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A prospective clinical multicentre study on adult pulmonary Langerhans' cell histiocytosis

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Abstract. *Background*: To date the clinical picture of pulmonary Langerhans' cell histiocytosis has been described only in retrospective reports. For a better understanding, the German Scientific Study Group on the Treatment of Lung Disease (WATL) conducted an open, prospective, clinical observation study. *Methods*: During the period between 1994 and 2002 77 patients (40 men and 37 women) were recruited. The median observation period was 38.2 (3.2-86.7) months. *Results*: At the initial examination 50 patients were active smokers, 26 ex-smokers and 1 had never smoked. 36% of the patients showed reduced vital capacity, 28% signs of airways obstruction. On chest radiography, 74% of the patients who stopped smoking (24/50) showed regression, while 13% remained unchanged and 13% revealed progression. In the group that continued to smoke (25/50) chest radiography showed regression in 58% of cases, no change in 25% and progression in 17%. The difference was not significant, which was also true for lung function values. 3 patients died within the observation period. *Conclusion*: The data underline the key role of smoking as the sole known risk factor. A significant effect of smoking cessation on the course could not be confirmed. The overall prognosis was good in this series as compared to previous reports. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 132-138)*

Key words: Langerhans' cell granulomatosis, histiocytosis X, interstitial lung disease

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Introduction

Pulmonary Langerhans' cell histiocytosis (pLCH) is a rare granulomatous disorder of unknown etiology that occurs predominantly in young and middle-aged smokers. To date descriptions of the clinical features of pLCH have been published mainly in a small number of reports on larger retrospective series. In 1978 a working group led by

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Françoise Basset reported on 87 patients (1), and in 1981 Friedman published results on a series of 100 patients (2), providing the first comprehensive data. In 1993 more specific details on lung function and treatment were reported in a series of 42 patients based on data from the work of Karl Ludwig Radenbach (3). Also in 1993, Travis et al. focussed on clinicopathological aspects in 48 cases (4). In 2002, Vassallo et al. presented data on 102 clinically well-documented cases from the Mayo Clinic (5).

In 1994 the German Scientific Study Group on the Treatment of Lung Disease (WATL) was prompted by the retrospective character of the previous reports (1-4), differences in the data presented on the cause, clinical picture, complications and prognosis of pLCH to commence a prospective multicentre study in German-speaking countries. The objective was to contribute to a better understanding of the most important clinical aspects of the symptomatology, treatment and course of pLCH. The present paper is the study group's final report on the project.

Methods

The study was conducted as an open, prospective, clinical observation study. Only newly diagnosed patients in whom pLCH had been confirmed by open lung biopsy were included. Diagnosis on the basis of bronchoalveolar lavage was not considered sufficient. Patients were required to be not less than 18 years of age at inclusion and to have given their consent to an anonymous evaluation of their data. The data were recorded by the central co-ordinator (Lungenklinik Heckeshorn). The study was approved by the Ethics Committee of the Ärztekammer Berlin (Medical Association of Berlin).

All patients were asked to fill in a detailed questionnaire on their symptoms, histories, concomitant diseases, smoking habits, and particularly potential causes of pulmonary and respiratory disease (6). Chest radiography, thoracic CT, spirometry, body plethysmography and, where possible, the diffusion capacity for carbon monoxide or blood gas analysis at rest and during exercise were performed. Basic laboratory data (blood count, serum electrolytes, serum glucose, serum kidney and liver values) were also collected.

In cases without respiratory insufficiency, without severe bronchial obstruction and without clinically relevant extrapulmonary granuloma (e.g. a bone granuloma in the region of the orbit), the study protocol recommended simply smoking cessation and observation. Chest radiography and lung function tests (preferably body plethysmography) were to be carried out every three months. Improvement of chest X-ray was defined as a decrease in reticular and/or nodular interstitial shadowing, deterioration as an increase, stabilitiy as no change. There was no central reading of the chest radiographs, the assessment was done by the local site investigators.

In cases with respiratory insufficiency, severe bronchial obstruction or clinically relevant extrapulmonary granuloma the protocol recommended initiation of corticosteroid therapy with 0.5 mg/kg body weight prednisolone, which was then to be reduced stepwise over a period of not less than six months. However, in all cases it was left to the treating physician to establish the indication and to manage the corticosteroid therapy.

