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Immunity to Diphtheria in Haemodialysis Patients

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Abstract: Problem statement: The incidence of infectious diseases is increased in patients with chronic renal failure. Chronic renal failure severely influences the immune functions of the host. Diphtheria is of great epidemiological concern. Although mainly observed during childhood, unvaccinated adults and relatively immunocompromised patients are at increased risk for acquiring diphtheria. **Approach:** To evaluate the anti-Diphtheria immunity level in southern Iranian patients with end stage renal disease undergoing hemodialysis and to find its association with sex, age, blood hemoglobin, serum albumin and duration of dialysis. This cross sectional study was carried out on a total of 52 patients, who were on hemodialysis and 52 age and sex matched healthy individuals with without any underlying renal disease as a control group. Subjects in the both groups receiving anti-diphtheria toxoid vaccine or immunoglubins a year prior to the study were excluded. The serum anti-diphtheria IgG antibody levels were measured by an ELISA method. **Results:** Diphtheria protected individuals in the patients and the control groups were 34.6 and 63.30% respectively. Of the evaluating factors just hemodialysis duration found to affect on diphtheria immunity. **Conclusion:** Diphtheria protected individuals in the patients group were significantly less than diphtheria protected individuals in the control group ($p = 0.011$). Hemodialysis duration has significant effect on anti-diphtheria immunity level.

Key words: Hemodialysis patients, chronic renal failure, control group, End-Stage Renal Disease (ESRD), Chronic Kidney Disease (CKD), toxoid vaccine, diphtheria toxoid

INTRODUCTION

Infectious diseases are the leading cause of death in End-Stage Renal Disease (ESRD) patients, second only to cardiovascular disease. They also contribute to a significant morbidity in patients with earlier stages of Chronic Kidney Disease (CKD) (Kausz and Gilbertson, 2006).

The incidence of infectious diseases is increased in patients with chronic renal failure (Laube *et al*., 2002). This is thought to be due to an immunosupressed status in this population (Litjens *et al*., 2008; Vacher-Coponat *et al*., 2008; Kaliuzhina *et al*., 2006). This is thought to be related to an impaired T cell activation by antigen presenting cells (Girndt *et al*., 1993; 1995), impaired immune Responses and Antigen-Specific Memory CD4+ T Cells (Litjens *et al*., 2008), defects in NK cell function (Vacher-Coponat *et al*., 2008), immunodeficiency status manifested decrease in the number of CD3+, CD4+ and CD72+ cells and phagocytosis intensification (Kaliuzhina *et al*., 2006), T and B-lymphocyte abnormalities and impaired responses to T cell dependent pathogens such as hepatitis B virus (Argani and Akhtarishojaie, 2006) and endothelial dysfunction (Hussein, 2010). Opportunistic infectious disease such as toxoplasmosis has more prevalence than healthy subjects (solhjoo *et al*., 2010).

Diphtheria is of great epidemiological concern. Although mainly observed during childhood, unvaccinated adults and relatively

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immunocompromised patients are at increased risk for acquiring diphtheria (Karakus *et al*., 2007). Recent epidemiological studies indicate a low immunity to diphtheria in adults in industrialized countries and indicate that the number of insufficiently protected individuals has increased especially in the elderly (Kruger *et al*., 1999).

In 2004, WHO reported the incidence of diphtheria, tetanus and pertussis in Iran to be 6, 11 and 98 cases, respectively while in 2005, the respective incidences were 15, 8 and 125 (WHO, 2006).

Vaccination is the most effective means of preventing infectious diseases. Immunization programs are of great importance in the prevention of infectious diseases in immunocompromised individuals. However, the immune response to various vaccinations is impaired in patients with chronic renal failure (Kruger *et al*., 1999), requiring multiple boosts to generate a robust protective response (e.g., diphtheria, pertussis and tetanus) (Storsaeter and Wolter, 2006).

The tetanus, diphtheria and pertussis vaccination programme in Iran has been running since 1950 using a local vaccine manufactured by Razi Institute (Razi-DTwP), Tehran, Iran and the efficacy of the vaccine was confirmed by previous studies. These vaccinations have decreased the incidence and changed the epidemiology of these diseases (Zarei *et al*., 2007), but there is no routine vaccination for hemodialysis patients and So far only a few studies have focused on seroresponse to tetanus toxoid in these patients in Iran (Sagheb *et al*., 2009; Jahromi *et al*., 2009).

MATERIALS AND METHODS

Subjects: This cross sectional study was carried out on a total of 52 patients (36 men and 16 women), with a mean age of 57.75±14.26 years, who were on hemodialysis therapy due to end-stage renal disease in the Hemodialysis Center of Jahrom University of Medical Sciences in 2010. Fifty two healthy individuals (35 men and 17 women) with normal serum levels for ceratinine and BUN and without any underlying renal disease with a mean age of 58.98±14.32 years as a control group were enrolled in this research.

There were not significant differences between age ($p = 0.912$) and sex ($p = 0.112$) in the cases and the controls.

As there were not data indicating past history of vaccination in both groups, the control group was randomly selected among the same community of patients group to increase the reliability of the results. Individuals in the both groups receiving anti-diphtheria toxoid vaccine or immunoglubins a year prior to the study were excluded.

