

## Prevalence of anergy among hospitalized drug users in southern Tehran

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### ABSTRACT

**Background:** Prevention strategies rely heavily on the use of tuberculin test to identify persons harbouring tuberculosis. Anergy undermines these strategies in persons at the highest risk for tuberculosis infection and subsequent active disease.

**Materials and methods:** Patients with a history of drug use for more than 6 month who were admitted in Loghman Hakim and Imam Hussein hospitals between January 2005 and October 2006 were recruited. The tuberculin PPD, tetanus toxoid and candida skin tests were performed and read at 48–72 hours. Anergy was defined as the absence of reaction to either any of the three antigens or by  $\leq 2$  mm induration in response to all of tetanus, candida, and tuberculin antigens.

**Results:** A total of 221 patients (216 male, mean age  $43.5 \pm 14.3$  years) were studied. Tuberculin skin test results showed that 87 subjects (39.4%) tested positive for TB reactivity. Reactivity to tetanus and candida antigens were observed in 214 (96.8%) and 197 (89.1%), respectively. Skin test anergy was found in 5 subjects (2.3%). Anergic cases were all male, HIV seronegative and opium users.

**Conclusion:** Skin test anergy is uncommon among drug users and the PPD skin test may be reliably used for the identification of latent TB infection in the population.

**Keywords:** Drug addiction, Tuberculin test, Anergy, HIV infection  
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### INTRODUCTION

The Tuberculin skin testing is the standard method of identifying individuals infected with *Mycobacterium tuberculosis* (TB). If positive, the patient's risk for developing tuberculosis must be assessed and a clinical decision made as to whether the benefits of chemoprophylaxis outweigh its potential risks (1). However, with human

immunodeficiency virus (HIV) infection, cell-mediated immune function is impaired and anergy-unresponsiveness to skin test antigens- occurs. It is possible, therefore, that an individual may have a negative reaction to the tuberculin skin test and yet be infected with TB (2). Prevention strategies rely heavily on the use of tuberculin purified protein derivative (PPD) to identify persons harbouring TB (3). Anergy undermines these strategies in persons at the highest risk for tuberculosis infection and subsequent active disease (4).

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It has been shown that some opioids (e.g. morphine) can decrease the effectiveness of several functions of both natural and adaptive immunity, and significantly reduce cellular immunity (5). Drug addicted individuals are at an increased risk for tuberculosis, even before the appearance of the acquired immunodeficiency syndrome (AIDS) (4). Several studies have reported high prevalence rates of anergy among IV drug users and HIV infected patients (1,2,4,6-7), but to our knowledge, the impact of drug use by other routes on anergy has not been studied. Our aim was to investigate the prevalence of skin test anergy among hospitalized drug users in southern Tehran.

## PATIENTS and METHODS

This study was conducted in 2 hospitals (Loghman Hakim and Imam Hussein) in southern Tehran, whose patients are mainly from a low socioeconomic class. The study subjects were recruited between January 2005 and October 2006 from patients who were admitted in these hospitals. Eligibility criteria were: age  $\geq 18$  years; self reported use of illicit drugs (opium, heroin, crack, cannabis, norjizak) for at least six months before the time of enrolment; and no treatment for substance abuse within the previous six months. Patients anticipated to be discharged before 48 hours, those admitted in the ICU or with a critical medical condition, decreased level of consciousness (unable to respond to questions), and history of surgery in the last two weeks were excluded.

The study protocol was explained to the patients and those who accepted to participate were asked to provide written informed consent. Participants were interviewed about demographic characteristics, drug use patterns, incarceration history and other risk factors for anergy (corticosteroids, chemotherapy, and rapid weight loss).

The tuberculin skin test (TST) was performed by intradermal injection of 0.1 ml of PPD (5 tuberculin units; Pasteur Institute of Iran) on the volar aspect of the forearm. Study subjects also underwent delayed-type hypersensitivity skin testing with tetanus toxoid (Pasteur Institute of Iran) and candida (Bahar Laboratories, Tehran, Iran). Skin tests were read at 48–72 hours by a trained resident of infectious diseases utilizing the ballpoint technique (8). Anergy was defined as the absence of reaction to either any of the three antigens or by  $\leq 2$  mm induration in response to all of tetanus, candida, and tuberculin antigens. The HIV serostatus was determined using standard ELISA (enzyme-linked immunosorbent assay) techniques with confirmation by Western Blot.

The study protocol was approved by the institutional review board of the Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti Medical University.

Descriptive analyses were used to characterize the study sample and 95% confidence intervals (95% CI) were calculated. Quantitative variables are presented as mean  $\pm$  standard deviation (SD). The Chi-square test (or the Fischer's exact test where appropriate) was used to assess the association between anergy and qualitative variables. The independent samples t-test was used to compare the means of quantitative variables between anergic and non-anergic subjects. A p-value  $< 0.05$  was considered statistically significant. All analyses were performed with SPSS for Windows, version 13.0 (SPSS, Chicago, IL, USA, 2004). Binomial confidence intervals were calculated using 'intercooled STATA 8.0 for windows' (Texas, USA).

## RESULTS

A total of 221 patients (mean age  $43.5 \pm 14.3$  years) were eligible and entered the study. We were able to read the results of the skin tests in all participants in a timely manner. Demographic and

clinical characteristics of participants are summarized in table 1.

