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Langerhans cell histiocytosis in adults Report from the International Registry of the Histiocyte Society☆

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Abstract

Langerhans cell histiocytosis (LCH), characterised by the infiltration of one or more organs by large mononuclear cells, can develop in persons of any age. Although the features of this disease are well described in children, they remain poorly defined in adults. From January 2000 to June 2001, 274 adults from 13 countries, with biopsy-proven adult LCH, were registered with the International Histiocyte Society Registry. Information was collected about clinical presentation, family history, associated conditions, cigarette smoking and treatment, to assist in future management decisions in patients aged 18 years and older. There were slightly more males than females (143:126), and the mean ages at the onset and diagnosis of disease were 33 years (standard deviation (S.D.) 15 years) and 35 years (S.D. 14 years), respectively. 2 patients had consanguineous parents, and 1 had a family history of LCH; 129 reported smoking (47.1%); 17 (6.2%) had been diagnosed with different types of cancer. Single-system LCH, found in 86 patients (31.4%), included isolated pulmonary involvement in 44 cases; 188 patients (68.6%) had multisystem disease; 81 (29.6%) had diabetes insipidus. Initial treatment consisted of vinblastine administered with or without steroids, to 82 patients (29.9%), including 9 who had received it with etoposide, which was the sole agent given to 19 patients. 236 patients were considered evaluable for survival. At a median follow-up of 28 months from diagnosis, 15 patients (6.4%) had died (death rate, 1.5/100 person years, 95% Confidence Interval (95% CI) 0.9–2.4). The probability of survival at 5 years postdiagnosis was 92.3% (95% CI 85.6–95.9) overall, 100% for patients with single-system disease ($n=37$), 87.8% (95% CI 54.9–97.2) for isolated pulmonary disease ($n=34$), and 91.7% (95% CI 83.6–95.9) for multisystem disease ($n=163$). Survival did not differ significantly among patients with multisystem disease, with or without liver or lung involvement) 5-year survival 93.6% (95% CI 84.7–97.4) versus 87.5% (95% CI 65.5–95.9), respectively; P value 0.1). LCH in adults is most often a multisystem disease with the highest mortality seen in patients with isolated pulmonary involvement. It should be included in the differential diagnosis of disseminated or localised disease of the bone, skin and mucosa, as well as the lung and the endocrine and central nervous system, regardless of the age of the patient. A prospective international therapeutic study is warranted.

Keywords: Langerhans cell histiocytosis; Adults; Histiocyte society; International registry

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1. Introduction

The term Langerhans-cell histiocytosis (LCH), formerly known as histiocytosis X, encompasses a spectrum of diseases characterised by the proliferation and infiltration of organs by pathological Langerhans cells [1]. The clinical manifestations of the disease are largely related to the pattern of infiltration of the several organs and organ systems that may be involved, including bone, skin, hypothalamus, liver, lung and lymph nodes [2]. The term 'eosinophilic granuloma' [3] has been used in the past to indicate localised forms of the disease, whereas a number of terms have been used to indicate multisystem forms of the disease [4], including Abt-Letterer-Siwe [5–7] and Hand-Schuller-Christian [8–10] diseases.

The current classification developed by the Histiocyte Society provided uniform criteria for the diagnosis and clinical evaluation of patients with LCH. 'Definitive diagnosis' requires the finding of Birbeck granules in lesional cells by electron microscopy or demonstration of CD1a antigenic determinants on the surface of lesional cells; 'diagnosis' is justified when the lesion is characteristic by light microscopy and the lesional cells show the presence of two or more of the following features: positive stain for ATPase, S-100 protein, or alpha-D-mannosidase, or characteristic binding of peanut lectin in lesional cells; 'presumptive diagnosis' is warranted when findings, on study of conventionally stained biopsy material alone, are merely 'consistent' with those defined in the literature [11,12].

The aetiology and pathogenesis of LCH remains largely undefined. Although LCH has been considered a sporadic disorder, some authors have recently reported a familial clustering in which a second affected relative was found in nearly 1% of cases, suggesting a familial predisposition [13]. Furthermore, chromosomal instability has been identified as a frequent abnormality in peripheral blood lymphocytes from patients with LCH [14]. Whether this abnormality represents the result of a constitutional predisposing factor or perhaps a hallmark of an environmental event associated with development of LCH remains to be assessed [15].

