

Classification of Hypersensitivity Pneumonitis

A Hypothesis

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Key Words

Hypersensitivity • Pneumonitis, classification • Extrinsic allergic alveolitis • Cluster analysis

Abstract

Background: Regardless of the causative antigen, hypersensitivity pneumonitis (HP) is usually classified as 'acute', 'subacute' or 'chronic'. Considerable confusion still surrounds this classification because there are no widely accepted criteria to distinguish the various stages. The objective of this study was to determine whether the current classification of HP truly reflects categories of patients with distinct clinical features. **Methods:** Data obtained from a large prospective multicenter cohort study (the HP Study) were used to divide a cohort of patients with HP into a limited number of categories (clusters) with maximally differing clinical patterns, without prejudgment. The results of this cluster analysis were compared with the current classification of HP (acute, subacute or chronic). **Results:** 168 patients were included in the analysis. A 2-cluster solution best fitted the data. Patients in cluster 1 (41 patients) had more recurrent systemic symptoms (chills and body aches) and normal chest radiographs

than those in cluster 2 (127 patients) who showed significantly more clubbing, hypoxemia, restrictive patterns on pulmonary function tests and fibrosis on high-resolution computed tomography (HRCT). All p values were <0.0001, using Fisher's exact test. Nodular opacities were seen on HRCT as often in cluster 1 as in cluster 2. There was considerable disagreement between the current classification of HP and the results of our analysis. **Conclusion:** The current classification of acute, subacute and chronic HP is not supported by our analysis. Subacute HP is particularly difficult to define.

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Introduction

Hypersensitivity pneumonitis (HP) is a pulmonary disease with symptoms of dyspnea and cough resulting from the inhalation of an antigen to which the subject has been previously sensitized [1]. HP is typically classified as 'acute', 'subacute' or 'chronic' (table 1) [2]. Considerable confusion surrounds this classification, which is strictly based on patients' clinical presentation rather than patho-

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Table 1. Richerson's classification of HP [2]

Classification	Clinical description
Acute HP	Symptoms begin 2–9 h after exposure, peak typically between 6 and 23 h, and last from hours to days. Influenza-like symptoms often predominate: chills, fever, sweating, myalgias, lassitude, headache and nausea. Respiratory symptoms, such as cough and dyspnea, are common but not universal.
Subacute HP	May appear gradually over several days to weeks. Marked by cough and dyspnea, and may progress to severe dyspnea and cyanosis, leading to hospitalization.
Chronic HP	Insidious onset over a period of months. Increasing cough and exertional dyspnea. Fatigue and weight loss may be prominent symptoms.

physiological processes. This classification was suggested well before the use of computed tomography to describe HP [3–6]. HP can have a distinctive histologic appearance when bronchiolocentric cellular interstitial pneumonia, noncaseating granulomas and organizing pneumonia are seen [7, 8]. However, it is not clear whether these histologic findings represent subacute or chronic changes, although fibrotic remodeling is assumed to reflect chronicity [9, 10]. Moreover, little is known about the histologic findings of acute HP [7, 8].

The classification is further complicated by the fact that chronic HP may still be active and progressive. It has been suggested that classification should take into account the progression of the disease (acute intermittent, acute progressive, chronic progressive, chronic nonprogressive), but this can only be assessed retrospectively [11, 12]. A recent workshop by the National Heart, Lung, and Blood Institute (NHLBI) proposed to classify cases considered to be chronic HP as 'recurrent' or 'insidious' [12]. We have previously proposed that HP patients should be considered as having either active or residual disease, the latter representing late emphysematous or fibrotic sequelae of the disease in which the typical alveolar lymphocytosis of active HP has disappeared [13]. None of these suggestions have been validated.

We took advantage of the HP Study [14], a large prospective multicenter cohort study designed to develop a clinical prediction rule for the diagnosis of HP, to determine whether the current classification of HP (i.e.

acute, subacute or chronic) truly reflects categories of patients with distinct clinical features. This study is in response to the NHLBI workshop's recommendation that disease phenotypes should be better characterized [12].

Subjects and Methods

Patients

Details regarding the methods and results of the HP Study have been published elsewhere [14]. In brief, consecutive patients aged ≥ 18 years who presented with a pulmonary syndrome for which active HP was considered in the differential diagnosis were eligible for the study. This cohort thus included patients with and without HP in a proportion that was unspecified a priori. The current analysis involves only those whose final diagnosis was HP.

