Precipitins in bird breeder's disease: how useful are they?

C. Reynaud*, D.O. Slosman**, B.S. Polla*

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ABSTRACT: Precipitating antibodies to avian antigens play a controversial role in the diagnosis of bird breeder's disease (BBD). In order to establish the sensitivity, specificity and accuracy of precipitins in our laboratory, we conducted a prospective study including 128 sera received in 1988 for determination, by immunoelectrophoresis, of avian precipitins. Accurate information was obtained for 90 patients; definitive clinical diagnosis was given by the patient's own physician. We found a high sensitivity (86%), specificity (93%) and accuracy (92%) of avian precipitins in the diagnosis of BBD. Bayes' theorem was applied to determine the predictive value of the test with varying disease prevalence, and established that precipitins were particularly valuable for low or medium a priori probability. Using the receiver operating characteristic (ROC) curve we evaluated the effects of varying the positivity threshold of precipitins. The threshold used in this study appeared to offer the best compromise between sensitivity and specificity. These results suggest that the diagnostic value of avian precipitins in the work-up of BBD should be reconsidered, also because they represent a simple, cheap and non-invasive diagnostic test.

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For a long time inhalation of organic dusts by sensitized subjects has been known to be involved in the pathogenesis of extrinsic allergic alveolitis (EAA). Whereas farmer's lung is most common in rural areas, bird breeder's disease (BBD) is frequently encountered in urban environments. Although the diagnosis of EAA is straightforward when the patients report typical symptoms and a specific antigen exposure, in many cases, the aetiological diagnosis remains elusive because of the difficulties in correlating the patient's history with a specific antigen. Besides precipitins, many different tests have, therefore, been used in the diagnostic work-up of EAA and in particular in BBD: skin tests, specific immunoglobulin E (IgE) or immunoglobulin G, (IgG), determinations, activity of serum angiotensin converting enzyme, bronchoscopy with transbronchial biopsies and/or bronchoalveolar lavage and analysis of T-lymphocyte subpopulations [1–5]. None of these methods, however, can definitely differentiate between antigen exposure and disease.

Since the initial description of BBD, in 1965 [6], demonstration of precipitating antibodies to avian antigens has played an important but controversial role in the diagnosis of this disease. Most studies report a high percentage of positive precipitins among exposed subjects without BBD [7–9]. Several methods for determination of precipitins or total IgG antibodies (immunodiffusion, immunoelectrophoresis, enzyme-linked immunoabsorbent assay (ELISA)) and different antigen preparations (crude sera, purified avian serum proteins, purified components from avian droppings) have been investigated and compared [10–13]. However, the sensitivity and specificity of avian precipitins in the diagnosis of BBD have not been studied in detail.

In order to establish the sensitivity, specificity and accuracy of avian precipitins in the diagnosis of BBD, we have undertaken a prospective study including all sera sent to our laboratory for this purpose during 1988. The sera of 128 patients sera were tested by immunoelectrophoresis against crude avian sera or dropping extracts. To optimize the use of our tests in the clinical decision process Bayes' theorem was then applied to determine the predictive value of the test with varying disease prevalence [14]. Using the receiver operating characteristics (ROC) curve [15] we also evaluated the effects of varying the positivity threshold of precipitins (from one to three precipitation arcs) on true positive and false positive fractions.

Patients and methods

Subjects

During 1988, we have received from private doctors or hospitals throughout Switzerland, 128 sera for
determination of serum precipitins against avian antigens. Patient’s own physicians gave us their definitive clinical diagnosis within 9 mths after precipitin determination. They answered a specific questionnaire including: exposure to birds, symptoms (dyspnoea, cough, fever), chest X-ray, pulmonary function tests, and histology when performed, as well as smoking history. We obtained accurate clinical and biological information for 99 patients (77%). Nine cases were excluded because of uncertainty regarding diagnosis by the end of the study. Our study was, therefore, based on 90 patients. In addition, as a non-exposed control group, we selected 12 healthy, normal controls, of which all except one were nonsmokers.