Experience in randomised trials conducted by the Histiocyte Society in children has led to the identification of the diagnostic features of LCH [16] and of the factors that influence the response to therapy [17]. LCH may be diagnosed at any age, from birth to those aged over 80 years [18,19]. Children with multisystem disease present at a median age of 18 months. Although a younger age at presentation has often been linked to a higher probability of disease reactivation and dissemination, resulting in a worse prognosis [20], the LCH-II trial demonstrated that age is not an independent prognostic factor in childhood LCH [17].

Reports of studies of adults with LCH have been available for many years, but the lack of large series or of prospective trials has impeded the acquisition of knowledge of the disease in this age group. Some of the reported series may have inherent biases in their

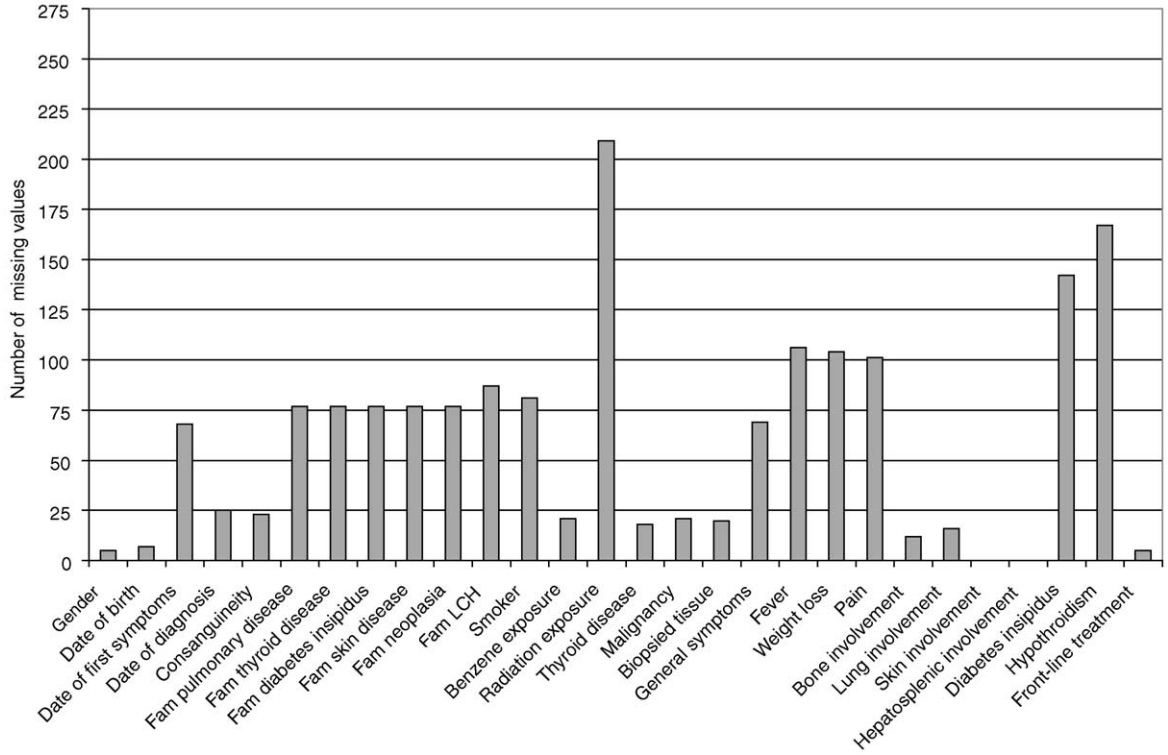

Fig. 1. Distribution of missing values among variables studied in 274 adult patients with Langerhans cell histiocytosis (LCH). Fam; family history.

demographics and treatments because of the types of centres they originate from.

To address this issue, the Histiocyte Society established a registry for LCH in adults. We report here, the preliminary results of an analysis of the first 274 cases collected in this registry.

2. Patients and methods

Since 1 January 2000, the International Registry for LCH in Adults has circulated a standard data form among the members of the Histiocyte Society to collect retrospective or prospective information on patients with LCH. The form was also distributed by the Histiocytosis Association of America among its participants, who forwarded it to LCH patients for recording clinical facts, possibly with the help of their physician. The types of data collected include details of family history, clinical and laboratory features at disease onset, treatment and follow-up.

2.1. Eligibility criteria

All patients 18 years or older with a diagnosis of LCH, made according to Histiocyte Society criteria [16], were included in the analysis.