Data collection: Data including sex, age, hemoglobin, serum albumin, duration of dialysis, Body Mass Index (BMI) were obtained from all of the hemodialysis patients and their medical records.

Serologic evaluations: Anti-diphtheria toxoid IgG level was determined on serum samples taken from patients before starting hemodialysis. Sera were separated and stored at -70°C until analysis. Antibody levels were measured by commercial ELISA kits (IBL-Hamburg GmbH, Hamburg, Germany). Optical density was measured at 450 nm using ELISA reader (Awerness Instruments, USA). Based on the EPI Program of WHO, the assay cut-offs for protective level of tetanus antibody was set at 0.1 International Units (IU mL^{1}) (Sagheb *et al*., 2009; (Olander *et al*., 2009). Concentrations above the assay cut-offs were considered to be seroprotective.

Ethics: The protocol of this study was approved by the ethics committee of Jahrom University of Medical Sciences.

Statistical analysis: Statistical analyses were performed using SPSS ver.11.5 software (SPSS Inc., Chicago, Illinois) Statistical differences of various clinical and laboratory parameters between groups were evaluated by Chi-Square or Mann-Whitney U tests. To compare the means of two groups, the two independent sample t-tests were used. p-values of less than 0.05 were considered as significant.

RESULTS

The mean serum anti-diphtheria IgG level of hemodialysis patients was 0.086±0.062 and 0.613±0.725 IU mL^{-1} in the control group ($p = 0.001$).

The patients and the control groups were divided into 3 groups by their anti-diphtheria IgG level.

Group 1: IgG<0.1 IU mL^{-1} which are not protective and need basic immunization through tetanus booster vaccine.

Group 2: 0.1<IgG<1 IU mL^{-1} who need to be controlled in 1-2 years and group 3: 1<IgG<5 IU mL^{-1} who need to be controlled in 2-4 years. Therefore 34 (65.40%) patients were not protected against diphtheria because their IgG less than 0.1 IU mL^{-1} (Cameron *et al*., 2009; Sagheb *et al*. 2009). Table 1 illustrates the characteristics of the patients and the control groups.

Among the contributing factors studied, only the patients with longer duration of hemodialysis had lower anti-diphtheria IgG level ($p = 0.021$).

Table 1: Comparison of the characteristics of patients and control groups

Variables	Hemodialysis patients	Control group	p-value
Age (years)	57.75±14.26	58.98±14.32	p = 0.900
Gender	36 (69.23%) men	35 (67.30%) men	
	16 (30.77%) women	17 (32.70%) women	p = 0.900
Anti-diph. IgG (IU mL^{-1})	0.086±0.062	0.613±0.725	p = 0.001
Level of protection	11 (21.15%)	17 (32.70%)	p = 0.012

Table 2: Comparison of the characteristics of protected patients (group 2-3)

Anti-diphtheria	Factors affecting Level 2 (7 patients)	Level 3 (4 patients)	p-value
Age (years)	48.3±12.6	51.4±10.8	0.82
BMI	24.8±4.4	25.2±4.7	0.72
Albumin (g dL^{-1})	4.3±0.68	4.7±0.83	0.43
Hb (g dL^{-1})	8.9±1.6	8.5±1.3	0.72
Duration of hemodialysis (weeks)	28.75±22.35	13.76±24.45	0.03

It is also noteworthy that patients with the highest anti-diphtheria IgG and immunization against diphtheria (level 3) have the shortest duration of dialysis (p = 0.03) (Table 2).

DISCUSSION

The immunodeficiency in patients with chronic renal failure makes them prone to more fatal outcomes of infectious diseases. A few studies were done on immunization against anti-diphtheria in patients with chronic renal failure (Kruger *et al*., 1999; Kreft *et al*., 2000; Sagheb *et al*., 2009).

Diphtheria protected individuals in the patients group were significantly less than tetanus protected individuals in the control group (21.15% Vs 2.70%) (p = 0.011).

Kruger reported 16% of patients were unprotected against diphtheria compared with 19% of the control group, his results and our results approximately are the same (Kruger *et al*., 1999).

The mean serum anti-diphtheria IgG level of the hemodialysis patients was significantly lower than the mean serum anti-diphtheria IgG level in the control group (p = 0.001). We found a significant negative effect by the duration of hemodialysis on anti-diphtheria IgG level in our patients group (p = 0.03) and we did not find any significant effect by the other contributing factors on anti-diphtheria IgG level in either chronic hemodialysis or in the all hemodialysis patients. Also there was not statistically meaningful difference between the protected against diphtheria patients (n = 11) and those not protected (n = 41). The same results were showed by (Sagheb *et al*. 2009).

According to previous studies rapid decline in the titer of anti-diphtheria IgG in vaccinated hemodialysis patients who had a protected status after 6 months, among the different factors considered, only age significantly impaired or reduced the diphtheria immunity level (Kreft *et al*., 2000).

CONCLUSION

To conclude, it seems that most of our hemodialysis patients need booster or re-vaccination of diphtheria vaccine to increase their anti-diphtheria immunity. We recommend frequent monitoring of antibody levels after re-immunization against diphtheria in hemodialysis patients.

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