Original Article

THE SPECTRUM OF MACROPHAGE INHIBITORY FACTOR CYTOKINE RESPONSES IN PADIATRIC BCG VACCINEE

Tiba Ahmed Kareem[1], Ibrahim M. S. Shnawa[2]

[1]Department of Biotechnology, College of Biotechnology, Green University of Qasim/Babylon/Iraq

[2]College of Biotechnology, Green University of Qasim And Hilla University College/Babylon/IRAQ

Abstract

At most BCG vaccination in childhood is being finalized with scar formation. Absence of BCG scar formation few days post-vaccination can be a state of anergy. Though, gradual scar fade up may demonstrate a case of waning immunity. The present work was performed onto three groups of healthy children. Scar bearing BCG vaccinee child, non-scar bearing BCG vaccinee child and non-vaccinated child as controls. Age, scar size and macrophage inhibitory factor MIF cytokines were determined. A fraction of scar bearing BCG vaccinee were showing lower MIF concentration than normal controls. A state of waning cytokine responses in spite of the presence of scar. Likewise, a fraction of non-scar bearing BCG vaccinee were showing MIF concentrations lower than that of normal healthy controls ,a state of waning cytokine responses that parallels the waning of gross manifestation of the scar reactions. These findings point out the condition of heterogeneity or divergency of the immune response to BCG vaccines in childhood. MIF cytokine herd response were showing low moderate, and high responders in vaccinated children. The MIF cytokine herd response plots were of Gaussian distribution plots.

Keywords: BCG, MIF, Scar, anergy.

Introduction

BCG vaccine is still in use standard biological product that possess specific and non-specific immune potentials as; vaccine, vaccine adjuvant ,nonspecific immune stimulant ,child mortality reducer and protects against heterologous pathogen[1].In BCG vacinee child there found to be variable degrees of innate and adaptive cellular and humoral immune responses. The adaptive cellular immune responses and delayed type hypersensitivity reactions resulted in scar formation. Thus scar formation can be an indication for immune system function and cellular immunity operability. Scar may fade up on time last post-vaccinaion[1,2,3].MIF cytokines profiles act as a marker of cell mediated immunity delayed hypersensitivity to BCG vaccine.Variable degrees of MIF cytokine responses have been documented[4,5,6,7,8,9].THE BCG immune response heterogeneity pose to a question, could scar fade up stand on cellular immune inactivity?

The answer of this question tempted in the present work which focused on scare fade, age and MIF response in scar and non-scar bearing BCG vaccinee child subjects.

Materials and methods

A population of 90 child healthy subjects[comorbidities , chronic and genetic diseases were excluded] were elected and sub-grouped into 30 BCG vaccine with scar,BCG vaccine without scar and 30 non-vaccinated as controls. Scar were measured for the nearest millimeter from three different diameters and means were fixed.

Address for correspondence: Tiba Ahmed Kareem
College of Biotechnology, Green University of Qasim/Babylon/Iraq

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From each subgroup 15 subjects were elected from each subgroup using simple random sampling method. MIF cytokine determination was measured following the manufacturer instructions for ELISA assay.

RESULTS

1-BCG Scar Fade Up :

The age of about one year developed a mean scar size of 5.3 mm. While that of about two years was with scar size mean 6.1 mm. Age range of 3-5 years have shown scar size means of 3-3.1mm.Therefore ,the scar size decreased as the age increase up to five years old.Table-1.Figure – 1,2..Simple linear regression analysis has shown moderate inverse correlation between age and scar size. The correlation was of simple negative linear regression analysis with correlation coefficient of 0.199.Figure 1,Figure 2 showed this correlation.

Table -1 ;Age range and scar size correlation

Age range in months	Mean scar size to the nearest mm	No. of subjects
1-11	5.3	5
12-23	6.1	3
24-35	3.1	2
36-47	3.0	1
48-59	3.0	2

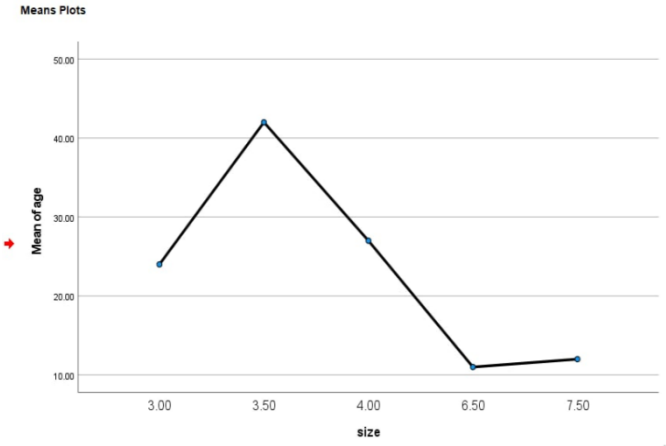

Figure 1: Simple linear regression analysis of the scar size and age of child.