2.2. Statistical analysis

Information from the standard form was stored in a database built in Microsoft Access and was analysed with a Stata 7 environment (Stata Corp, College Station, TX, USA). Continuous variables were described with means and standard deviations (S.D.) or medians and interquartile ranges (IQRs) for skewed distributions. Absolute and relative frequencies were calculated for categorical variables. The percentages were computed over the whole case series, including missing values. Death rates were computed with 95% Confidence Intervals (95% CIs) and were expressed as deaths per 100 person-years. Kaplan–Meier estimates of cumulative survival were calculated with the 95% CIs. The log-rank test was used to compare the survival curves. Chi-square analysis was used to compare the distribution of smokers among the different types of LCH cases. A two-tailed P value <0.05 was considered statistically significant. Data entry was completed on 15 June 2001. Although the data-set was checked closely for completeness, most had missing values (Fig. 1).

3. Results

3.1. Study population

A total of 274 patients from 13 countries were studied (Italy, 68; Germany, 66; France, 54; United States of America (USA), 46; Russia, 14; Austria, 8; Sweden, 7; Argentina, 4, United Kingdom (UK), 3; Australia, Greece, Switzerland, Slovenia, 1 each). The vast majority of cases were diagnosed after 1991 (Fig. 2). 143 patients were male (52%) and 126 females (46%) (5 not known). Their mean age at the first manifestation of LCH was 33 years (S.D. 15 years). The mean age at diagnosis was 35 years (S.D. 14 years).

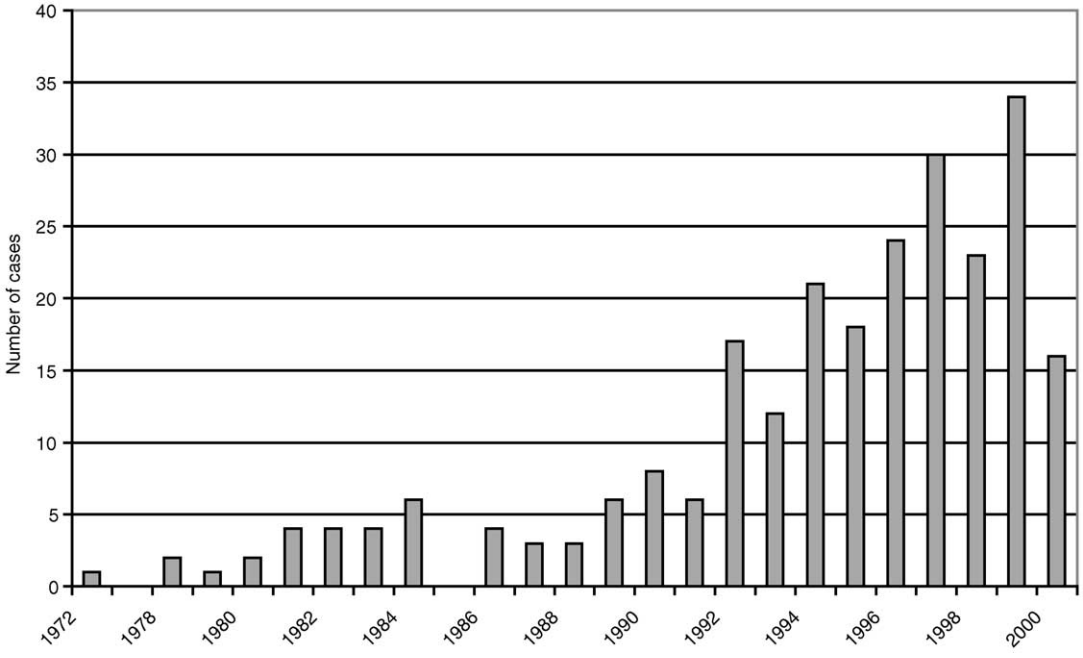

Fig. 2. Year of diagnosis of LCH in 249 patients aged 18 years or older.

The peak age of patients diagnosed with LCH ranged from 20 to 30 years. There were only a few recorded cases in the 60- to 90-year-old group (Fig. 3).

3.2. Family history

The patients' family histories included neoplasms ($n=27$, 9.9%), pulmonary disease ($n=16$, 5.8%), thyroid disorders ($n=10$, 3.6%), skin disorders ($n=6$, 2.2%), and diabetes insipidus ($n=8$, 2.9%). 2 patients had consanguineous parents (0.7%), while another (0.4%) had a sibling with a diagnosis of LCH.

