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Measles and rubella vaccine antibody levels in children with acute lymphoblastic leukemia following chemotherapy

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Abstract

Background: Children in remission from acute lymphoblastic leukemia (ALL) have a high prevalence of immune system defects; one of them is the decrease of vaccine-induced antibody seropositivity rates. This antibody deficiency may place children with ALL at risk for the development of vaccine- preventable diseases, even after completion of chemotherapy, and they could function as a reservoir for additional spread of these diseases in the population. The aim of the present study was the assessment of the levels of vaccine- induced antibodies against measles and rubella viruses in ALL children following chemotherapy. **Subjects and methods:** Antibody levels against measles and rubella vaccine viruses were evaluated by ELISA technique in 96 children with ALL after completion of chemotherapy, in addition to 30 healthy children (non cancer controls of matched age and sex). **Results:** All healthy children were seropositive for measles and rubella antibodies.On the other hand, out of 96 children who received chemotherapy, only 19 (19.8%) were seropositive for measles antibodies, while 70 (72.9%) were seropositive for rubella antibodies. Most of measles seropositive cases (57.9%) had low levels of measles antibodies while among control group most children (56.7%) had high levels of measles antibodies. Similarly among children who received chemotherapy, most of the seropositive cases (45.7%) had low levels of rubella antibodies, while among control group, most of children (36.6%) had high levels of rubella antibodies. Seropositivity rate of measles was found to be related to the age at diagnosis and disease duration, while that of rubella was found to be related to the disease duration only. **Conclusion and recommendations**: Most of children who have been treated with chemotherapy for ALL had lost measles antibodies and to less extent rubella antibodies. Among seropositive cases, levels of measles and rubella antibodies are low following treatment with chemotherapy compared to levels among normal controls. Therefore, revaccination of children with ALL following completion of chemotherapeutic treatment against measles and rubella is recommended.

Key words: Acute lymphoblastic leukemia, measles, rubella, vaccine.

INTRODUCTION

Measles is a highly contagious, serious viral disease. It remains a leading cause of death among young children globally, despite the availability of a safe and effective vaccine. Children usually do not die only from measles, but from its complications such as pneumonia and diarrhea as a result of the immunosuppression

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associated with measles infection.[1] On the other hand rubella, is a mild viral disease as long as it is not contracted during pregnancy, otherwise it is the leading cause of miscarriage, stillbirth or the risk of congenital rubella syndrome (CRS) in a large proportion of children born to infected mothers.[2]

In the early 1970s, a triple vaccine containing attenuated measles, mumps and rubella viruses (MMR) was introduced worldwide.[3]MMR vaccine played a major role in decreasing the morbidity and mortality rate worldwide, its effectiveness depends mainly on the age at vaccination and receipt of a booster dose.[4] The objective is to provide two doses ofMMR vaccine at appropriate intervals for all eligible individuals.Over 90% of individuals will seroconvert to measles, mumps and rubellaantibodies after the first dose of the MMR vaccines.[5] The first dose of MMR should be given ideally at thirteen monthsof age, as the immunization before this age providesearlier protection in localities where therisk of measles is higher, but residualmaternal antibodies may reduce the response rate to the vaccine. The optimalage chosen for scheduling children is therefore a compromise between risk ofdisease and level of protection.[6]

A second dose is normally given before school entry but can be given routinelyat anytime from three months after the first dose. Comprehensive vaccination has dramatically decreased measles morbidity and mortality, both in developing countries and the developed world.[7]Measles elimination has been achieved and sustained in the World Health Organization (WHO) Region of the Americas since 2002. In 2010, the World Health Assembly established three milestones for measles eradication to be reached by 2015.[8,9]

Cancer and its treatment are important causes of secondary immunodeficiency in childhood.[10] Leukemia constitutes the most frequent malignancy in the pediatric

age. In 95-98% of patients, leukemia is acute, and of this 75-80% corresponds to acute lymphoblastic leukemia (ALL).[11] Immune disorders associated with cancer are varied, and one of these disorders is the decrease of antibody synthesis. At the same time, immune changes in these children are also secondary to the treatment they receive, wherechemotherapy and radiotherapy are the only curative treatments for children who are affected by malignancy, and their use in recent decades has led to significant improvements in disease-free survival for patients with all types of tumors.[12,13]