**Table 1. Demographic and clinical characteristic of 221 hospitalized drug users in Loghman Hakim and Imam Hossein hospitals, Tehran, Iran**

	No.	Percent (95% CI)
Male sex	216	97.7 (94.8-99.3)
Education		
Illiterate	30	13.6 (9.4-18.8)
Primary	72	32.6 (26.5-39.2)
Intermediate	66	29.9 (23.9-36.4)
High school	46	20.8 (15.7-26.8)
University	7	3.2 (1.3-6.5)
Homelessness	5	2.3 (0.7-5.2)
Marital status: married	168	76.0 (69.8-81.5)
Occupation: working	178	80.5 (74.7-85.5)
Hx of tetanus vaccination	220	99.5 (97.5-99.9)
Incarceration history*	72	32.6 (26.5-39.2)
Hx of common syringe	17	7.7 (4.5-12.0)
Body Mass Index < 20	86	38.9 (32.5-45.7)
Risk factor for anergy		
Systemic steroid	2	0.9 (0.1-3.2)
Chemotherapy	1	0.5 (0.01-2.5)
Rapid weight loss	17	7.7 (16.9-28.2)
Age >55	49	22.2 (4.5-12.0)

\* Mean duration of jail was  $17.8 \pm 29.9$  months in those with a positive history.

Patterns of drug use are presented in table 2.

**Table 2. Patterns of drug use in 221 hospitalized drug users in Loghman Hakim and Imam Hussein Hospitals, Tehran\***

Drugs	Number	Percent	
Opium	Oral	64	29.0
	Inhalation	86	38.9
	Both	5	2.3
Heroin	Inhalation	9	4.1
	Injection	27	12.2
	Both	6	2.7
Crack**	Inhalation	16	7.2
	Injection	8	3.6
	Both	5	2.3
Cannabis	29	13.1	
Norjizak***	12	5.4	

\*Some cases used more than one drug type.

\*\*The drug named "crack" in Iran is not exactly cocaine crack and is a compound mainly consisting of heroin.

\*\*\*This drug is used intravenously and consists of buprenorphine and a very high dose of dexamethasone.

HIV serology was performed in 219 subjects and 7 cases (3.2%, 95% CI: 1.3%-6.5%) were HIV seropositive by ELISA, which was confirmed by Western Blot in two (0.9%, 95% CI: 0.1%-3.3%). The HIV status of the other five uncooperative cases was not determined.

TST results showed that 87 subjects (39.4%, 95% CI: 32.9%-46.1%) tested positive for TB reactivity. Reactivity to tetanus and candida antigens were observed in 214 (96.8%, 95% CI: 93.6%-98.7%) and 197 (89.1%, 95% CI: 84.3%-92.9%), respectively. Skin test anergy was found in 5 subjects (2.3%, 95% CI: 0.7%-5.2%). Anergic cases were all male, HIV seronegative and opium users. One of them was also a heroin IV drug user; two were aged more than 55 years; one was homeless; and three had a BMI less than 20. No risk factor for anergy could be identified in one subject. Statistical tests were unable to detect any significant association between anergy and any of the factors assessed in this study.

## DISCUSSION

Our study found a low rate of anergy among drug users in Tehran, which shows that diminished delayed-type hypersensitivity response in this group of patients is not a significant issue in testing for latent TB infection.

The prevalence of anergy in healthy populations has been reported low (0% to 5%) (2,9-10). A higher rate of anergy was found among prisoners referred to methadone detoxification programs in New York (24.7%) (2) and drug users in Puerto Rico (30.3%) (6). In contrast to these studies, Kunins et al. observed an absent response to a Multitest antigen panel in 3.2% of HIV-seronegative subjects with a history of current or former drug use (11). Our results indicate that the prevalence of anergy among drug users may be similar to that of the general population. The increased prevalence of anergy in the former

studies (2,6) may be related to HIV infection. It has been shown that in populations infected with HIV, the prevalence rises significantly among those with CD4<sup>+</sup> cell counts <200/mm<sup>3</sup> (4,6) and HIV-seropositive patients with CD4 levels above 600 cells/mm<sup>3</sup> were no more likely to be anergic than were controls (4).

PPD reactivity was found in 39.4% of our patients. In a recent report from Iran, Mohraz et al reported reactive PPD in 47.6% of their HIV-seropositive patients with CD4 levels above 500 cells/mm<sup>3</sup> (12). These rates are much higher than the results from drug users in Puerto Rico (8.3%) (6) and New York (15.3%) (1). BCG vaccination and endemicity of TB in Iran may explain this difference.

We did not use a population-based sample of drug users and chose hospitalized patients. However, we believe that immunocompromised patients for other reasons may have been left out by excluding critically ill patients. Medical care costs are heavily subsidized in our hospitals and virtually all costs of deprived patients are covered by the government. In fact, some of our patients were homeless drug users without family support, who were brought to hospital by social services. Therefore, there is no financial barrier for drug users for their access to our centres. Thus, we conclude that our results can be generalized to the population of drug users in southern Tehran.

Skin test anergy is uncommon among drug users and the PPD skin test may be reliably used for the identification of latent TB infection in the population. Whether or not anergy testing should be routinely provided to these patients requires further studies.

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