

LANGERHANS'-CELL HISTIOCYTOSIS IN 58 ADULTS

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Abstract: Previous studies on Langerhans'-cell histiocytosis (LCH) were mostly retrospective and patients had been recruited over a long time period. The aim of the present study was to establish data on the clinical presentation, diagnosis and treatment of currently affected patients. Data on the clinical history, diagnostic work-up and course of histologically confirmed LCH in 58 adults were obtained with the aid of a questionnaire.

A differentiation of the patients (average age 43.5 ± 7.7 years, 66% women, 34% men) by the various clinical forms, revealed single-organ involvement in 42 of the patients (72 %), and multisystem involvement in the remaining 16 patients (28%). In the 42 patients, who had involvement of a single system, 23 had pulmonary involvement only. Multilocal osseous involvement was observed in 9 patients. In both single-organ or multisystem LCH the most common affected site was pulmonary involvement (62%), followed by osseous (50%) and cutaneous involvement (15%). 51 patients (88%) were smokers or ex-smokers. Dyspnoea (60%) and cough (47%) were the most frequent initial symptoms.

In adults with LCH the pulmonary system is most frequently involved, however almost one-third of the patients present with multisystem disease.

Key words: Langerhans'-cell histiocytosis, clinical manifestations

INTRODUCTION

The term Langerhans'-cell histiocytosis (LCH) describes a spectrum of diseases that are characterized by an aetiologically as yet unknown local or generalized proliferation of histiocytes that belong to the differentiated cells of the monocyte macrophage lineage.

Single-system disease with unilocal involvement of an organ or organ system e.g. monostotic bone involvement is differentiated from multilocal involvement (e.g. multiple lymph node involvement). From these, disseminated involvement of several organs with or without functional disturbance is distinguished as multisystem disease [20].

It is assumed that, in adults, the isolated pulmonary form represents a polyclonal proliferation of histiocytes and exclusively affects smokers, while in another forms clonal proliferation of histiocytes has been demonstrated [20, 24, 25]. The clinical forms of LCH differ in adults in comparison with children by a predominance of pulmonary involvement in adults and a

predominance of osseous involvement in the latter [8, 9]. A number of studies of LCH have been carried out in which the patient data were analysed at a centre [8, 18] or a specialized department [9, 20, 21], so that a selection bias must be assumed. The aim of the present study was to acquire and analyse, independently of centre and specialty the data of recently affected patients with LCH to characterise the various forms of LCH in adults.

PATIENTS AND METHODS

For this study, LCH patients were recruited via self-help group.

For evaluation purposes, a standardised questionnaire was sent to all members of a self-help group within a period of twelve months. The questionnaire first requested information on anthropomorphic data (height, weight and sex); it was structured into sections "previous history", "symptoms", "establishment of the diagnosis", and "course of the disease". As a rule, the questions were posed in a multiple choice format.

The section "previous history" contained questions on occupation, onset of the disease, family history, previous illnesses, regular use of medication and smoking habits. Thereafter, the patient was questioned on the symptoms that led to consultation of the physician. Here, a differentiation into various organs was given. Subsequent questions elicited information on the time lapse between the onset of symptoms and the diagnosis, the basis of diagnosis establishment, and the course of the disease. The term "course of treatment" summarises data on the therapy applied after establishment of the diagnosis, duration of the therapeutic measures, and the outcome of treatment. The patients were required to provide their written consent to allow relevant reports to be requested from medical letters and findings. Patients were admitted to further analysis when histological confirmation of the diagnosis was available as well as medical data documenting organ involvement. The study was approved by the local ethical committee.

RESULTS

By self help group 93 questionnaires were retrieved. Of the completed questionnaires returned, 58 (62%) containing the relevant information were used for the analysis.

The ratio of women to men was 66% to 34% (Table 1). The average age at diagnosis was 43 ± 7.7 , and

ranged from 18 to 76 years. The age peak at diagnosis was located in the 30 to 40 year age group (45% of the patients), one patient was 18 years old, three were older than 60.