An unavoidable drawback of chemotherapy is hematologic toxicity in the form of severe B andT-cell depletion which results in clinical complications related to immune incompetence.[14,15] Children who were treated with chemotherapy had lower levels of antibodies against common viral vaccination antigens such asmeasles ,mumps, rubella, and polio which results in transient immunodeficiency.[16,17]

This antibody deficiency may place children with ALL at risk for the development of vaccine-preventable diseases, even after completion of chemotherapy, and they could function as a reservoir for additional spread of these diseases in the population.[18]

In particular, it has yet to be established whether the degree of immune dysfunction after standard chemotherapy demands a booster dose outside the recommended schedule, revaccination, or no intervention at all.[18,19]

The aim of the present study was the assessment of the levels of vaccine-induced antibodies against measles and rubella viruses in ALL children following chemotherapy.

Subjects and methods

This cross sectional study was carried out duringthe period from March 2010 to September 2010. The study included ninety six leukemic children (54 boys and 42 girls)

attending the hematology clinic in Al Shatby University Hospital for follow up after completion of their chemotherapy,their ages ranged from 4 to 12 years old. All had been previously vaccinated for measles and rubella viruses and their therapies had been stopped for at least 6 months before enrollment in this study. In addition to thirty apparently healthy children, sex and age matched, not suffering from malignant conditions and had not received any chemotherapy.

All candidates were subjected to complete history taking with special emphasis on history of immunization (Data regarding vaccination before and after chemotherapy was obtained by a questionnaire and verified through vaccination certificates), age at diagnosis of ALL, duration of the disease, and duration since end of chemotherapy. An informed consent was obtained from the parents of each child.

Five ml of venous blood was collected aseptically from each child, blood was centrifuged, serum was collected and stored at -20℃ until used for determination of antibodies against measles and rubella viruses by ELISA technique (DRG International, Incorporation, USA) according to the manufacturer's instructions. The cutoff for protective levels for measles antibodies was set to be > 11 DU and the cutoff for protective levels for rubella antibodies was set to be > 15 IU/ ml. The study was approved by the “Ethics Committee” of the High Institute of Public Health, Alexandria University.

Statistical assessment was carried out with the SPSS version17.0 for windows statistical software. Quantitative variables were described using mean, standard deviation, median, minimum and maximum. **The Mann-Whitney test** was used for comparing two groups as the data was not normally distributed as tested by **Kolmogorov-Smirnov test** of normality. Categorical variables were describedusing frequencies and percentages.**The chi-square test** was used for testing associations.

To indicate statistical significance, the threshold for *p* values was taken at 5% level ($p < 0.05$). All tests used in this study were two-sided.

RESULTS

Antibody titers to measles and rubella were measured in ALL children after cessation of therapy and in their matched controls. Nineteen (19.8%), and 70 (72.9%) of the 96 ALL children had retained protective levels of antibodies against measles and rubella viruses respectively. In their age-matched normal controls, 100% of children had protective antibodies against measles and rubella viruses. This difference was statistically significant (Table 1).

Table 1: Presence of measles and rubella antibodies among ALL children following chemotherapy and control group

Antibodies	Cases (96)		Controls (30)	
	No.	%	No.	%
Measlesantibodies				
Seronegative	77	80.2	0	0
Seropositive	19	19.8	30	100
$X^2 = 61.876^*$, $p = 0.001$				
Rubella antibodies				
Seronegative	26	27.1	0	0
Seropositive	70	72.9	30	100
$X^2 = 10.237^*$, $p = 0.001$				

*Significant $p < 0.05$

Table 2 (a, b) shows that most of measles seropositive cases (57.9%) had low levels of measles antibodies while among control group most children (56.7%) had high levels of measles antibodies. These results were statistically significant. (p=0.001) Similarly among children who received chemotherapy, most of the seropositive cases (45.7%) had low levels of rubella antibodies, while among control group, most of children (36.6%) had high levels of rubella antibodies.

Table 2 (a): Levels of measles antibodies among seropositive ALL children following chemotherapy and control group

Levels of measles antibodies	Positive Cases (19)		Controls (30)	
	No.	%	No.	%
11 - < 14	11	57.9	2	6.7
14 - < 17	6	31.6	11	36.6
≥ 17	2	10.5	17	56.7
$X^2 = 50.786^*$, p=0.002				

*Significant $p < 0.05$

Table 2 (b): Levels of rubella antibodies among seropositive ALL children following chemotherapy and control group

Levels of rubella antibodies	Positive Cases (70)		Controls (30)	
	No.	%	No.	%
15 –<50	32	45.7	3	10.0
50 –<100	14	20.0	5	16.7
100 –< 150	12	17.1	3	10.0
150 – 200	10	14.3	8	26.7
> 200	2	2.9	11	36.6
$X^2= 15.786^*$, p= 0.001				

*Significant $p< 0.05$

Table 3 shows that age at diagnosis and duration of disease had significant effect on the presence of measles antibodies (p=0.015, 0.001 respectively), while table 4 shows that duration of disease had significant effect on the presence of rubella antibodies (p=0.049).