3.3. Personal history

114 patients reported their occupations: office worker ($n=37$; 32%), home worker ($n=31$; 27%), blue-collar worker ($n=13$; 11%), student ($n=12$; 11%), professional ($n=11$; 10%), trader ($n=7$; 6%), executive ($n=3$; 3%). Environmental exposure to benzene ($n=3$, 1.1%), but not to radiation was noted. Cigarette smoking was reported by 129 patients (47.1%): daily consumption of 1–10 cigarettes ($n=18$, 6.6%), 11–20 cigarettes ($n=35$, 12.8%), 21–30 cigarettes ($n=11$, 4.0%), and more than 30 ($n=5$, 1.8%). 11 patients (4.0%) had previous thyroid disorders, while 17 (6.2%) had been diagnosed with cancers of the following types: non-Hodgkin's lymphoma ($n=5$, including 1 initially diagnosed only as a 'mediastinal mass'), skin carcinoma ($n=2$), and chronic lymphocytic leukaemia, acute lymphoblastic leukaemia, breast cancer, prostate cancer, endometrial carcinoma, 'malignant histiocytoma', or other undefined ($n=4$).

3.4. Disease manifestations

Details on histological diagnoses were fully reported in 253 cases. It was made from bone ($n=98$, 38.8%), lung ($n=80$, 31.7%), skin ($n=39$, 15.4%), lymph nodes ($n=16$, 6.3%), mucous mebranes ($n=11$, 3.9%) or other tissues ($n=10$, 3.9%). Overall, 26 patients (9.5%) were referred for fever and 31 (11.3%) for weight loss; 93 (33.9%) had local pain. The pattern of involved sites is shown in Table 1. Diabetes insipidus was diagnosed in 81 patients (29.6%).

3.5. Initial treatment

Initial therapeutic approaches are summarised in Table 2. Vinblastine was given to 82 patients (29.9%), with or without steroids, including 9 who received it with etoposide. Etoposide alone was administered as a primary therapy to 19 patients (16 with multisystem disease and 3 with single-system disease). 3 patients received 2-chlorodeoxyadenosine (2-CDA), 1 interferon and 15 other miscellaneous chemotherapy, including antileukaemic regimens. Cessation of smoking was prescribed to some of the patients.

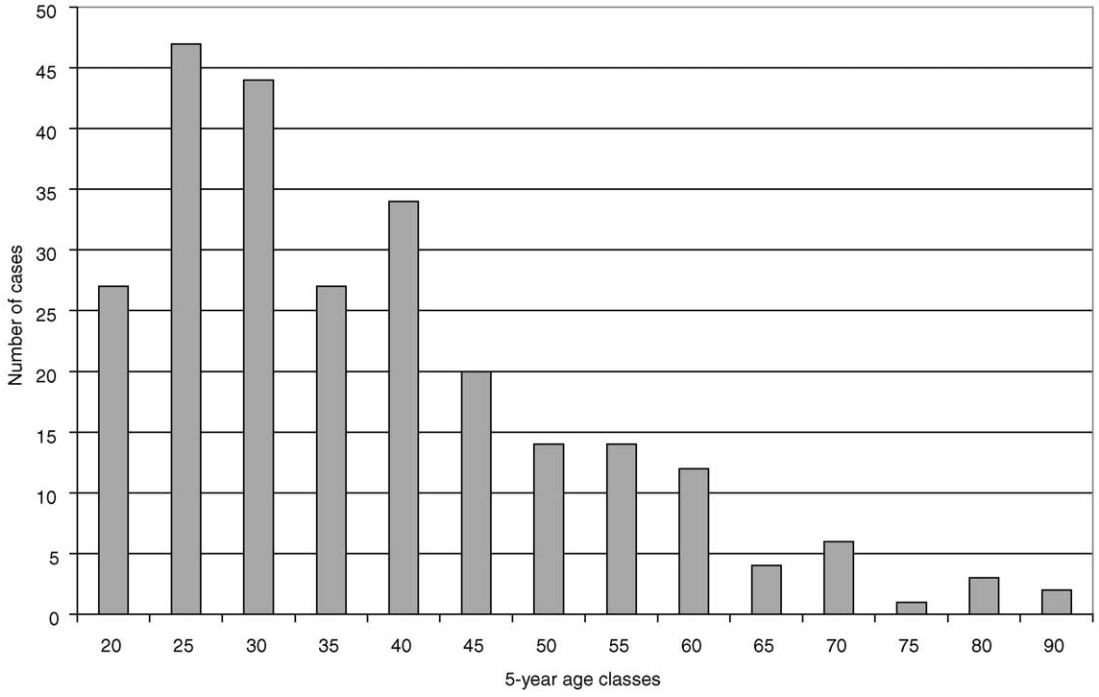

Fig. 3. Age distribution for patients with LCH diagnosed at 18 years or older.

