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Factors associated with positive inhalation provocation test results in subjects suspected of having chronic bird-related hypersensitivity pneumonitis

Masahiro Masuo, M.D., Yasunari Miyazaki, M.D., Kozo Suhara, M.D., Masahiro Ishizuka, M.D., Toshihide Fujie, M.D., Naohiko Inase, M.D.*

Department of Respiratory Medicine, Tokyo Medical and Dental University, Japan

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ABSTRACT

Background: Chronic bird-related hypersensitivity pneumonitis (BRHP) is often misdiagnosed as other interstitial lung diseases. While the utility of the inhalation provocation test (IPT) has been reported, the test is not commonly performed. In this study, we aimed to identify significant clinical variables associated with positive inhalation provocation test results in subjects suspected of having chronic BRHP. This would help clinicians decide whether to perform IPT in patients suspected of having chronic BRHP in real-life practice.
Methods: We retrospectively evaluated 107 patients who underwent the IPT for suspected chronic BRHP. We used the IPT as the gold standard diagnostic tool for chronic BRHP.
Results: Specific antibodies against pigeon dropping extract were documented in 52% of the IPT-positive patients but also in 38% of the IPT-negative patients ($p=0.172$). By using the logistic regression model, three significant predictors of IPT results were identified as follows: (1) a history of raising birds (odds ratio [OR] 3.112), (2) exposure to birds from the surrounding environment (OR 7.321), (3) white blood cell count ($\times 10^2/\mu l$; OR 0.959).
Conclusions: This study demonstrates that current or past exposure to avian antigens is a positive predictor of positive IPT results in patients suspected of having chronic BRHP.

Abbreviations: BALF, bronchoalveolar lavage fluid; BRHP, bird-related hypersensitivity pneumonitis; CVD, collagen-vascular-disease; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IPT, inhalation provocation test; IPT-PS, inhalation provocation test prediction score; LPT, lymphocyte proliferation test; OR, Odds ratio; PDE, pigeon dropping extract; SLB, surgical lung biopsy; TBLB, transbronchial lung biopsy; WBC, white blood cell count.

*Correspondence to: Health Administration Center, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Tel.: +81 3 5803 5079; fax: +81 3 5803 0107.
E-mail addresses: masupulm@tmd.ac.jp (M. Masuo), miyazaki.pilm@tmd.ac.jp (Y. Miyazaki), suhara.pulm@tmd.ac.jp (K. Suhara), mishizuka.pulm@tmd.ac.jp (M. Ishizuka), tfujie.pulm@tmd.ac.jp (T. Fujie), ninase.pulm@tmd.ac.jp (N. Inase).

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1. Introduction

Hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease caused by inhalation of a wide variety of antigens. HP is clinically classified into acute, subacute, and chronic forms [1]. Environmental avian antigens such as pigeon serum, droppings, and feathers produce bird-related hypersensitivity pneumonitis (BRHP), one of the most common variants of HP [2].

A comparison of the registries in Europe indicates that HP represents 4% to 13% of all interstitial lung diseases (ILDs) [3], with an incidence rate of 0.9 cases per 100,000 person-years [4]. In their study, Hanak et al. identified avian antigens as the most common (34%) cause of HP in a population of 85 HP patients in whom the disease was histopathologically confirmed at a rate of 75% (64/85 patients) [5]. An epidemiologic survey of chronic HP in Japan demonstrated that BRHP was the most prevalent form of HP, accounting for over 60% of all chronic HP cases [6].

The clinical characteristics of chronic HP are similar to those of idiopathic pulmonary fibrosis (IPF) [7]. Challenges in in the diagnosis of chronic HP often lead to it being misdiagnosed as IPF [8], while the criteria for diagnosing chronic HP are not well standardized. Positive precipitating antibodies are reported to be significantly predictive of acute and subacute HP (odds ratio 5.3) [9], but the utility of serological tests in the diagnosis of chronic BRHP is controversial [10,11]. Ramírez et al. demonstrated the utility of the inhalation provocation test (IPT) using pigeon serum for the diagnosis of chronic BRHP [12]. Morell et al. recommended that among the noninvasive diagnostic examinations available, the IPT should be regarded as the gold standard [13]. While the methods and criteria for the IPT are yet to be standardized, the utility of the test is becoming well known [14]. In our practice, we also use the IPT as the gold standard diagnostic tool for chronic BRHP. The sensitivity and specificity of the IPT for diagnosing chronic BRHP in our previous study were as high as 92.9% and 94.7%, respectively [15].