51 patients (88%) were smokers or ex-smokers. 42 patients (72%) had involvement of a single organ, of

Table 1. Characteristics of the patients with Langerhans'-cell histiocytosis (LCH)

Age at diagnosis	43 ± 7.7
Men	20 (34%)
Women	38 (66%)
Smoking behaviour	
Smokers	31 (54%)
Ex-smokers	20 (34%)
Nonsmokers	7 (12%)
Single organ involvement	42 (72%)
Of which lungs	23
Multilocal involvement	10
Multiorgan involvement	16 (28%)

which 23 had pulmonary involvement only. In 16 (28%) of the patients more than one organ was affected. Multilocal osseous involvement was observed in 9 patients.

In 36 patients pulmonary involvement - either single-organ or multiorgan disease - was established, with additional osseous or other organ involvement in 36% of this group. In 29 cases, hospital documentation revealed bone involvement; in 45% no other site was found to be affected. The various clinical forms of LCH are shown in Figures 1 and 2. Pulmonary involvement was the most common location, with bony involvement in second place. In 9 patients, cutaneous involvement was noted, but only 4 patients revealed cutaneous alone. Three patients had lymph node involvement, and two patients had cerebellar LCH.

The most common initial symptoms (Fig. 3) that prompted the patient to consult a physician were dyspnoea (60%) and cough (47%), but also cutaneous efflorescences (22%), fatigue (36%), and weight loss (27%) were commonly reported.

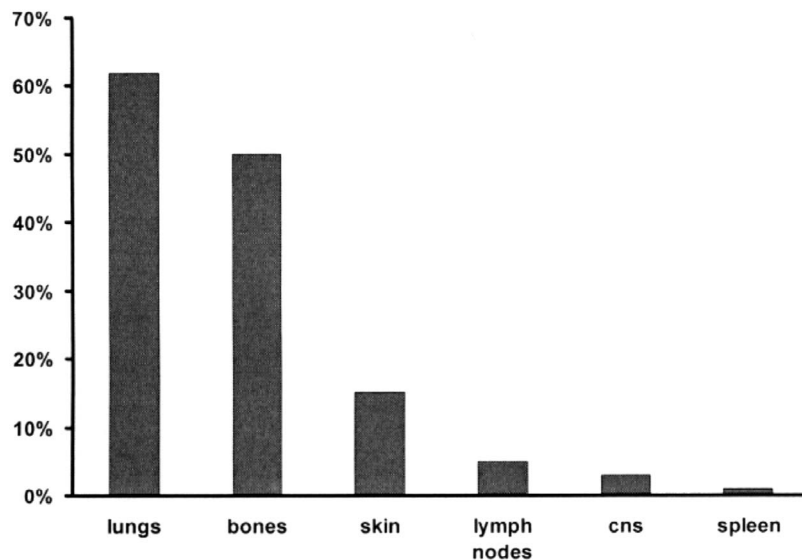


Fig. 1. Organ involvement (more than one site possible)

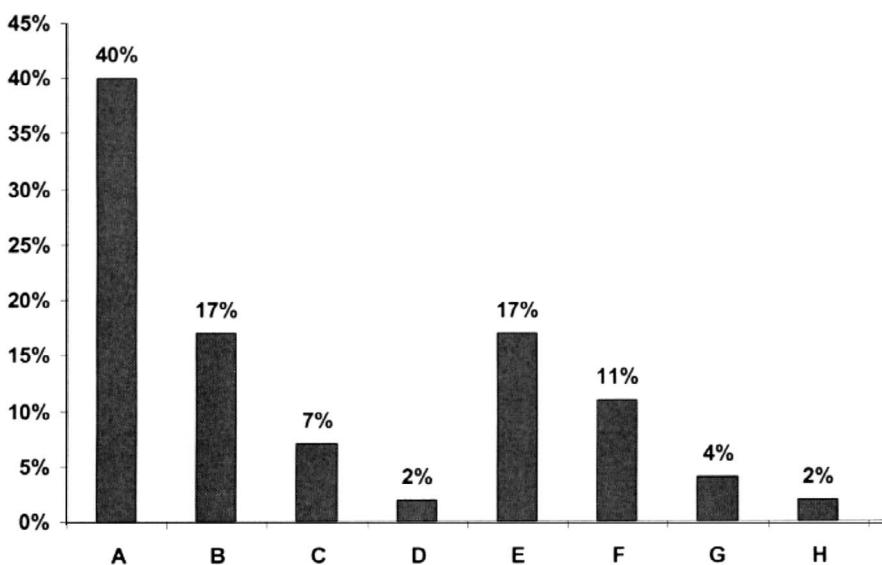


Fig. 2. Clinical forms of LCH: A pulmonary; B osseous; C cutaneous; D lymph nodal; E pulmonary and osseous; F cerebellar, cutaneous and osseous; G cutaneous osseous and pulmonary; H pulmonary and cutaneous; Single organ disease A -D; multi-organ disease E-H.