Diagnostic Procedures

Clinical data were systematically recorded for every patient before the final diagnosis was obtained. Symptoms and physical signs were recorded on a standardized form during the initial clinical interview. Symptoms and physical signs were recorded as present or absent. Spirometry was performed according to the American Thoracic Society requirements [15]. Lung volumes were measured by plethysmography [16]. Carbon monoxide diffusion capacity (D_{LCO}) was measured with the single-breath method [17]. Predicted values currently used within each laboratory were accepted. Arterial blood gases were measured while breathing room air. Partial pressure in oxygen was adjusted for altitude and reported as if obtained at sea level [18]. Serum precipitating antibodies against suspected antigens were tested in all patients using either ELISA or electrosyneresis [19]. In each center, the investigators selected a panel of antigens most likely to be encountered in their respective environment. The presence of antinuclear antibodies was tested by indirect immunofluorescent antibody staining of fixed cells [20]. Precipitating antibodies and antinuclear antibodies were reported as either positive or negative, according to a center-specific predefined threshold value. The chest radiograph available at the time of the consultation with the investigator was used for assessment.

The final diagnosis of HP relied on high-resolution computed tomography (HRCT), bronchoalveolar lavage (BAL) and the opinion of experts. BAL lymphocytosis ($\geq 30\%$ for non- and ex-smokers, and $\geq 20\%$ for current smokers [21]) and HRCT findings compatible with HP were required for the diagnosis of HP to be accepted. When the association of both HRCT and BAL did not allow the investigators to confidently arrive at a final diagnosis, the decision regarding additional procedures (including surgical lung biopsy) was left to the investigators, according to their usual practice. An adjudication committee composed of 4 clinicians, 1 pathologist and 1 radiologist was responsible for the ascertainment of the final diagnosis (HP vs. non-HP). Finally, cases were categorized as acute, subacute or chronic HP according to Richerson's classification (table 1) by the submitting investigator.

Statistical Analysis

Cluster Analysis. Cluster analysis is a statistical tool used to search for subjects with similar attributes in a data set [22]. We used cluster analysis to divide our study population into a limited number of categories (clusters) with maximally differing clinical patterns, without prejudgment. The clinical variables included in the analysis are listed in table 2. One should note that we purposely chose not to consider the duration of symptoms, because patients' ability to recall past health-related events is very limited and such data lack validity [23]. Therefore, clinical evaluation was limited to current symptoms. This analysis consists of merging the 2 closest individuals or clusters to form a new cluster that replaces them and iterating the process with the new group until complete regrouping. We used the hierarchical agglomerative clustering method with Ward's minimum variance and Gower's distance methods [24, 25], and decided on the number of clusters that best fit the data set from the highest pseudo F statistic [26].

Internal Validation. Cross-validation is necessary to minimize the bias produced by having clusters developed to fit the data. We used the leave-one-out method in which the data from 1 subject at a time are excluded before obtaining new clusters using all of the remaining data, and then seeing if the new clusters correctly classify the excluded patient [27]. The misclassification rate corresponds to the proportion of incorrectly classified patients.

Clusters versus Richerson's Classification. In order to examine the proportion of patients with acute, subacute or chronic HP in each of the k clusters obtained from the cluster analysis, we constructed a 3 × k contingency table (acute HP, subacute HP, chronic HP vs. cluster 1, cluster 2, ... cluster k). We compared these proportions using a χ^2 test. In addition, we examined the concordance between the 2 classifications using the Goodman and Kruskal λ statistic. This statistic is interpreted as the probability of improvement in predicting the results of a classification scheme given knowledge of the results of another classification [28]. A λ of 0 would indicate total disagreement, whereas a λ of 1 would indicate perfect agreement. In this analysis, the level of significance was set at 0.05.

Description of Clusters. Finally, we used descriptive statistics (proportions, means and standard deviations when appropriate) to describe the clusters that we also compared using the Fisher's exact test for categorical variables and the nonparametric Mann-Whitney test for continuous variables. Given the large number of planned statistical comparisons, the level of statistical significance was set at 0.001.

Results

Patients

We enrolled 199 patients with HP in the HP Study. 31 were excluded from the cluster analysis because of missing data in one or the other of the variables used, leaving 168 patients to contribute to the analysis (table 3). Of note, 93 of the 115 patients (81%) considered as having chronic HP had either pigeon breeder's or bird fancier's disease.

Table 2. Variables included in the cluster analysis

Domain	Variables
Clinical symptoms/history	Gender, smoking status, wheezing, cough, tightness of chest, chills, body aches, weight loss, recurrent symptoms after exposure
Physical signs	Fever, cyanosis, clubbing, inspiratory crackles, wheezing
Blood work	Positive serum precipitins, antinuclear antibodies, pO ₂
Pulmonary function tests ¹	FEV ₁ % predicted, FEV ₁ /FVC, FEF _{25–75%} , D _{LCO} % predicted
Chest radiograph	Site of abnormalities (normal chest X-ray vs. upper zone predominance vs. lower zone predominance vs. diffuse infiltrates)
HRCT	Ground-glass infiltrates, nodular opacities, fibrosis
BAL	Lymphocyte count (%)

¹ FEV₁ % predicted = forced expiratory volume in 1 s, percent of predicted value; FVC = forced vital capacity; FEF_{25–75%} = forced expiratory flow, percent of predicted value; D_{LCO} % predicted = carbon monoxide diffusion lung capacity, percent of predicted value.