All data were anonymized and stored in a central data bank at Lungenklinik Heckeshorn, the coordinating study center.

Statistical analysis and data processing

The data on lung function and laboratory parameters at baseline and at the time of follow-up studies were pre-processed. In a first step the lung function parameters were adjusted for potential confounders such as age, gender and body height according to European Community for Steel and Coal in order to transform the data into percentages of the predicted value (7, 8). Key ratios such as forced expiratory volume were also calculated in 1 s/vital capacity (FEV1/VC) and residual volume/total lung volume (RV/TLC). In a second step the resulting variables were recoded into categorical groups. Restrictive impairment was defined as TLC <80% pred., obstructive impairment as FEV1/VC <70%. The laboratory parameters were recoded into categorical groups on the basis whether they were normal or abnormal. The time that had elapsed between the first examinations and the respective subsequent examinations was calculated. The resulting periods were reviewed and grouped into four periods as follows: 0 months, 3 to <6 months, 6 to <12 months, >12 months. The-

se periods of time points were required due to the large variation between examination dates within the study population.

The pre-processed data on lung function and laboratory parameters were then subjected to univariate analyses in order to obtain the descriptive parameters and frequency distributions for each of the four periods of time points. The comparison of the adjusted values for lung function at the first and last examinations was performed for both the entire study group and the subgroups based on the category 'smoking' using paired t-tests or, for comparison of variables that were not normally distributed, the Wilcoxon signed-rank test for paired data. Unpaired t-tests were also performed for the whole study sample and all four groups of time points across the categories smokers and non-smokers and between those patients who had received corticosteroid therapy vs. those who had not. Similarly, the chi square statistic was used to test the distributions of the categorical variables derived from the data on lung function and laboratory parameters. For all tests, a p value <0.05 was considered to be statistically significant. All analyses were conducted by ARGUS GmbH, Berlin, with SPSS for Windows from SPSS Inc. (Chicago, USA).

Results

During the period between 1994 and 2002 77 patients (40 men (52%) and 37 women (48%)) were recruited to the study (Table 1). The mean age for both, men and women was 38 years. The median observation period was 38.2 (3.2-86.7) months. 3 patients died during follow-up.

Symptoms

At the initial examination 50 patients were active smokers, 26 ex-smokers and 1 had never smoked. In the course of the study 25/50 (50%) of the smokers stopped smoking and 25/50 continued smoking. In 7/77 (10%) of the patients the diagnosis was discovered by chance, while in 70 pulmonary symptoms led to further evaluation and final diagnosis. 60/70 patients had a cough, 43/70 dyspnoea, 26/70 chest pain, 5/70 pneumothorax 3/70 hemoptysis, 21/70 weight loss (>5% body weight), 21/70 tiredness, and 8/70 had bone manifestations. No patient had diabetes insipidus.

Table 1. Participating centers with number of patients

Centers	N
Lungenklinik Heckeshorn, Berlin	13
Ruhrlandklinik, Essen	13
Asklepios Fachkliniken Gauting, Munich	7
Heidehaus, Hanover	6
Zentralklinik Bremen Ost	5
Krankenhaus Großhansdorf, Hamburg	3
Fachkrankenhaus Coswig	3
20 other centers	27

Lung function

Lung function data at baseline are shown in table 2.

At the initial examination which was done by body plethysmography in 76/77 patients, 49/77 patients (64%) had a VC > 80% pred., 23/77 (30%) pts. a mildly reduced VC (VC % pred. 60-80%) and 5/77 (6%) a moderately reduced VC (VC % pred. 40-60%). TLC was mildly reduced (TLC % pred. 60-80%) in 9/76 (12%) cases and moderately reduced (TLC % pred. 40-60%) in 1/76 patients (1%). The mean VC at the initial examination was 89% pred.(standard deviation 18.8%) (n=77). At the final examination the mean VC was 95% pred. (standard deviation 20.3%) (n=60, Fig. 1). There were no statistically significant differences between VC at the four time periods.

