

New clinical score for disease activity at diagnosis in Langerhans cell histiocytosis

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Background

The clinical presentation and course of Langerhans cell histiocytosis (LCH) are variable, ranging from an isolated, spontaneously remitting bone lesion to multisystem disease with risk organ involvement. Treatment of LCH ranges from a wait-and-see attitude to intensive multidrug therapy and, in some cases, bone marrow transplantation. It is necessary to develop an objective score for assessing disease activity in patients with LCH. We propose a new clinical scoring system to evaluate disease activity at diagnosis that can predict the clinical outcomes of LCH and correlate it with clinical courses.

Methods

Clinical data, obtained from children diagnosed with LCH at Asan Medical Center and Hanyang University Hospital between March 1998 and February 2009, were studied retrospectively. The scoring system was developed according to the basic biological data, radiological findings, and physical findings and applied to a database containing information on 133 patients.

Results

The median age of the 133 patients (74 male, 59 female) was 52 months (range, 0.6-178 months), and LCH was diagnosed based on CD1a positivity. At diagnosis, the score distributions were highly asymmetrical: the score was between 1 and 2 in 75.9% of cases, 3-6 in 15.8%, and greater than 6 in 8.3%. Initial scores above 6 were highly predictive of reactivation and late complications.

Conclusion

This new LCH disease activity score provides an objective tool for assessing disease severity, both at diagnosis and during follow-up.

Key Words Histiocytosis, Langerhans cells, Disease activity, Clinical score

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disorder with diverse clinical presentations and prognosis [1, 2]. Patients with localized disease need minimum or even no treatment, whereas patients with multi-organ involvement, more frequently young children, might benefit from cytotoxic drugs and steroids [1-3].

Disease activity is currently assessed using the Scoring System of the Histiocyte Society Protocol LCH III [4]. This

assessment system is semi-quantitative, with the following 4 categories: non-active disease, active disease-better, active disease-stable, and active disease-worse. The main drawback is that, by definition, each assessment is based on a comparison of the situation before and after therapy (or a 6-week interval) and is, in part, subjective. Donadieu et al. [5] developed a new quantitative scoring system for LCH disease activity at diagnosis as an objective tool for therapeutic decision-making. This scoring system also had some limitations; the authors did not evaluate the involvements of risk organs in the endocrine system or the central nervous system (CNS)



and leukocytopenia. Furthermore, pulmonary function tests are not easy to perform in individuals less than 5 years of age, but this test was included in their study as an important tool.

To treat LCH appropriately, it is essential to investigate disease activity and choose the optimal treatment options. In this study, our aim was to develop a new quantitative scoring system for LCH disease activity at diagnosis that is easy to apply to patients and can help therapeutic decision-making in the context of the wide spectrum of clinical features of LCH.

MATERIALS AND METHODS

1. Patients

Children diagnosed with LCH between March 1998 and February 2009 at Asan Medical Center and Hanyang University Hospital were included in this study. The diagnosis of LCH was confirmed by immunohistochemical staining with antibodies to CD1a, S100, or identification of Birbeck granules. Patient medical records were reviewed retrospectively for organ involvement at diagnosis, disease course, reactivation, and late sequelae. Single-system involvement was defined as unifocal or multifocal involvement of a single organ system, whereas multisystem involvement was defined as the involvement of multiple organ systems, with or without organ dysfunction [1-3]. Risk organs were the liver, spleen, lung, and the hematopoietic system [1-3]. Reactivation was defined as the development of a new bone lesion (old or new site) or new organ involvement, while the patient was not receiving therapy [6]. According to the LCH III definition, response after a 6-week follow-up period

was defined as better, intermediate, or worse. Better response was divided into 2 groups: complete resolution (non-active disease) and regression (active disease-better). Intermediate response was divided into two groups: mixed (new lesions in one site, regression in another site) and stable (unchanged). Worse response was defined as progression of signs or symptoms and/or the appearance of new lesions.