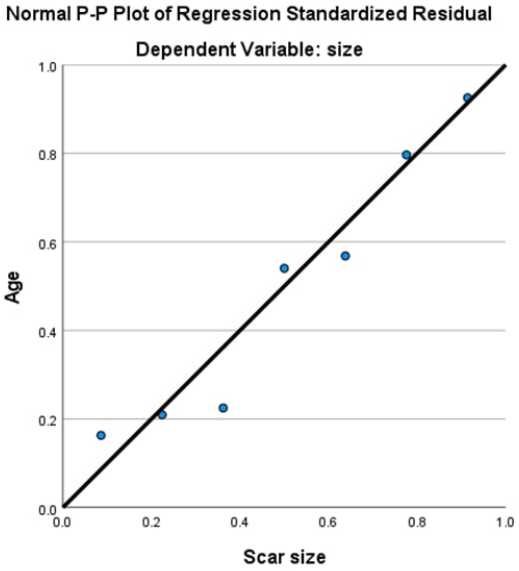

Figure 2: Plot of the mean scar size as related to age of the child.

2-MIF Cytokine Response Features;

The mean concentration of non-scar bearing child subjects was higher 12.341 ng/ml. than that of scar bearing child subjects9.783 ng/ml. as compared to normal healthy non-vaccinated child subjects 6.459 ng/ml. Both vaccinee groups have shown a spectrum of ; low, moderate and high MIF concentration.

Table 2: MIF cytokine responses among BCG vaccinee and non-vaccinee child

Sequence	MIF conc. Scar bearing ng/ml.	MIF conc.No-scar bearing ng/ml.
1-	5.809	12.341
2-	0.309	4.237
3-	5.586	28.677
4-	6.369	22.273
5-	2.845	9.279
6-	4.598	7.857
7-	6.128	3.785
8-	5.918	3.671
9-	22.430	4.038
10-	2.369	5.701
11-	8.954	29.21
12-	26.189	5.622
13-	22.303	15.632
14-	5.779	22.563
15-	20.665	21.906
Mean of scar bearing	9.783	
Mean of non-scar bearing		12.341
Mean of non-vaccinated	6.459	

3- Spectrum of MIF Cytokine Responses :

The lower limits of MIF concentrations for the scar bearing BCG child vaccinee were lower than that of non-vaccinated control child. While, the lower limits of the non-scar bearing vaccine e child subjects were higher than those of controls. The mean of MIF concentrations for vaccinated was higher than that of non-vaccinee control. Non-scar bearing vaccinee MIF concentration means was higher than scar bearing child subjects. The differences between vaccinated and non-vaccinated child subjects were statistically significant at the level of P0.069 but not at the level of P0.05.Tables 2,3.Paired t test and F test to differences between scar bearing and non-scar bearing BCG vaccinee were statistically non-significant at P 0.05 but significant at P 0.4.

Table 3: Biometery of MIF cytokine responses In BCG vaccine child as compared to normal healthy child

Statistical Features	BCG scar	BCG non-scar	Control
Minimum	0.309*	0.954	0.863
Mean	9.783	12.341	6.459
Median	5.918	3.671	8.604
Maximum	26.189	29.219	8.604
Range	0.309-26.189	o.945-29.219	0.8-8.773

- Concentrations in ng/ml.

4-MIF Cytokine Herd Responses

The herd MIF immune response fractions were noted as; lowe, moderatee and high responderse. Low, moderate and high MIF cytokine responders were noted both in scar and non-scar bearing child subjects as compared to non-vaccinated subjects Table - 4. The MIF herd plots were of were of Gaussian distribution plots .Figures 3and 4..