The “gold standard” used in this study for positive diagnosis of BBD was the physician’s final diagnosis; indeed, there is as yet no other recognized “gold standard” for the diagnosis of BBD, and histology was obtained in too few cases (10%) to be used as such. In order to control the validity of the diagnosis, we established a clinical score of probability to have BBD using the five criteria described above. The score was established as follows: i) definite exposure to birds = 2, doubtful exposure =1, no exposure = 0; ii) three symptoms (dyspnoea, cough and fever) = 2, one or two of these symptoms = 1, no symptoms = 0; iii) diffuse reticulonodular or interstitial infiltrate = 2, localized infiltrate or other alterations =1, normal chest X-ray or examination not performed =0; iv) decreased total lung capacity or alterations in carbon monoxide diffusion test = 2, obstructive lung disease=1, normal pulmonary function test or test not performed = 0; and v) histology or bronchoalveolar lavage compatible with EAA = 2, other alterations in lung histology = 1, histology normal or not obtained = 0.

**Statistical analysis**

The sensitivity (TP/(TP+FN)) corresponds to the ratio of patients that have the disease and a true positive test (TP) to all patients with the disease and with either a true positive test or a false negative test (FN). The specificity (TN/(TN+FP)) corresponds to the ratio of patients that do not have the disease and have a true negative test (TN) to all patients without the disease and with either a true negative test or a false positive test (FP). Accuracy corresponds to the ratio of all true diagnostic tests (TN+TP) to all tests, whether true or false (TN+TP+FN+FP).

To estimate the *a posteriori* probability that a patient does have the disease given a positive or a negative result, Bayes’ theorem was used, provided an estimate of the *a priori* probability of the disease (the prevalence of the disease) [17]. Bayes’ theorem is a classical way to determine the impact of the result of a test (precipitins) on the clinical diagnosis (*a posteriori* probability). Bayes’ theorem also allows determination of the situations in which the test’s result is most helpful, i.e., does modify the subsequent clinical decision process.

With the receiver operating characteristics (ROC) curve, by plotting the FP fraction against the TP fraction and varying the threshold of precipitin positivity from + to ++++, we defined the positivity threshold offering the best compromise between lowest FP fraction and highest TP fraction [18, 19].

To compare the intensity of precipitin results between the TP and the FP fraction we used a non-parametric test (Mann Whitney U test). To compare the intensity of precipitin results using budgerigar dropping or sera as antigens we used the Spearman coefficient of correlation and the paired Wilcoxon test.

**Results**

**Patients and diagnosis**

Ninety patients, 52 women and 38 men, aged 44.3±18.5 yrs (mean±std) have been included in this study. Fourteen patients (16%) have been diagnosed as having BBD (42±17 yrs, 9 women, 5 men). Among the 14 patients with BBD, all were exposed to birds, either at home, or at home and in their work place; 12 were nonsmokers and 2 ex-smokers. The clinical presentation of the 14 patients having BBD is shown in table 1.

Among the 76 patients without BBD 45±19 yrs, 43 women, 33 men), 70 (92%) were exposed to birds; 58 (76%) were nonsmokers or ex-smokers. For these 76 patients without BBD, the final diagnosis included asthma (30 cases), interstitial pneumonopathy (6 cases), chronic bronchitis (6 cases), upper respiratory tract infection (4 cases), pneumonia (4 cases) and psittacosis (2 cases). In 10 cases, BBD was definitively excluded, but no other precise diagnosis was made. The remaining diagnosis, in one or two cases each, were chronic obstructive lung disease, adult respiratory
Table 1. – Clinical presentation of the 14 patients with BBD