Table 2. Lung function data at baseline

Parameter	Patients (n)	Mean	Standard deviation	Range
TLC (% pred.)	76	98	17.3	53-136
VC (% pred.)	77	89	18.8	45-129
FEV1 (% pred.)	76	79	21.5	18-126
FEV1/VC (%)	76	74	12.7	30-96
RV (% pred.)	72	125	39.0	33-214
RV/TLC (%)	72	38	10.4	16-66
DLCO (% pred.)	49	60	17.7	33-113

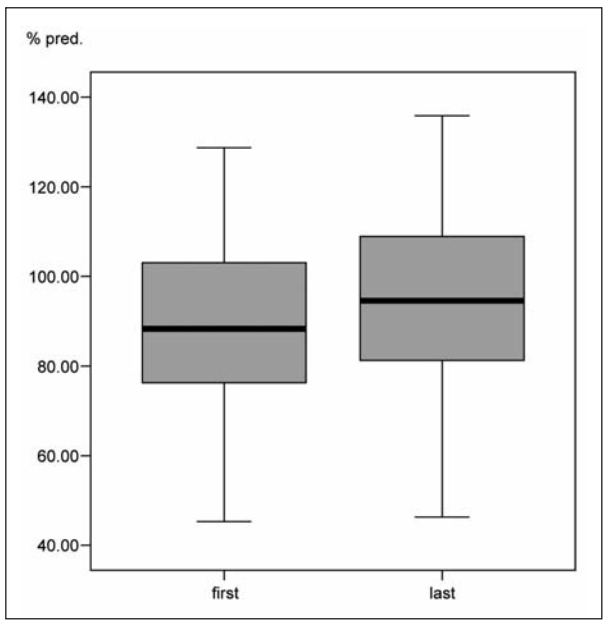

Fig. 1. Vital capacity, % pred., at the first (n=77) and last examination (n=60); median, interquartile ranges, minimum and maximum values

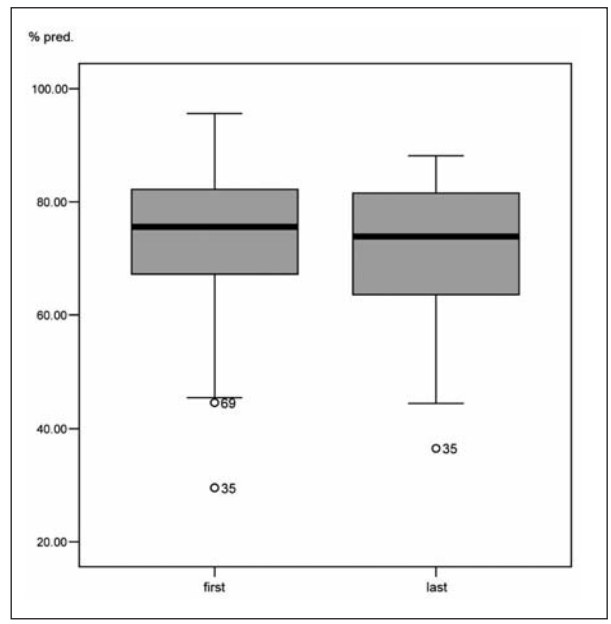

Fig. 2. Forced expiratory volume in one second, % VC, at the first (n=76) and last (n=60) examination; median, interquartile ranges, minimum and maximum values

21/76 patients (28%) had an obstruction (FEV1/VC ratio of below 70%) at the initial examination. At the last examination 40/60 patients (40%) had an obstruction. Yet the difference between mean FEV1/VC (74%, standard deviation 12.7%) at the initial examination and mean FEV1/VC at the last examination (71%, standard deviation 11.8%) was not statistically significant (Fig. 2).

At the initial examination 16/49 (33%) patients had a normal carbon monoxide transfer (DLCO). The percentage of patients with reduced DLCO increased by 11% in this group (Fig. 3). The difference was not statistically significant. 34 patients underwent exercise tests, 12 of those had an abnormal alveolar-arterial oxygen gradient ($AaDO_2$). At the last examination the number of patients with an abnormal $AaDO_2$ had increased by 1 to 13.

Course of the disease after cessation of smoking

The VC of those patients who had stopped smoking were compared with those who had not. Of the 25 smokers who stopped smoking, 56% had an initial VC >80% pred. and 36% had a mildly reduced initial VC (VC 60-80% pred.), while 8% had a moderately reduced initial VCs (VC 40-60% pred.). At the last examination 80% had normal VC (VC >80% pred.), 8% still had a mildly reduced VC (VC 60-80% pred.) and 12% had a moderately reduced VC (VC 40-60% pred.).