Table 4: Herd responder fractions of MIF[conc.ng/ml]* cytokine responses

Responder type	Scar bearing BCG vaccinated	Non-scar bearing BCG vaccinated	Control
Low	0.3-4*	0.9-5	0.3-3
Moderate	5-9	6-18	4-15
High	10-27	19-29	16-21

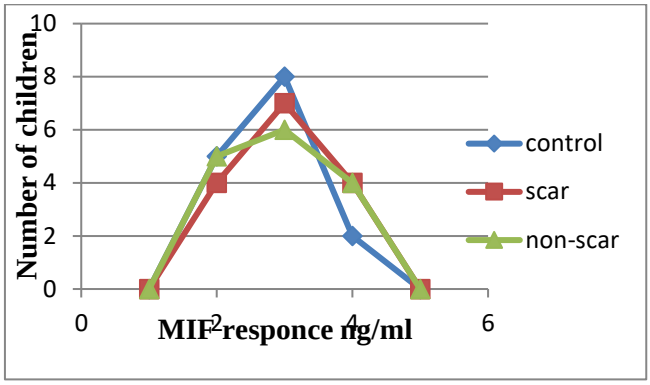

Figure 3: Normal distribution of MIF concentrations in BCG vaccine and non-vaccinated control child.

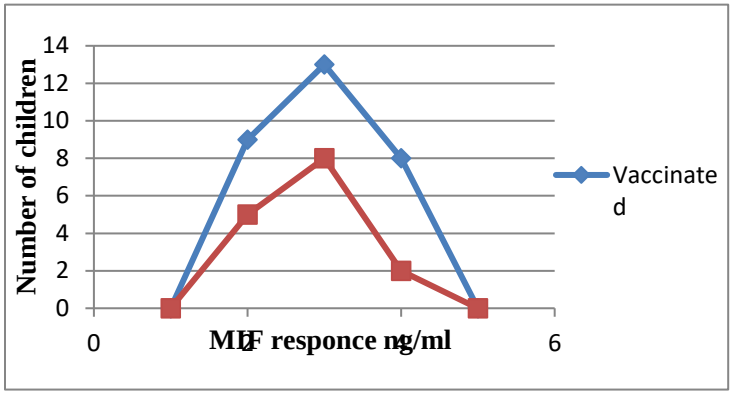

Figure 4: Normal distribution of MIF concentrations in scar ,non-scar bearing BCG vaccinee and non-vaccinated child

Discussions

The scar formation post to BCG vaccination in child subjects stands as the net results of T cell mediated immune and delayed type hypersensitivity responses. Some children when BCG vaccinated they did not form a scar at all a case of gross manifestation of anergy[10,11,12]. Others were developing the scar but the scar may fade up as age progress. The present investigation ,it was found that scare begins to fade up in the age of three years till the age of five years, and the simple linear regression analysis of scar size and age of child vaccinee was of simple negative linear regression type. The correlation was moderate inverse relationship. The correlation coefficient was 0.199.That is to say that around 20% of age variability is explained by the scar size. In line with these findings ,Kumar et al.2005 have been documented that BCG scar detorurate as the age progressed. Non-scar bearing subjects was also reported by other workers[13,14,15].

MIF is a lymphokinee involvede in cell mediated immunity ,immune regulatione, inflammation and regulation of macrophage defensive functions[16,17].It is produced by ;T cells, dendritic cells and macrophags. When these cells activated they synthesize and secret MIF which in turn modulate the expression of TNF alpha, nitric acid and cyclooxygenase-2[18].The functional polymorphism of MIF

was found to be associated with disease susceptibility or clinical severity[19].

MIF cytokine responses are initiated in cases of T cell mediated immune responses to intracellular bacterial pathogens and in delayed type hypersensitivity reactions to microbial antigens[16,17].The lower MIF cytokine concentrations than in control could be attributed to; child age effect, BCG make to make differences in the nature of antigenic constitution of BCG vaccine, there might be the presence of an immunosuppressive epitope and/or presence of an immunosuppressive environment in the subject immune system compartment[2,3,7,20,21,22,23].The nature of the herd plots for cytokine responses were in line with what has been reported in this area[,24,25,26].The BCG vaccine immune response in this vaccinated children appeared to be of marked heterogeneity or divergence ,scar bearing and non-scar bearing BCG vaccine both included high ,moderate and low responders. Absence of scar does not mean absence of immune reaction and the presence of scar does not mean a grantee for good immunity conferred by the BCG vaccine[Prentice and Dockrell 2020,Boar et al.2015,Whittaker et al.2018].

Conclusion

MIF concentration means of BCG vaccinee were higher than those of non-vaccinated control. The MIF cytokine responses were heterogenic or divergent both in scar bearing and non-scar bearing BCG vaccinee .BCG scar fade as the child age progressed up to five years. The presence of scar does not be a grantee for good cellular immunity and absence or fade up of the scar does not be a sign for poor cellular immunity. Hence BCG scaring may and may not be associated with cellular immune reactivity. Herd immunity principle is operable in BCG vaccinated child so far this study indicated. Since three fractions of immune responses were noted among vaccinated child and the plot was of Gaussian distribution curve type.

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