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Exposure</th>
<th>Tobacco</th>
<th>Symptoms</th>
<th>Chest X-ray</th>
<th>Pulm. func.</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>52</td>
<td>home</td>
<td>0</td>
<td>D,C,F</td>
<td>interstitial diff.</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>48</td>
<td>home</td>
<td>0</td>
<td>D,C</td>
<td>reticulo. nod. diff.</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>18</td>
<td>home</td>
<td>0</td>
<td>D</td>
<td>interstitial diff.</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>50</td>
<td>home</td>
<td>0</td>
<td>D,C</td>
<td>other</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>54</td>
<td>home</td>
<td>0</td>
<td>D,C</td>
<td>interstitial restr.</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>38</td>
<td>home/work</td>
<td>0</td>
<td>D</td>
<td>interstitial restr. +</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>45</td>
<td>home</td>
<td>ex sm.</td>
<td>C,F</td>
<td>interstitial normal</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>20</td>
<td>home</td>
<td>0</td>
<td>D</td>
<td>interstitial restr. +</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>35</td>
<td>home</td>
<td>0</td>
<td>D,C,F</td>
<td>interstitial restr. +</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>40</td>
<td>home</td>
<td>0</td>
<td>D,C</td>
<td>normal</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>56</td>
<td>home</td>
<td>0</td>
<td>D</td>
<td>interstitial restr. +</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>44</td>
<td>home</td>
<td>ex sm.</td>
<td>D,C,F</td>
<td>interstitial restr. ND +</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>13</td>
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<td>13</td>
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<td>D,C,F</td>
<td>other</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>10</td>
<td>home</td>
<td>0</td>
<td>D,C</td>
<td>interstitial restr. +</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

F: female; M: male; ex sm: ex-smoker; D: dyspnoea; C: cough; F: fever; interstitial: interstitial infiltrate; reticulo. nod: reticulonodular infiltrate; other: other alteration; diff.: diffusion trouble; restr.: restrictive syndrome; ND: not done; +: alveolitis or lympho-plasmocytic infiltrate or bronchoalveolar lavage compatible with EAA; BBD: bird breeder's disease; EAA: extrinsic allergic alveolitis.

Table 2. – Clinical score from 0 to 10, established for the 90 patients using the five criteria described under "patients and methods", and their repartition into four groups, according to diagnosis and precipitins’ results

<table>
<thead>
<tr>
<th>Score</th>
<th>All included</th>
<th>BBD+ Precipitins+</th>
<th>BBD+ Precipitins-</th>
<th>BBD- Precipitins-</th>
<th>BBD- Precipitins+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
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<tr>
<td>2</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>-</td>
<td>-</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
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<td>-</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>2</td>
<td>-</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
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<td>7</td>
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<td>2</td>
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<tr>
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<tr>
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<tr>
<td>10</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Total 90 12 2 71 5

BBD: bird breeder's disease.

distress syndrome, alveolar carcinoma, systemic lupus, sarcoidosis, tuberculosis, cardiac failure or psychogenic dyspnoea.

The diagnosis was established in a hospital or by a pulmonary specialist in 12 of the 14 cases having BBD, and in 66 of the 76 cases not having BBD. In the remaining 12 cases, the diagnosis was established by a generalist (9 cases), an internist (1 case), an allergologist (1 case) or a cardiologist (1 case).

Using the diagnostic criteria previously described, clinical scores were defined for each patient. With these criteria, 12 of the 14 patients with BBD had a clinical
score at or above 6, and 68 of the 76 patients not having BBD had a score at or below 5 (table 2). With the exclusion of histology or bronchoalveolar lavage, which were obtained in only nine patients (5 TP and 4 TN) there was no significant difference between the number of criteria obtained in patients having or not having BBD. In the 14 patients having BBD (TP and FN), 4 criteria were obtained in 8 cases and 3 in 1 case. For the 76 patients not having BBD (TN and FP), 4 criteria were obtained in 53, 3 criteria in 18 and 2 criteria in 1 patient.

Table 3. - Matrix relating diagnostic test result (presence or absence of precipitins) to the presence or absence of the disease (BBD)

<table>
<thead>
<tr>
<th></th>
<th>T+</th>
<th>T-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+</td>
<td>12 (TP)</td>
<td>2 (FN)</td>
<td>14</td>
</tr>
<tr>
<td>D-</td>
<td>5 (FP)</td>
<td>71 (TN)</td>
<td>76</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>73</td>
<td>90</td>
</tr>
</tbody>
</table>

T: test; D: disease; TP: true positive; FP: false positive; FN: false negative; TN: true negative. Sensitivity: (ability of a test to identify the patients with the disease in the population tested) = TP/(TP + FN) = 86%. Specificity: (ability of a test to identify the absence of the disease in the population tested) = TN/(TN + FP) = 93%. Accuracy: (TP + TN)/(TP + TN + FP + FN) = 92%.