In the present study, we aimed to identify significant clinical variables associated with positive IPT results in subjects suspected of having chronic BRHP. This would help clinicians decide whether to perform IPT in patients with suspected chronic BRHP in real-life practice.

2. Materials and methods

2.1. Study population

The medical records of patients with ILDs who were admitted at the Tokyo Medical and Dental University Hospital between January 2004 and March 2013 were retrospectively reviewed. The patients underwent IPT with pigeon dropping extract (PDE) if they were suspected of having BRHP based on their history of avian antigen exposure, findings on high-resolution computed tomography (HRCT), lung biopsy findings, or results of immunological examinations with the lymphocyte proliferation test (LPT) or specific antibodies to avian antigens. Chronic BRHP was diagnosed based on IPT results. The patients diagnosed with chronic BRHP and those diagnosed with other chronic ILDs were then assigned to IPT-positive and IPT-negative groups, respectively.

The following clinical variables on admission were analyzed: (1) clinical background; (2) clinical history, including a history of raising birds, exposure to birds from the surrounding environment, and the use of feather quilts; (3) physical examination findings; (4) blood work, including measurement of levels of anti-PDE antibodies and LPT; (5) pulmonary function test; (6) HRCT; and (7) bronchoalveolar lavage fluid (BALF). We obtained detailed clinical history about antigen exposure by a questionnaire about antigen exposure.

Serum anti-PDE antibodies, LPT, and BALF were not routinely measured on admission, so we used the closest variables before performing the IPT. Levels of serum or BALF antibodies against PDE and LPT of the peripheral blood mononuclear cells were assessed according to techniques developed in our hospital [16]. Information about this protocol was disclosed to the study participants through the institutional review board, on the Web page, and was approved by the ethical research committee of the Tokyo Medical and Dental University in accordance with the Declaration of Helsinki (approval date: July 29, 2014; Approval no. 1840). The requirement for written informed consent was waived.

2.2. Antigen

Fresh PDEs were collected and stirred with 20 volumes of phosphate-buffered saline solution for 24 h. The extracts were saturated with 50% ammonium sulfate to obtain a partially purified fraction. The partially purified fraction was extensively dialyzed against distilled water, lyophilized, and stored in small portions at −20 °C. Before the IPT, 10 mg of freeze-dried PDE was stirred with 1 mL of distilled water and centrifuged three times at 12,000 revolutions/min for 30 min. The supernatant was collected and sterilized by filtration (Millex-GV, Millipore; Bedford. MA). The protein concentration in the PDE was 340 μg/ml.

2.3. Inhalation provocation tests

The patients inhaled 2 ml of 10 mg/ml PDE through a hand nebulizer. The maximal exposure duration to the antigen was approximately 10 minutes, as previously described [17]. Chronic BRHP was diagnosed based on the IPT prediction score (IPT-PS) as follows: IPT-PS = 1 × Δwhite blood cell count (WBC; %) + 2 × ΔP[A − a] O_2 (mmHg). The sensitivity and specificity of the IPT-PS were both confirmed to be high (92.9% and 94.7%, respectively). WBC and arterial blood gas levels were measured immediately before and at 6 and 24 h after the challenge. The cutoff IPT-PS was set as 35 [15].

2.4. High-resolution CT evaluation

HRCT scans were analyzed at the level of the aortic arch, carina trachea, right pulmonary vein, and top of the right diaphragm in each lung. Each image was reviewed independently by two experienced respiratory physicians (Y.M. and M.M.). Fibrotic change was evaluated based on the Kazerooni fibrosis score [18]. Ground-glass opacity and micronodules were graded on a scale of 0–5 as follows: 0 (0% of lung

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