3.6. Survival analysis

A total of 236 patients were evaluable for survival at median follow-up times of 54 months (IQR 26–115) from disease onset and 28 months (IQR 10–67) from diagnosis. 15 patients died (6.4%), for a death rate of 1.1/100 person years (95% CI 0.7–1.8) from disease onset and 1.5/100 person years (95% CI 0.9–2.4) from diagnosis. The probability of survival at 5 years was 92.3% (95% CI 85.6–95.9).

Table 1
Pattern of disease involvement in 274 patients with LCH diagnosed at 18 years of age or older

	Single system (86 patients) *n* (%)	Multisystem (188 patients) *n* (%)	Total (274 patients) *n* (%)
Bone	33 (38.3)[a]	124 (66.0)	157 (57.3)
Skin	6 (7.01)	95 (50.5)	101 (36.9)
Lung	44 (51.1)	116 (61.7)	160 (58.4)
Diabetes insipidus	0	81 (43.1)	81 (29.6)
Hepatosplenomegaly	1 (1.2)	44 (23.4)	45 (16.4)
Hypothyroidism	0	18 (9.6)	18 (6.6)
Other	2 (2.4)		

[a] Multifocal in 13 patients (4.7%).

Table 2
Initial treatment in 269 patients with LCH diagnosed at the age of 18 years or older, according to the pattern of disease manifestation

	Chemotherapy *n* (%)	Immunotherapy[a] *n* (%)	None *n* (%)
Single system	10 (34.5)	1 (3.4)	18 (62.1)
Single-system multifocal	9 (69.3)	0	4 (30.8)
Pulmonary isolated	9 (20.9)	4 (9.3)	30 (69.8)[b]
Multisystem	110 (59.8)	16 (8.7)	58 (31.5)

[a] With prednisone and/or cyclosporine.
[b] Smoking cessation was prescribed in some cases.

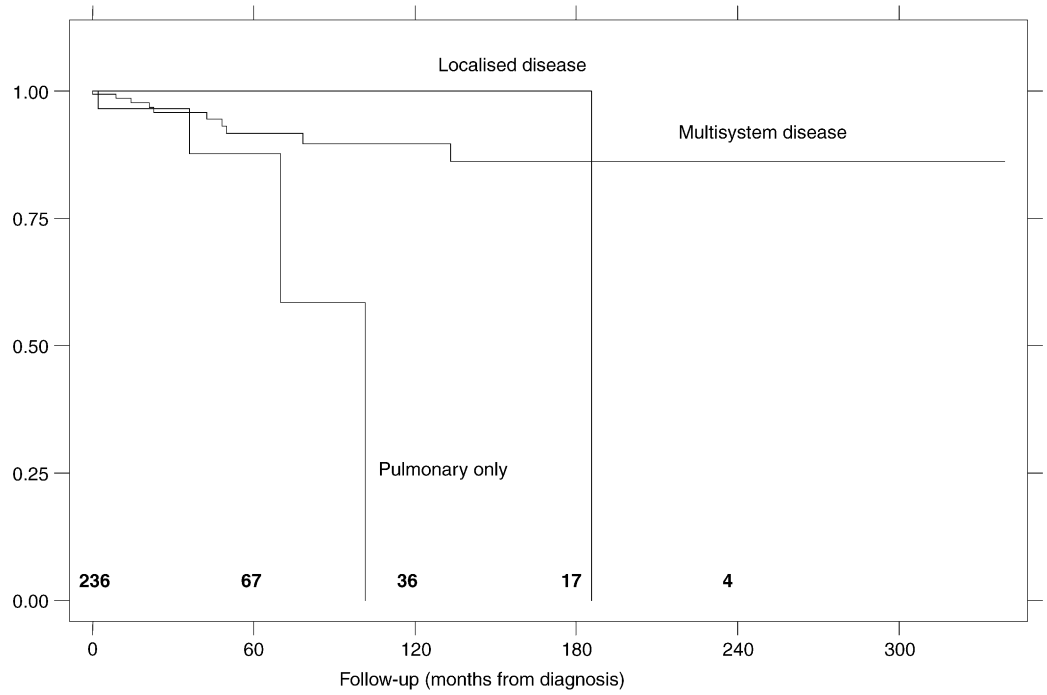

Fig. 4. Kaplan–Meier estimates of survival of 236 patients with LCH diagnosed at the age of 18 years or older, according to disease extension. Number of cases at risk is reported beneath the curve. Log-rank test, $P = 0.019$.