Precipitin results: sensitivity and specificity

Among the 14 patients with BBD, precipitins against avian antigens were present in 12. There were no precipitins detected in 71 out of the 76 patients having another disease. Therefore, the sensitivity of avian precipitins to detect BBD was 86%, their specificity 93%, and their accuracy 92% (table 3). There was no significant difference as to sex or smoking habits among the four groups of patients as classified in table 3 (TP, FP, TN, FN). None of the 12 non-exposed healthy controls had any precipitin.

As described previously [16] we found an important cross-reactivity between the different bird species, but precipitins against birds to which patients were exposed were always present, and usually more important. Budgerigar was the bird most frequently involved in BBD: 67% of the TP group were indeed exposed to budgerigar. The intensity of precipitins varied from + to +++ for the TP group and from + to ++(+) for the FP group. There were no significant differences in the intensity of precipitins between these two groups (using the Mann Whitney U test). On the other hand, we found a good correlation between precipitins results obtained using either budgerigar droppings or budgerigar sera as antigens (Spearman correlation coefficient: r=0.91) and, in no patient without precipitins against antigens from bird sera did we find any precipitins against dropping antigens.

Bayes' theorem and ROC curve

Figure 1 shows the graphic expression of Bayes' theorem for both positive and negative tests. Bayes' theorem application shows that in our study population precipitins are most useful for low or medium a priori probability. For example, when the a priori probability to have the disease is 50%, the a posteriori probability increases to 92% with a positive test, whereas a negative
test reasonably allows to exclusion of the diagnosis (a posteriori probability, 13%). The ROC curve (fig. 2) on the other hand, indicates that the threshold settled at 1+ gives the best compromise between an acceptable false positive fraction (FPF=7%) and the highest sensitivity (TPF=85%). Indeed, when we varied the precipitins’ positivity threshold (more than 1+), we observed that any increase in specificity was at the expense of a disproportionate loss in sensitivity: for example, given a positive precipitin test at 3+ the specificity increased to 100% (FPF=0%) but the sensitivity decreased from 86% to as low as 14%.

Discussion

In this study, we investigated the sensitivity and specificity of avian precipitins in the diagnostic evaluation of BBD. In our study population and with the methods used (immunoelectrophoresis and crude bird sera), we found high sensitivity (86%), specificity (93%) and accuracy (92%) of avian precipitins in the diagnosis of BBD. The low ratio of false positive results found in our study (5.6%) contrasts with previous reports. Reeb et al. [6], who reported the first three cases of BBD, already mentioned that seven members of a local pigeon racing club, none of whom had any symptoms related to their contact with pigeons, had precipitinating antibodies against avian antigens; however, the authors suggested that there may be a quantitative difference in the amount of precipitins between asymptomatic exposed subjects and symptomatic patients. In our study there was an important variation in the intensity of precipitins and we found no significant difference between the TP and the FP group with respect to the intensity of positivity. It is possible that this lack of difference is due to a type β error [20] (only 12 and 5 cases, respectively): increasing our patients samples may well unmask a significant difference of intensity of precipitins between TP and FP [20].

Taking into account the sensitivity and specificity of avian precipitins, and the clinical a priori probability of BBD, the application of Bayes’ theorem indicated that precipitins are most helpful when the clinical estimate of BBD is low to medium. On the other hand, sensitivity and specificity are dependent upon the criteria used to define a positive test; changes in this threshold will result in corresponding changes in the FPF and TPF. The ROC curve indicated that the threshold used represented indeed the best compromise between sensitivity and specificity.

A number of potential biases have been ruled out in our study. Firstly, there were no differences among groups with respect to sex, smoking habits, age, bird exposure, or the type of physician who made the diagnosis. Secondly, the prevalence of BBD among our cases (16%) was similar to that reported by others: Christensen et al. [8] for example investigated 53 pigeon fanciers and found a clinical picture compatible with BBD in 21%. Thirdly, since in our study population all patients were symptomatic and BBD was suspected in all of them, if anything, this should actually upgrade our specificity. Because of the design of the study, we could not precisely determine the impact of positive test results on the physicians diagnosis. Because the literature available to date reports a high ratio of positive precipitins in healthy controls [6–9] it is, however, unlikely that the clinicians’ diagnosis relied solely on a positive test. Furthermore, we applied a clinical score based on a combination of characteristic symptoms, physical findings, chest X-ray abnormalities, pulmonary function, and histology or bronchoalveolar lavage, excluding the precipitin’s results. The agreement between the diagnosis made using these criteria with the physicians diagnosis suggests again that the test’s results were not essential for the physicians’ diagnosis. In any case, the knowledge, by the physicians, of positive precipitins could not artificilly decrease the FP number, and hence not affect specificity.