Table 3. Distribution of diagnoses

	Richerson's classification		
	acute HP	subacute HP	chronic HP
Pigeon breeder's/bird fancier's disease	5	15	93
Farmer's lung	17	5	13
Humidifier's lung	0	1	0
Suberosis	0	0	1
Summer type HP	1	0	0
Various exposures to fungi	5	4	6
HP of unknown origin	0	0	2
Total	28	25	115

Cluster Analysis

A 2-cluster solution best fitted the data (pseudo F statistic 40.1; fig. 1). Cluster 1 included 41 patients whereas there were 127 in cluster 2. The comparison between the results of the cluster analysis and Richerson's classification is presented in table 4. The result of the χ^2 test only indicated that the proportions of patients with acute, sub-

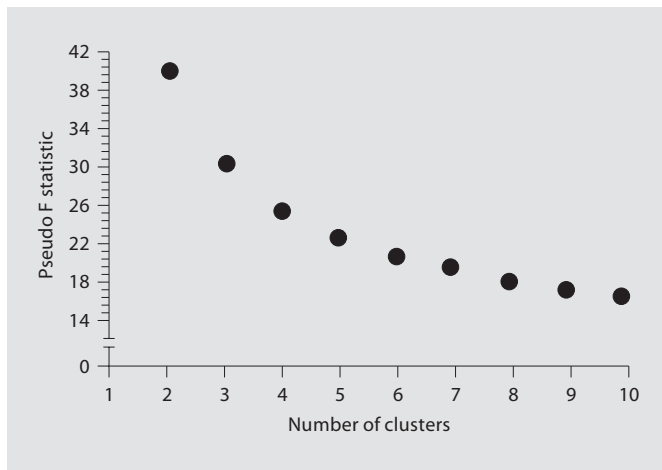


Fig. 1. Cluster analysis divides a population into a limited number of categories (clusters) with maximally differing clinical patterns. The number of clusters that best fits the data is from the highest pseudo F statistic.

Table 4. Comparison between the results of the cluster analysis and patient classification according to Richerson's definitions

Cluster	Richerson's classification			Total
	acute HP	subacute HP	chronic HP	
1	21	7	13	41
2	7	18	102	127
Total	28	25	115	168

acute or chronic HP in each of the 2 clusters were different (total χ^2 49.72, degrees of freedom 2, $p < 0.0001$). However, we found considerable disagreement between the 2 classification schemes. The probability of improving the prediction of the results of Richerson's classification given the results of the cluster analysis was not statistically significant from total disagreement (λ 0.15, $p = 0.13$).

Internal Validation

Of the 41 patients in cluster 1, 38 were correctly identified to this cluster in the validation studies. Similarly, 124 of the 127 patients in cluster 2 were correctly identified to this cluster. Overall, the misclassification rate was only 3.6%.

Clinical Manifestations: Cluster 1 versus Cluster 2

We compared the clinical features of the patients in cluster 1 to those in cluster 2 (table 5). Patients in cluster

Table 5. Comparison between the 2 clusters of patients with HP

	Cluster 1 (n = 41)	Cluster 2 (n = 127)	p value
Clinical symptoms/history			
Gender, % male	68	12	<0.0001
Age, years	46 (10)	50 (13)	0.06
Current smoker, %	12	1	0.004
Exposure to antigens, %	100	97	0.6
Dyspnea, %	98	99	0.4
Cough, %	88	94	0.2
Chills, %	71	10	<0.0001
Tightness of chest, %	61	17	<0.0001
Weight loss, %	49	34	0.1
Body aches, %	54	8	<0.0001
Wheezing, %	27	36	0.3
Chest (pleuritic) pain, %	15	2	0.007
Symptoms 4–8 h after exposure, %	66	7	<0.0001
Recurrent episodes of symptoms, %	98	17	<0.0001
Physical signs, %			
Fever	20	9	0.1
Inspiratory crackles	68	94	<0.0001
Wheezing	5	17	0.07
Clubbing	2	36	<0.0001
Supraclavicular or cervical adenopathies	0	2	1.0
Laboratory blood work			
Positive precipitins to known antigens, %	73	76	0.8
pO ₂ , mm Hg	85 (22)	72 (14)	0.002
White blood cell count, $n \times 10^9/l$	7.8 (2.3)	7.8 (2.1)	0.8
Lymphocytes, %	25 (10)	29 (9)	0.03
Eosinophils, %	4 (7)	3 (2)	0.2
Positive antinuclear antibodies, %	12	20	0.4
Pulmonary function tests, % predicted			
FEV ₁	82 (22)	66 (22)	<0.0001
FEV ₁ /FVC	97 (15)	104 (12)	0.01
FEF _{25–75%}	76 (34)	81 (35)	0.9
D _{LCO}	76 (24)	55 (25)	<0.0001
Functional residual capacity	106 (30)	85 (31)	0.0005
Total lung capacity	94 (19)	72 (23)	<0.0001
Chest radiograph, %			
Normal	29	3	
Apical opacities	7	3	
Basal opacities	44	28	
Diffuse opacities	20	66	<0.0001
HRCT, %			
Ground-glass opacities	83	91	0.3
Nodular opacities	27	24	0.8
Fibrosis	5	37	<0.0001
BAL, %			
Lymphocytes	49 (23)	58 (19)	0.02
Neutrophils	10 (11)	4 (6)	0.003