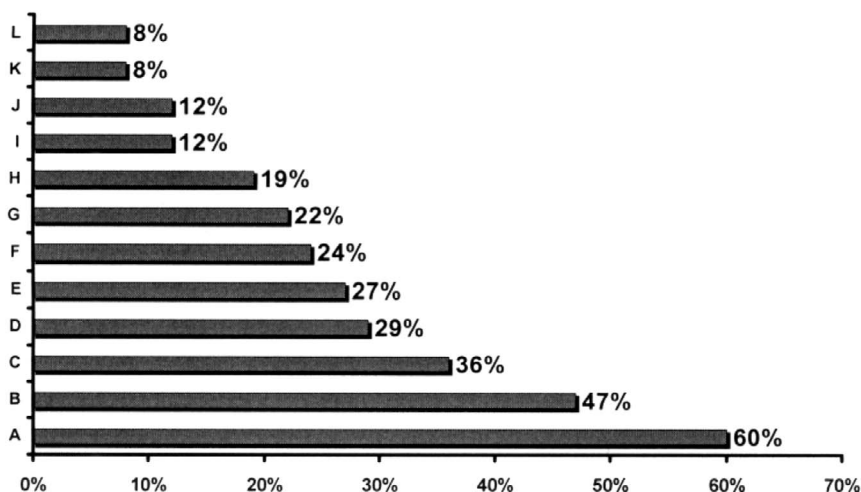


Fig. 3. Initial symptoms (More than one answer possible): A dyspnoea; B cough; C cutaneous efflorescences; D fatigue; E weight loss; F fatigue; G nocturnal sweating; H pruritis; I increased thirst; J lymph node enlargement; K nausea; L fever.

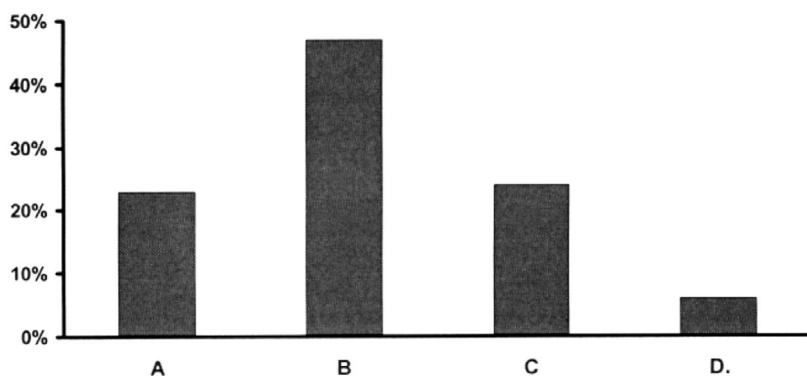


Fig. 4. A Treatment: corticosteroid monotherapy; B combination treatment (corticosteroids, radiotherapy, chemotherapy); C no treatment; D other forms of treatment.

The average time lapse between the onset of symptoms and establishment of the diagnosis was 15.7 months, with a median of 6 months. In three patients, the diagnosis was established incidentally after a surgical intervention or an endoscopic examination with following diagnostic histological work-up. In ten patients, 10 years passed before the diagnosis was made.

For diagnostic confirmation, a diagnostic CT scan was performed in 32 patients and skeletal scintigraphy in 14 patients. In all the patients, histopathological confirmation of the diagnosis was obtained.

In the group investigated, monotherapy with corticosteroids was initiated in 23% of the patients. In a further 47%, various combinations with chemotherapy, radiotherapy and corticosteroids were applied. Twenty-four percent of the patients received no treatment (Fig. 4).

The course of the illness in the patients investigated was, in the main, considered positive. Half of the patients (45%) reported a subjective improvement; 43% continued to experience symptoms, but remained in a stable state; 12% of the patients reported a worsening of their illness, and one patient with pulmonary involvement has since died. By way of complications, 4 patients experienced a spontaneous pneumothorax, 6 patients spontaneous fracture (n = 1 vertebra, n = 5 ribs); three patients developed diabetes insipidus.