Table 3: Factors affecting the presence of measles antibodies among ALL children following chemotherapy

Factors	Measles seronegative cases (n=77)		Measles seropositivecases (n=19)		*Z*	*p*
	Mean ±SD	Median (min.-max.)	Mean ±SD	Median (min.-max.)		
Age at diagnosis (in years)	3.0±1.7	3 (1-7)	4.32±2.1	4 (1-8)	2.433	0.015*
Duration of disease (in years)	2.9±1.3	3 (2-6)	1.84±0.95	2 (2-4)	3.198	0.001*
Duration since end of chemotherapy (in months)	19.4±11.5	12 (6-60)	24.2±11.4	24 (6-48)	1.916	0.055

*Significant *p<0.05*

Table 4: Factors affecting the presence of rubella antibodies among ALL children following chemotherapy

Factors	Rubella seronegative cases (n=26)		Rubella seropositive cases (n=70)		*Z*	*P*
	Mean±SD	Median (min.-max.)	Mean±SD	Median (min.-max.)		
Age at diagnosis (in years)	3.4±1.9	3 (1-8)	3.1±1.8	3 (1-8)	0.703	0.482
Duration of disease (in years)	3.15±1.3	3 (2-6)	2.5±1.2	2 (2-5)	1.971	0.049*
Duration since end of chemotherapy (in months)	17.6±10.4	12 (6-48)	21.4±11.9	24 (6-60)	1.549	0.121

*Significant *p<0.05*

DISCUSSION

Measles is not only a major cause of immediate mortality, but residual effects of measles infection contribute to malnutrition andincreased mortality from otherdiseases for many subsequent months.[20]

Rubella is a mild disease as long as the infected female is not pregnant; otherwise CRS is the major consequence of rubella infection during pregnancy.[21] MMR vaccine played a major role in decreasing the morbidity and mortality rate worldwide, its effectiveness depends mainly on the age at vaccination and receipt of a booster dose.[4] Today one of the hygienic determinants in each country is vaccine coverage which is accompanied with effective prevention and disease control resulting in surveillance raise in the community. Chemotherapy and radiotherapy treatment is common method in children with malignancies. Children treated for cancer are immunosuppressed during treatment and for a variable period after completion of chemotherapy or radiotherapy which may place these children at risk for the development of vaccine- preventable diseases. [22, 23]

In this study, out of 96 children who

received chemotherapy, only 19.8% were seropositive for measles antibodies, while 72.9% were seropositive for rubella antibodies. On the other hand, all the 30 children (100%) among the control group were seropositive for measles and rubella antibodies. These results were statistically significant.

Zignol et al., (2004) [19] demonstrated that chemotherapy induced loss of protective serum antibody titers for measles and rubella in 25% and 18% of patients respectively. These findings were supported by Caver et al., (2004) [24] who demonstrated that the reason for the loss of antibodies acquired on vaccination is not fully understood, but such losses have been linked to more severe susceptibility to chemotherapy and to longer B lymphocyte recovery times.

Feldman et al.,(2003)[25] evaluated a group of 39 children who were treated for leukemia (and who had been vaccinated previously for MMR) at diagnosis and at the end of chemotherapy. They found decreases in seropositivity rates of 13% for measles, 18% for mumps, and 21% for rubella.

Nilsson et al., (2002) [18] analyzed serum antibody levels in 43 children after chemotherapy and demonstrated the persistence of protective levels against measles and rubella in only 60% and 72% of patients, respectively. Brodtman et al.,(2005) [22] observed 52% positivity for measles and 76% for rubella among 99 children treated for ALL and off therapy for one year.

The finding of loss of antibodies after chemotherapy suggests that B cells that are important for prolonged antibody production, such as memory B cells and plasma cells, may be impaired after chemotherapy. Ek et al., (2005)[26] found that the loss of antibodies is induced both by the underlying disease and by antineoplastic treatment, being more intense the more aggressive the treatment employed.