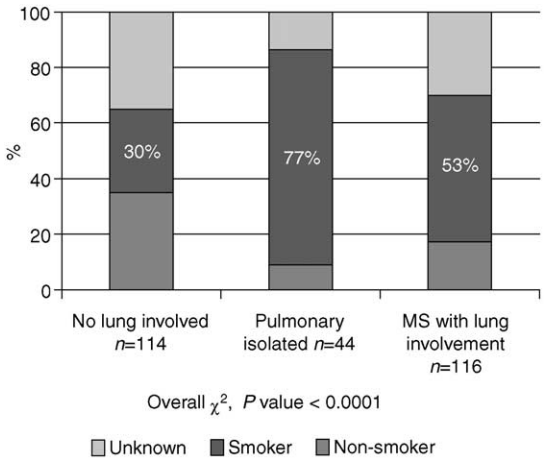

Fig. 5. Relation of smoking habit to lung disease in 274 adult patients with LCH. MS, multisystem disease.

Kaplan–Meier estimates of 5-year event-free survival according to disease extension were as follows: single-system disease ($n=37$), 100%; isolated pulmonary disease ($n=34$), 87.8% (95% CI 54.9–97.2); multisystem disease ($n=163$), 91.7% (95% CI 83.6–95.9) (Fig. 4).

In an attempt to assess the prognostic value of lung and liver involvement in patients with multisystem disease, we compared cumulative survival estimates of 117 such patients with those of patients whose multisystem LCH did not involve these organs. The results did not differ significantly ($P=0.1$). The 5-year survival probabilities were 93.6% (95% CI 84.7–97.4%) versus 87.5% (95% CI 65.5–95.9%), respectively.

4. Discussion

Retrospective studies such as this one always face the difficulty of obtaining complete information. As shown in Fig. 1, there was only a small amount of missing data for some variables, such as sites of disease involvement, age and other recognised clinical features, but for less quantifiable factors, including radiation exposures and hypothyroidism, the proportion of missing data in increased. While appreciating the inherent reporting biases that may affect the interpretation of these data, we believe that the spectrum of adult LCH characteristics presented here is the most valid and comprehensive reported to date.

Although a few patients were diagnosed from 1972 to 1988, the vast majority were diagnosed from 1992 to 2000. Thus, the effect of biases associated with changing attitudes over the preceding decades would be slight. Finally, the data were collected through the cooperation of specialists from a number of different medical fields, which may have reduced selection biases and contributed to a more realistic picture of the disease than would have been possible had all patients been seen in one or two specialised centres. For example, the proportion of patients with LCH restricted to the lungs was limited to 16%, while 69% had multisystem disease. The apparent increase of multisystem LCH diagnosed during the last 8 years of patient accrual (data not shown) might describe a learning effect among histiocytosis specialists, a phenomenon which is well known to have occurred in the diagnosis of other rare diseases.

In our series, both genders were affected, with a slight preponderance of males (52%). This contrasts to a recent report by Islinger and colleagues [21], who observed a 75% predominance of men in an orthopaedic series of 211 adult patients with LCH. In our study, although the mean age at diagnosis was 35 years, 25% of the patients were older than 43 years, and 10% older than 55 years (Fig. 3). The diagnosis of LCH was often delayed. The median latency time was 4 months, with an IQR of 0–22 months, but in 5% of cases it spanned 10 years, confirming that the rarity of the disease may be responsible for a suboptimal awareness in some cases. In particular, for patients presenting with isolated diabetes insipidus, the median latency time was 11 months (IQR 0–48).

The pathogenesis of LCH remains largely obscure. Recently, evidence of a genetic predisposition with familial clustering has been documented [13]. In the present series, only 1 patient (0.4%) had evidence of familial LCH. 2 others (0.7%) had parental consanguinity and, more importantly, 8 patients had a family history of diabetes insipidus, a rare disease in itself [22]. Thus, we suggest that the 0.4% incidence of familial disease should be regarded as the lower limit of a likely more frequent phenomenon and is in keeping with the 1% incidence documented in children [13].

