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Cutaneous Anergy in Patients Receiving Long Term Hemodialysis

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ABSTRACT

Background: *Hemodialysis patients are at risk of acquiring tuberculosis, which is most often due to reactivation of the infection. As a result, screening for tuberculosis is recommended in hemodialysis patients. In this study, the rate of response to cutaneous PPD along with tetanus and diphteria toxoid antigens have been evaluated to define in hemodialysis patients.*

Materials and Methods: *This clinical trial was conducted on 67 chronic hemodialysis patients in Labbafi Nejad Hospital during March- May 2001. PPD, tetanus and diphtheria toxoid solutions, with 1/10 dilution were administered by Manteaux technique and the induration was evaluated 48-72 hours, 7 and 9 days after.*

Results: *Of 64 patients, 18.8% had positive PPD tests and 26.6% had negative anergy tests through the first evaluation. The degree of constancy in the results of PPD and anergy tests during the three-time evaluation period were 23.4% and 18.7%, respectively, and the degree of induration was increased or decreased among the rest.*

Conclusion: *Hemodialysis patients are at the increased risk for acquiring tuberculosis. Thus, negative cutaneous PPD results should certainly be revised and evaluated using anergy tests and repetitive readings of the test results. Attention must be paid to the "Delayed Type Hypersensitivity" (DTH) phenomenon presenting for the first time in the analysis of cutaneous test results. Finally, it is recommended to reconsider the value of cutaneous PPD test and its method of analysis in hemodialysis patients.* ***(Tanaffos 2002; 1(2): 21-26)***

Keywords: *Cutaneous anergy, Hemodialysis, Delayed Type Hypersensitivity(DTH), Tuberculosis.*

INTRODUCTION

Immunocompromised patients including those undergoing hemodialysis are at risk of acquiring tuberculosis which is mostly due to a reactivation process (1,2,3,4).

Therefore, screening for tuberculosis is recommended in hemodialysis patients. Delayed Type Hypersensitivity (DTH) skin reaction tests are practical and sensitive tools for evaluating the host cellular defense. They are also used for the diagnosis of intracellular pathogens such as Mycobacterium

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tuberculosis or the exclusion of anergy in patients(5,6).

Hemodialysis patients have reduced cellular immunity, being attributable to reduced life span of lymphocytes, lymphocytopenia, lymphocyte transformation, and suppressor lymphocytes. These findings contribute to cutaneous anergy, impairment in tumoral surveillance of the body, as well as unusual response to hepatitis B infection and tuberculosis (7,8).

Malnutrition in hemodialysis patients has no significant correlation with the emergence of cutaneous anergy and does not impair cell-mediated immunity (9).

Meanwhile, it was shown in one study that supportive protein-calorie regimen would reverse the anergy to a normal skin response (10).

A number of studies were performed to introduce an effective antigen for cutaneous anergy tests. They varied according to the type of antigen exposure in each community. Nonetheless, the probability of a positive skin test was high for tetanus and diphtheria toxoid; medium for candida, proteus and streptococcus antigens;and low for tuberculosis and trichophyton (11).

In addition, while a child grows up, the probability of a positive skin reaction is increased (11).

In the present study the response rates of hemodialysis patients to PPD test and to tetanus as well as diphtheria toxoid antigen as cutaneous anergy tests were evaluated in order to reach new horizons in the interpretation of skin tests in patients undergoing long-term hemodialysis.

MATERIALS AND METHODS

Our study was designed as a clinical trial. The hemodialysis ward of Labbafi-Nejad hospital was chosen to conduct the study. We described the experiment to the patients and received their consent. Without a history of tuberculosis, all the patients who had been on dialysis for at least 1.5 months, twice a week were enrolled in the study. Patients suffering from any other kind of immunodeficiency such as HIV infection were excluded.

First, demographic data such as age, sex and location of residence; information regarding history of BCG vaccination, and duration and frequencies of dialysis were gathered using a questionnaire.

Then, using Manteaux technique, 0.1ml (5 units of tuberculin) of PPD (Purified Protein Derivative) manufactured by Iran Pasteur Institute, was injected to the volar surface of the shunt-free arm using an insulin syringe. At the same time 0.1 ml of 1/10 saline diluted solution of tetanus and diphtheria toxoid was injected intradermally, 10 cm distant to the other injection site. Both injection sites were marked and numbered. Then another observer recorded the induration size without knowing whether it was a PPD or an anergy test. Induration was recorded 48-72 hours, 7 days and 9 days following the injection. To determine the size of induration, an average was estimated (the sum of the longest diameters divided by two). The ball- point pen technique was used for evaluation. For the PPD skin tests, we considered the following:

- $<5^{mm}$ induration : unresponsive
- 5-10 ^{mm} induration: suspicious
- $>10^{mm}$ induration: positive test

Those subjects who had induration less than 5mm after 2-3 days received a booster in the 7 th day and results were recorded 48-72 hours later. We used the repeated measurement method for the statistical analysis.

RESULTS

64 out of 67 hemodialysis patients in Labbafi-Nejad's dialysis center were enrolled in the study; three of them were excluded due to prior tuberculosis infection or their unwillingness to cooperate. None of the subjects were HIV-positive and there were no

exclusions due to that. 75% of the patients had a history of BCG vaccination.