In this study, it was found that most of children who received chemotherapy had

low levels of measles and rubella antibodies (57.9% and 45.7% respectively), while most of children in control group had high levels of measles and rubella antibodies (56.7% and 36.6% respectively). These findings suggested that in spite of seropositivity for both measles and rubella antibodies, this seropositivity had low levels in comparison with normal children denoting that there is a high chance for waning immunity against both viruses.

These findings are coinciding with the findings of Nilsson et al., (2002) [(18)] who demonstrated that the antibody levels against measles and rubella viruses were significantly higher before than after completed chemotherapy in positive cases. Viana et al., (2012) [(27)] evaluated viral vaccine antibody levels in children with acute lymphoblastic leukemia after chemotherapy and after vaccine booster doses after chemotherapy. They reported that 75.9%, 67.9%, 59.3% and 51.7% of the patients showed low antibody titers that would be unlikely to protect against exposure to measles, rubella, hepatitis B and mumps, respectively. After receiving a vaccine booster dose for these antigens the patients had high antibody levels consistent with potential protection against measles, mumps and hepatitis B, but not against rubella.

Regarding the role of age at leukemia diagnosis as a factor affecting presence of measles antibodies among children who received chemotherapy, it was found that the mean age at diagnosis among negative measles antibodies children was 3.0**±**1.7 years, while mean age at diagnosis among positive children was 4.32±2.1 years; these results were statistically significant. Nilsson et al, (2002)[(18)]speculated that the developing B lymphocyte pool, especially bone marrow plasma cells, is more vulnerable in younger children during chemotherapy than B cell populations in older children.

On the other hand, age at diagnosis was not a significant factor affecting presence of rubella antibodies among children who received chemotherapy. Van Tilburg et al., (2006)[12] showed that the age at diagnosis is not a significant factor in the presence of both measles and rubella antibodies.

In the current study, the role of the duration of disease is a significant factor affecting presence of both measles and rubella antibodies among children who received chemotherapy where the mean duration of disease among negative measles antibodies children was 2.9±1.3 years while mean duration of disease among positive children was 1.84±.95 years. Regarding rubella antibodies, the mean duration of disease among negative rubella antibodies children was 3.15±1.3 years while mean duration of disease among positive children was 2.5±1.2 years. On the other hand Feldman et al. , (2003) [25] demonstrated different results where he did not found significant effect of the duration of the disease on the seropositivity rates.

Findings in this study demonstrated that the duration since end of chemotherapy is not a significant factor on the seropositivity of both measles and rubella antibodies among children who received chemotherapy. Similar findings were reported by Feldman et al., (2003) [25] who found no significant effect of the duration since end of chemotherapy on the seropositivity rate.On the other hand, Aytac et al., (2010) [28] demonstrated that the time interval between cessation of chemotherapy and analysis of serology tests was significantly longer in seropositive than seronegative cases (median 4.16 years versus 1.82 years, respectively).

Optimal primary vaccination and high herd immunity in the developed countries may reduce infection rates in ALL patients but increased migration and international travel might reduce herd immunity. Re-vaccination of the ALL patients must be a task of the treating hematology–oncology

center. In addition to impaired immunity, these children generally miss opportunity of booster vaccination at school during or after chemotherapy.[12]

Because of the risk of fatal infections in immunocompromised patients with cancer, it had been recommended that all children receiving leukemia therapy be given gamma globulin if they have been exposed to measles during a community outbreak.[25] At the same time, several studies recommended that ALL patients should be re-vaccinated following completion of chemotherapy. [18,19,28] On the other hand, Fioredda et al., (2005) [30] did not recommend administration of another complete vaccination schedule to each ALL subject over treatment, taking into account the economical aspect of vaccines and laboratory kits and they recommended continuation of the regular schedule of vaccination.

Current US guidelines recommend re-immunization no sooner than 3 months after standard chemotherapy. In the United Kingdom a booster of each vaccine 6 months after completion of chemotherapy was recommended.[31] Underestimation of re-vaccination may contribute to the spread of viral infections such as measles andrubella in the society.[18]

RECOMMENDATIONS

1. Revaccination of children with ALL following completion of chemotherapeutic treatment against measles and rubella.
2. Further studies should be conducted for the evaluation of antibody levels against different types of vaccine preventable diseases and in different types of cancer to assess immunological status.

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