Continuous variables are expressed as means with standard deviations in parentheses.

1 had more recurrent systemic symptoms (chills and body aches) and normal chest X-rays than those in cluster 2 who showed significantly more clubbing, hypoxemia, restrictive patterns on pulmonary function tests and fibrosis on HRCT (all p values were <0.0001 using the χ^2 test). Women were over-represented in cluster 2 (88 vs. 32% in cluster 1, $p < 0.0001$). This may only reflect a higher proportion of HP from domestic exposure to avian antigens in women than in men. Nodular opacities (which are often considered characteristic of subacute HP) were seen on HRCT as often in cluster 1 as in cluster 2.

Discussion

The current classification of acute, subacute and chronic HP is not confirmed by this cluster analysis. What is usually called subacute HP is particularly difficult to define and probably does not represent a separate entity. We hypothesize that the subacute presentation is a variant of the acute form of the disease, with similar but attenuated symptoms remaining days or weeks.

The purposes of classifying patients with respect to clinical manifestations are numerous. First, such a classification should ideally reflect pathophysiological processes. Suggestion has been made that the manifestations of HP are determined by the intensity and frequency of exposure to etiologic antigens [29]. If the pattern of antigen exposure truly determines the manifestations of HP, the results of this analysis would indicate that our patients exposed to bacteria and fungi had a much wider range of antigen exposure patterns than those with HP from avian protein exposure. An alternative explanation may be that the immune response to avian proteins is different from the response to other antigens [30, 31].

Second, such a classification should also provide clues to diagnosis, and thus guide clinical management. We believe that the most important contribution of a new classification would be in the investigation of patients presenting with respiratory disorders. HP must be considered in the differential diagnosis of patients presenting with respiratory symptoms and manifestations of systemic inflammation. Similarly, HP (and especially HP secondary to exposure to avian proteins) must be considered in patients with clinical evidence of interstitial fibrosis.

A third function of a classification scheme would be to convey prognostic information. In this regard, a limitation of our study is that long-term follow-up is not avail-

able. All patients were included in the HP Study at the time of their first evaluation and those with a previous diagnosis of HP were excluded. Nevertheless, it is noteworthy that 115 of the 168 patients (70%) who contributed to our study were classified as chronic HP at study entry, without previous systemic manifestations. Also, we know that the functional prognosis of HP presenting with systemic symptoms is usually good [32]. Few reports of long-term follow-up with repeated imaging with HRCT have been published [3, 4], and the number of patients involved is too small to arrive at a firm conclusion. These observations argue against the current belief that fibrosis (chronic HP) always follows inflammation (acute HP). This hypothesis is in line with that put forward in idiopathic pulmonary fibrosis [33].

The results of this cluster analysis suggest that HP patients should be classified into only 1 of 2 categories on the basis of clinical evaluation, pulmonary function tests and HRCT findings (table 5). In the first category, patients would present with recurrent systemic symptoms (chills and body aches) and tightness of chest occurring a few hours following antigen exposure, inspiratory crackles would be frequent but not universal and chest X-rays would be normal in almost 30% of the cases. Patients in the other category would have features of advanced interstitial lung disease, clubbing would be seen in one third of the cases, inspiratory crackles would almost always be present and a restrictive pattern on pulmonary function tests and resting hypoxemia would be characteristic. Also, one third of the patients in this category would show fibrotic changes on HRCT. The words acute and chronic would not be used to describe the categories, since they imply that chronic HP follows acute HP, which is uncertain.

This classification scheme needs to be prospectively validated. Future research should be directed at a better understanding of the natural history of the disease. Also, a better exposure assessment and understanding the relationship between dose and response are needed [12].

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