The study population included 32(50%) males and 32(50%) females, with the mean age (±SD) of 47.4±18.6 years old (ranging from 10 to 81 years old).The mean duration of dialysis was 52.6±6.5 months (ranging from 4.5 to 206 months).They have been dialyzed averagely 50.6±15.8 months (ranging from 4.5 to 616 months). Of 64 cases tested with PPD, 23(35.9%) had indurations less than 5mm in 48-72 hours; they were classified as unresponsive (table 1). The recorded PPD results in 48-72 hours and in the 7th and 9th days are shown in table1.

Table 1. PPD test results after 48-72h, 7 and 9 days.

	Time period					
PPD result	48-72h (%)		7th day (%)		9th day (%)	
Negative	23	(35.9)	38	(59.4)	42	(65.6)
Positive	12	(18.8)	7	(10.9)	6	(9.4)
Suspicious	29	(45.3)	19	(29.7)	16	(25)

Considering the induration size after one week (recorded on the seventh day), 15 cases (23.4%) remained unchanged, 6 cases (9.3%) had increased induration, 43 cases (67.1%) had a decrease in induration size.

The induration sizes of cutaneous diphtheria-tetanus toxoid tests after 48-72 hours, 7 days and 9 days are shown in table2.

Table 2. Recorded anergy test results after 48-72h, 7th and 9th days

	Time period					
Anergy test result	48-72h (%)		7th day (%)		9th day (%)	
Negative	17	(26.6)	21	(32.8)	21	(32.8)
Positive	47	(73.4)	43	(67.2)	43	(67.2)

Considering the induration size of the anergy test recorded in the 7th day, 12 cases (18.7%) remained unchanged, 13 cases (20.3%) had increased induration, and 39 cases (61%) had a decrease in induration size.

Booster tests were negative in 4(14.8%), and positive in 9(33.3%) cases. The remaining 14 cases (51.9%) had suspicious results.

Through the first reading of PPD and tetanus-diphtheria toxoid cutaneous test results, 23 patients had PPD indurations of less than 5mm and 17 had negative anergy tests (<2mm). 9(52.9%) out of 17 patients with negative anergy tests in the first reading were female and 8(47.1%) were male. 6 out of 17 subjects (35.2%) had indurations >2mm in the 7th day and became responsive. 4(33%) out of the remaining 11patients had responsive PPD tests in the first reading; therefore, they could not be considered anergic. 4 (57.1%) out of the remaining 7 patients who had repeated negative anergy and PPD tests were responsive to a booster, and were thus excluded from the anergic group. Finally, only 3(4.6%) of the total of 64 patients were truly anergic.

There was no significant correlation between the duration of dialysis, age, sex, or history of BCG vaccination, and the condition of cutaneous anergy.

There was, however, a significant difference between induration size of PPD tests recorded on three- separate observations ($p<0001$). There was also a significant variation in the anergy test results in three separate recordings ($p<0.05$).

DISCUSSION

Our study results showed that 18.8% of the hemodialysis patients had positive PPD tests. Furthermore, 26.6% of the patients became anergic through the first evaluation.

In a study conducted by Smirnoff et al. the rate of anergy was estimated to be 45%(12). In Woeltje's study the prevalence of anergy was 33.7%, and 10.3% were reported to have positive PPD tests (13). In another study by Woeltje KF, the prevalence of anergy was reported to be 32%, which is the closest to our study results. In our study, as two studies conducted by Smirnoff and Yildiz (12,14) suggested,

there was no significant correlation between demographic factors such as age; sex; onset and duration of dialysis; BCG vaccination or PPD; and anergy responses.

The only study that has suggested a positive correlation between female gender, duration of dialysis, and anergy is the study conducted by Valderrabano et al. (15). In another study by Vine et al. the prevalence of anergy in the healthy population was reported higher in women. However, our study does not show this difference among hemodialysis patients (16).

Considering the results of cutaneous anergy and PPD test, one can find out the delayed type hypersensitivity phenomenon was evidently present among hemodialysis patients. The incidence of the phenomenon is 9.3% for the PPD test and 20.3% for the anergy skin test. Expansion of induration within a seven- day period can change the negative test result to positive. This phenomenon was previously reported in healthy oriental population living in the United States (17).

Our study however, is the first report on patients undergoing hemodialysis. The results indicate that contrary to the healthy population which have an unchanged size of induration in the first week following the test, the size is most often decreased and sometimes increased in hemodialysis patients. Therefore, special attention must be paid to the analysis of the recordings after 48-72 hours.

Meanwhile, it is important to add the 7th day recording in order to determine the real size of induration. By repetitive recording of induration and conducting booster tests, it is possible to define true anergic patients, including 4.6% of patients in our study.This number is almost equal to the prevalence of anergy in normal population during the first recording (48-72 hours after the test) (18).

Hemodialysis patients are at increased risk of acquiring tuberculosis, showing the need for preventive strategies in this immuncompromised group.

Considering the importance of PPD tests in screening projects for patients undergoing hemodialysis, a new evaluation must be designed including repetitive recording of the test results in days 2-3 and 7 as well as conducting a booster test in the 7th day, if needed. Moreover, in order to interpret negative PPD results, it is important to conduct anergy tests with at least two antigens and evaluate them with repetitive recordings. In the final analysis the combination of anergy and PPD test results must be used together to draw a more precise conclusion. In case of DTH response, the 7th day recording should be considered as the final result.

Finally, it is recommended to design new protocols based on repetitive recording of test results, in order to take advantage of delayed type hypersensitivity skin tests.

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