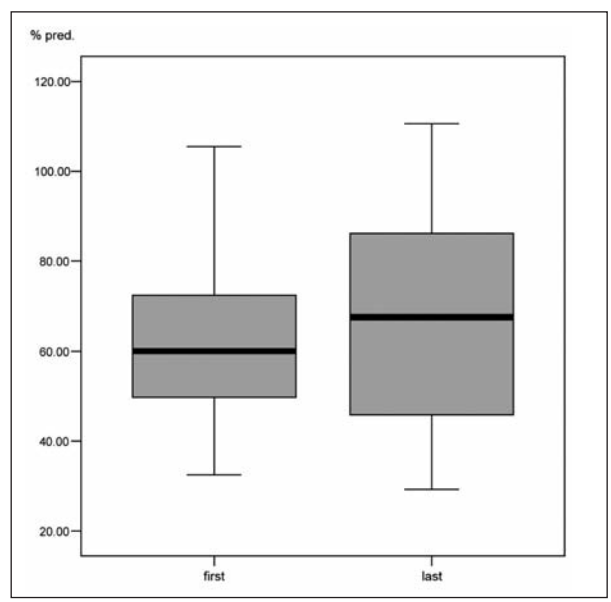

Fig. 3. Carbon monoxide transfer DLCO % pred., at the first (n=49) and last (n=39) examination; median, interquartile ranges, minimum and maximum values

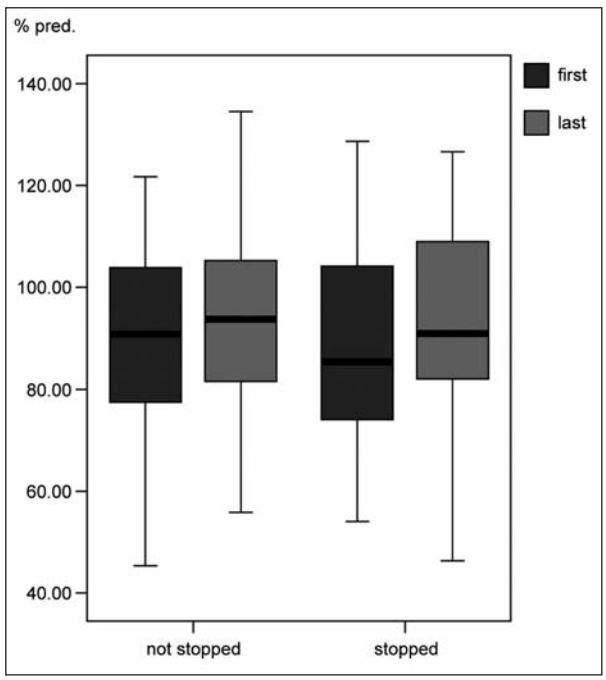

Fig. 4. Vital capacity % pred., patients who had stopped (first n=25, last n=21) and those who had not stopped smoking (first n=25, last n=19); median, interquartile ranges, minimum and maximum values

Initially, of the 25 patients who continued to smoke, 64% had a VC >80%, 28% had a mildly reduced VC (VC 60-80%), and 8% a moderately impaired VC (VC 40-60%). At the last examination 84% of these patients had a normal VC (VC >80% pred.), 12% a mildly reduced VC (VC 60-80% pred.) and 4% a moderately reduced VC (VC 40-60% pred.). No significant differences were observed between patients who had stopped and those who had not stopped smoking (Fig. 4).

In the patients who stopped smoking the chest radiograph showed regression in 74%, remained unchanged in 13% and showed progression in13%. In the group that continued to smoke the chest radiograph showed regression in 58%, no change in 25%, and progression in 17%. CT scan was repeated only in single cases during follow-up and thus, serial CT changes could not be analysed systematically.

Corticosteroid treatment

21/77 patients received corticosteroids initially or during follow-up, but mostly not according to the recommendations of the protocol. Therefore, no results about the possible influence on the course of the disease can be given.

Survival

Three patients died during the observation period. One male patient died after 59 months from metastatic osteosarcoma. Another male patient died after 38 months, a female patient after 54 months; the cause of death was unknown in both of them.