There are no known environmental or racial risk factors associated with LCH, the only exception being cigarette smoking in pulmonary disease. In our series, in which exposure to radiation and benzene was minimal or absent, 77% of patients with isolated pulmonary LCH were reported to be smokers, compared with 30% of those in whom the lungs were not involved ($P<0.0001$; Fig. 5). This finding is consistent with a previous report from the Mayo Clinic in which only 3 of 90 patients with isolated pulmonary LCH were non-smokers [19]. This association is strongly supported by other clinical observations [23–25] as well as by animal studies showing that a LCH-like interstitial granulomatous inflammation in mice exposed to tobacco smoke reversed after the exposure was withdrawn [26].

In a recent review of pulmonary LCH by Vassallo and colleagues [27], extrapulmonary symptoms accounted for only 5–15% of patients, suggesting that pulmonary disease is by far the main manifestation of LCH in adults. By contrast, in our series, multisystem disease represented over two-thirds (68.6%) of the total cases, with skin and pulmonary involvement being present in

51 and 62%, respectively. We believe this to be the more accurate representation of LCH due to the large number of specialists who participated in the study, thereby reducing the referral bias.

Diabetes insipidus is one of the most peculiar complications of LCH and developed in 29.6% of our patients. In the largest studies of childhood LCH cases reported to date, the incidence of this complication ranged from 25% in 71 cases followed for a median of 8 years [28], to 19.5% in 133 Argentinean patients followed for 3 years [29], to 17% in 348 French cases followed for a median of 3 years [30]. Thus, the risk of development of diabetes insipidus among adults with LCH is probably equal to or even greater than that of children with LCH. It is still likely that LCH patients presenting with isolated diabetes insipidus or few additional symptoms may remain undiagnosed for extended periods of time, leading to an underestimation of this sequela, which is permanent and does not respond to any LCH-directed treatment.

The therapeutic approach to LCH depends largely on the pattern of disease manifestations and involved sites. In our large, unselected series of adult patients, the initial treatment decision included a 'wait-and-see' approach in 40% of the patients. While this approach may be reasonable for patients with localised disease, it is surprising that 31% of patients with multisystem disease were managed in the same way. Chemotherapy was administered to 60% of patients with multisystem disease, with vinblastine (with or without steroids) being the most frequent choice. Recently, the Histiocyte Society has established the combination of vinblastine and steroids as the current standard for the treatment of multisystem disease in children [17]. Clinical trials of the Histiocyte Society do not support further use of etoposide, a drug associated with a remarkably high risk for the development of leukaemia, especially in patients who have received multiple treatments due to recurrent disease. Optimal therapy for pulmonary LCH remains controversial. In our series, this sub-set of patients had a death rate of 5.6 per 100 person/years (95% CI 2.1–15.04), which overall was more than 4 times higher than that of patients with multisystem disease (1.2 per 100 person/years (95% 0.6–2.2)). Moreover, survival may largely be an inadequate endpoint in this disease, since many patients with pulmonary involvement may have a limited quality of life due to recurrent episodes of lung complications, such as pneumothorax, or progressive respiratory failure requiring lung transplantation, even at a young age [31–35]. Thus, optimal therapy for isolated pulmonary LCH remains to be determined. The restricted use of chemotherapy, as primary treatment in this cohort, supports the need for a clinical trial comparing different therapeutic approaches for LCH. The puzzling finding that patients with pulmonary isolated disease have a worse outcome than patients with multisystem disease, including lung involvement, might reflect either a different pathogenic mechanism or perhaps a different attitude concerning treatment.

In conclusion, LCH should be included in the differential diagnosis for adults with disseminated or localised disease involving not only the bone, skin and mucous membranes, but also the lung, endocrine and central nervous systems. Possible familial occurrence should always be investigated. All patients should undergo a careful multidisciplinary evaluation and follow-up to screen for possible asymptomatic localisations that could warrant prompt treatment. The standard therapeutic approach to adult LCH has not yet been established. The Histiocyte Society, with its extensive experience in clinical trials for children, proposes to initiate a randomised therapeutic trial for adults with LCH and invites all physicians caring for such patients to join in this effort. Studies of population-based incidence and important quality of life and late effect studies could also result from a sustained cooperation in this project.

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