasts [30]. Therefore, measles, mumps and VZV immunoglobulin may be relevant in young ALL patients who are suffering from severe neutropenia and lymphopenia at diagnosis to achieve short lived protection until being vaccinated at the end of treatment.

Conclusion

The current study showed high percentages of seronegative individuals against measles, mumps and varicella zoster in studied acute leukemia patients and their controls. We recommend that MMR revaccination be adopted at the age of 2-3 years to control measles and mumps infection in Egypt. Also, immunogenicity of measles and mumps components in MMR should be re-evaluated. The high infection rate of varicella zoster in non vaccinated children recommends the implementation of varicella vaccine in our national immunization program. Booster dose of HB vaccine should be given to school aged children (1st grade) as more than 50% of immunized children showed a decline in their protective titer of anti- HBs. Revaccination of the ALL patients must be a task for the hematological oncology patients at the National Cancer Institute in Egypt.

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