Discussion

The results of the WATL prospective study clarify several aspects of pLCH.

As regards the cause, smoking was identified as the sole risk factor which is almost invariably present (9). This was the first survey in a large group of patients having used a detailed questionnaire including items on a broad spectrum of possible causes of pulmonary and respiratory diseases in the spheres of work, the environment, the home and family history. The results failed to show any clusters indicating other causes of the disease.

In this context, the study also demonstrated that spontaneous regression of the disease is possible both with and without cessation of smoking and that it is not restricted to isolated cases. Thus, there is unfortunately some doubt regarding the assumptions of previous reports that stopping smoking is the key to the treatment of pLCH (10-13). However, in view of the high incidence of obstructive functional changes and the risk of cancer this does not, of course, mean that doctors should not instruct all patients to abstain from smoking. Furthermore, there was a tendency to a higher radiological remission rate in individuals who stopped smoking, but the difference (74 vs. 58% of the patients) was not statistically significant.

There are several limitations of this study. First, information on smoking habits was based exclusively on self reports of the patients also during the follow-up , without being supported by objective measures such as the urinary cotinin content, which limits conclusions derived from the smoking status. Second, the protocol requested radiological follow-up by chest radiography only and not by CT scan; therefore it is not possible to analyse the outcome of

lung function according to the evolution of the CT pattern or to associate the effect of smoking cessation with CT changes. Third, since only a minority of our patients was treated with corticosteroids and this in an uncontroled way, the study cannot assess the efficacy of this treatment on the radiological or functional outcome.

In regard to the clinical picture, the evidence reported by the published retrospective studies (1-4) was to a great extent confirmed. Results of lung function tests showed a pattern of impairment that had been described previously (3-5, 15, 16). Parameters of gas exchange were more frequently reduced as compared to parameters of restriction or obstruction, respectively. It has also been described that even in case of radiological remission, parameters of impaired lung function remain more or less unchanged (3). The results of the WATL prospective study also failed to show any significant improvement of lung function during follow-up. As a possible reason for this discrepancy, the previously described pathological finding of intraluminal fibrosis in 78% of open lung biopsies may indicate that this alteration plays an important role in the pathogenesis of fibrotic remodeling in pLCH (4, 17).

There was only a statistically not significant trend to a better development of functional parameters in patients who stopped smoking than in individuals who continued to smoke. Besides the fact that the number of patients was certainly too small to achieve statistical significance, this finding may be associated with the observation of a slightly lower initial VC in patients who stopped smoking. Their potential for a functional recovery thus may have been greater, and this may even have affected their willingness to stop smoking.

Pneumothorax was a rare occurrence in our series with 6.5% of all patients, whereas in the largest of the previous series it was found in 12% of cases (2). The probability of its occurrence in a series is likely to be dependent on the frequency of advanced stages of the disease in the respective series, which is typically associated with the development of mainly subpleural bullae and diffuse fibrotic changes leading to reduced compliance (18). Bone granulomas were also rarely reported in the present series, whereas other authors have reported up to 20% (4). The differences remain unexplained. There is no radiographic screening procedure for bone lesions. Conventional bone scintigraphy is not suitable for this purpose, but somatostatin receptor imaging with ^{111}In-pentetreotide may be useful (19).

As discussed above as a limitation of this paper, the WATL study cannot provide a basis for judging the efficacy of systemic corticosteroid therapy. However, the results of earlier studies suggest that this substance class is effective (3,20). Since only three patients died during the observation period, the prognosis must be assessed as more favourable than indicated by other reports. Delobbe et al. reported that 12/45 patients (27%) died or underwent lung transplantation during a median follow-up period of 8.4 years (15), Aricò et al. described a 5 year survival rate of 87.8% for isolated pulmonary disease (n=34) (20). The difference between the present results and those of other reports is likely to depend on the number of patients diagnosed as being in an advanced stage of the disease.

In conclusion, the present study underlines the key role of smoking as the sole known risk factor for pLCH and reveals a trend that smoking cessation may favourably influence the course of the disease. Yet the number of patients seemed to be too small to demonstrate statistically significant differences between individuals who stopped smoking and those who continued. The overall prognosis was good in this series as compared to previous reports.

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