DISCUSSION

LCH is considered as a rare disease, some evidence regarding its incidence being provided by a pathological-anatomical study in which the incidence of pulmonary specimens with interstitial pulmonary diseases was investigated. Colby and Lombard [5] identified 15 patients with LCH as apposed to 274 patients with sarcoidosis. These numbers probably underestimate the incidence, since the disease can remain virtually symptom-free, and spontaneous remission can occur [3, 14].

Because of the low incidence of the disease, clinical information on LCH is mostly based on retrospective data collected over the long-term. In contrast to this, the patients in the present study were recruited via a self-help group. In this way, currently diseased patients were obtained.

The clinical forms of LCH differ in adults in comparison with children by a predominance of pulmonary involvement in the former and a predominance of osseous involvement in the latter [8, 9].

In many studies, however, the differentiation between adults and children varies considerably. E.g. children and adults were often pooled prior to investigation [9, 13, 22]. On the other hand Vasallo et al. [21] investigated adult patients with an age spectrum of between 18 and 70 years, however inclusion criteria was pulmonary LCH [21]. He found multisystem disease in only 17% in contrast to 28% in the present

study. These data are in accordance with those reported by Howarth et al. [8], who noted multisystem disease in 30.6 % of their patients.

In the present study, a predominance of women was to be seen (66%). These data are in accordance with data reported by Howarth et al. [8] and Vasallo et al. [21]. Other studies, [9, 11], reported a higher percentage of male patients; in these studies, however, the patients included mainly those with osseous LCH. A Russian study [10], which investigated 70 patients with histologically confirmed pulmonary LCH showed a marked predominance of males (87%). Since smoking is considered the major exogenous factor for LCH [1, 2, 4, 7, 16, 17, 23, 26], an explanation for this finding may be differences in smoking habits compared to Western countries with only a small differences in smoking behaviour of men and women. Thus, a markedly higher involvement of women of LCH in adults under comparable environmental conditions is to be found [5, 6, 16, 19].

In our study, most patients with a single-organ disease had pulmonary LCH (54%), followed by osseous LCH in 21%. In the case of the multisystem group of 16 patients, 83% presented with pulmonary involvement. These figures reveal a predominance of patients with pulmonary involvement in our study.

In some studies, in contrast, osseous LCH was the most common form [8, 9]. In the study by Howarth et al. [8] osseous involvement was seen in 60% of all those studied, with, however, 60% of the patients being younger than 20 years.

In the majority of studies, cutaneous involvement in LCH is the third most common site. In the study published by Howarth et al. [8], the proportion of patients with cutaneous LCH was 24.5%. In our study too, cutaneous LCH occupied third place at 16%.

Less common sites of organ involvement in our study were the lymph nodes (3 patients) and a generalized form with affliction of the spleen.

The most commonly reported symptom was dyspnoea at rest or exercise-related. The second most common symptom was productive or unproductive cough. Other, less frequent symptoms were tiredness, loss of weight, puritus, nocturnal sweating, increased thirst, nausea and fever. In contrast to this, Howarth et al. reported regional bony pain to be the most common symptom. Appreciably less common at only 14% were respiratory complaints. In patients with a pulmonary form of the disease [21], pulmonary symptoms were also predominant.

In our study the diagnosis of LCH was established on average 14 months after onset of symptoms – with a median of only 6 months, since one female patient experienced a delay of 10 years between symptom onset and diagnosis. In the study by Howarth et al. [8], the average time lapse between symptom onset and diagnosis was 1.5 years.

Treatment of LCH depends on its classification: immunosuppressants, cytostatic agents and radiotherapy have all been employed to treat osseous or multiorgan disease, although, overall, few reliable studies on the success of treatment are available in adults.

The prognosis is determined by the age of the patient, the extent of organic involvement, and the de-

gree of dysfunction of the afflicted organs. Nezelof and Basset [15] hypothesize a correlation between the number of organs involved and mortality. Since the course of LCH is not predictable, that is, either progression or spontaneous remission may occur, the prognosis is difficult.

In summary these data show differences in clinical features to studies pooling children and adults. Langerhans' cell histiocytosis is not only considered as a paediatric disease and a predominantly pulmonary involvement in adult .

Although the respiratory system is most commonly affected in adult LCH, multisystem disease occurs in almost one-third of the patients.

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