The review by Christensen et al. [8] emphasizes that the diagnosis of BBD is best made by a clinical score; indeed, in their study of the prevalence of the disease, the diagnosis of BBD was based on the association of systemic and local symptoms. Although a clinical score may not always be a gold standard per se, in the case of BBD the only alternative procedure, i.e. inhalation provocation tests, is disputed by many authors, and has been considered hazardous, “unnecessarily distressing” and not sensitive enough [21]. Terho [13] thinks that provocation tests for EAA are seldom justified ethically, whereas Harriss et al. [22] propose provocation tests to be used for the diagnosis of EAA only when chest X-ray remains normal. In “guidelines for the clinical evaluation of hypersensitivity pneumonitis” [23], the authors consider provocation tests as a research procedure, not required nor recommended for diagnosis. Indeed, no standardized antigens or techniques are available, thus interpretation of results may be difficult.

The nature of the antigens used is probably important in determining the accuracy of the test. Indeed, Barborak et al. [7] have investigated 200 asymptomatic pigeon breeders and found precipitins against bird droppings in over 40%. In contrast, precipitins were positive in only 20% of the same population when they used bird sera as antigens. Bergmann et al. [10] also found an increased FP ratio when using pigeon droppings as compared to pigeon serum. In our study, although the precipitins against serum antigens were usually more intense than against droppings antigens, we did not find any difference between these two antigens for the bird tested, i.e. budgerigar, the commonest species involved in BBD in our series. Finally, the method used could also be important in the results obtained, although the 90% agreement of results found in an inter-laboratory study comparing the Ouchterlony test with immunoelectrophoresis and immunofluorescence makes this possibility rather unlikely [10]. The comparison between immunoelectrophoresis and immunodiffusion has already been made for farmer’s lung antigens and has established that immunoelectrophoresis is identical to immunodiffusion in Agar gels with respect to qualitative detection of precipitins, and superior for quantitation.

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Skin tests
Specificity
In
lnunu­
Immmoglobulin E antibodies
"Farmer's
Patory srudy .
Precipitins to inhaled avian. antigens: results of an
Achterrath
11. Calvanico NI. - A component of pigeon dropping extract
8. Christensen LT,
5,
433-437.
3. Kitt
77, 262.
Barboriak
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Dans quelle mesure la détermination des précipitines est-elle utile dans la maladie des oiseleurs? C. Reynaud, D.O. Slosman,
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RÉSUMÉ: En raison du nombre élevé de précipitines positives
chez des sujets exposés mais en bonne santé, les anticorps
préципitins contre des antigènes aviaires jouent un rôle
controversé dans le diagnostic de la maladie des oiseleurs. Afin
prospective incluant les 128 séums reçus en 1988 pour la détection, par immunoélectrophorèse, de ces précipitines. Des informations cliniques complètes et le diagnostic définitif du médecin traitant ont été obtenus pour 90 patients. En classant les patients en 4 groupes selon leur diagnostic et les résultats des précipitines nous avons trouvé une haute sensibilité (86%), spécificité (93%) et précision du test (92%). Le théorème de Bayes a ensuite été appliqué afin de déterminer la valeur prédictive du test en variant la prévalence de la maladie, et nous avons pu établir que le résultat des précipitines est particulièrement utile pour de faibles ou moyennes probabilités “a priori”. En utilisant la courbe ROC (receiver operating characteristics) nous avons évalué les effets de la variation du seuil de détection des précipitines. Les résultats indiquent que le seuil de détection utilisé dans cette étude donne le meilleur compromis entre la sensibilité et la spécificité. Ces données suggèrent donc que la valeur des précipitines positives ou négatives - dans l’établissement du diagnostic de maladie des oiseleurs doit être reconsiderée, aussi du fait que les précipitines sont un test diagnostique simple, bon marché et non invasif.

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