2. Definitions of the new clinical score

The new clinical score was developed by the authors based on basic biological data, radiographical findings, and clinical manifestations, as follows. Basic biological data: 1) hemoglobin <10 g/dL, infants <9 g/dL (exclusion of iron deficiency), 2) white blood cell count with differential <4.0×10⁹/L, 3) platelet count 100×10⁹/L, 4) bone marrow involvement (CD1a positivity), 5) elevated liver function tests and bilirubin, 6) total proteins/albumin, 7) coagulation studies (prothrombin time [PT]/partial thromboplastin time [PTT], fibrinogen), and 8) abnormal urine osmolarity after overnight water deprivation. Radiological findings: 1) chest radiograph: interstitial pulmonary involvement, bullae, pneumothorax, or typical changes on high-resolution CT, and/or histopathologic diagnosis, and 2) skeletal radiologic survey: osteolytic lesion. Clinical manifestations: 1) fever, defined as temperature elevated above 38.5°C, 2) pulmonary function: tachypnea (60/m in infants, 30/m in children), cough, chest pain, dyspnea, cyanosis, 3) hepatomegaly >3 cm below costal margin, 4) splenomegaly >2 cm below costal margin, 5) bone (multifocal), 6) risk of CNS involvement: lesions in the orbital, temporal/mastoid, sphenoidal, zygomatic, or ethmoidal bones, maxilla, sinuses or anterior or middle cranial fossa, with intracranial soft tissue extension, demonstrated on magnetic resonance imaging (MRI); vault lesions

Table 1. New clinical scores of Langerhans cell histiocytosis at diagnosis.

Variable	Score
Fever (38.5°C)	1
Skin rash	1
GI involvement	1
Endocrine involvement	1
CNS-risk lesion involvement	1
Lymphadenopathy	1
Bone involvement	
Single	1
Multifocal	2
Hematopoietic involvement (with or without bone marrow involvement ^{a)})	
Anemia: hemoglobin <10 g/dL, infants <9 g/dL (exclusion of iron deficiency)	1
Leukocytopenia: leukocytes <4.0×10 ⁹ /L	1
Thrombocytopenia: platelets <100×10 ⁹ /L	1
Spleen involvement	
Enlargement ≥2 cm below costal margin	3
Liver involvement	
Enlargement >3 cm below costal margin and/or liver dysfunction (hyperbilirubinemia, hypoalbuminemia, transaminases, ascites, edema) and/or histopathologic diagnosis	3
Lung involvement	
Typical changes on high-resolution computed tomography and/or histopathologic diagnosis	3

^{a)}CD1a positivity.

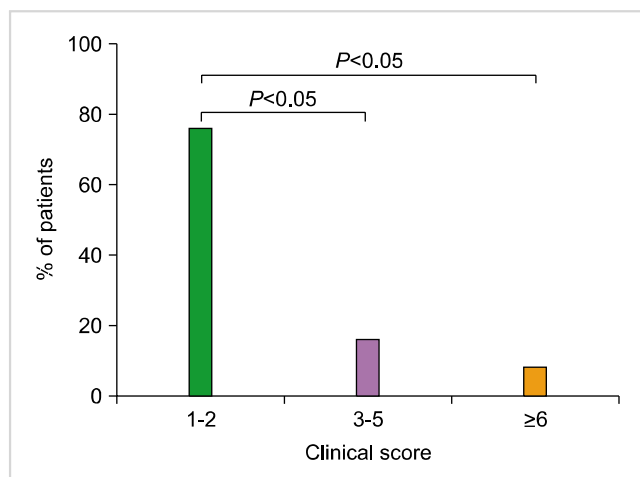


Fig. 1. The clinical score distribution at initial diagnosis. Scores between 1 and 2 were assigned to 75.9% (N=101) of cases, between 3 and 6 to 15.8% (N=21), and more than 6 to 8.3% (N=11). The number of patients with a score of 1 or 2 was significantly higher than the other groups.

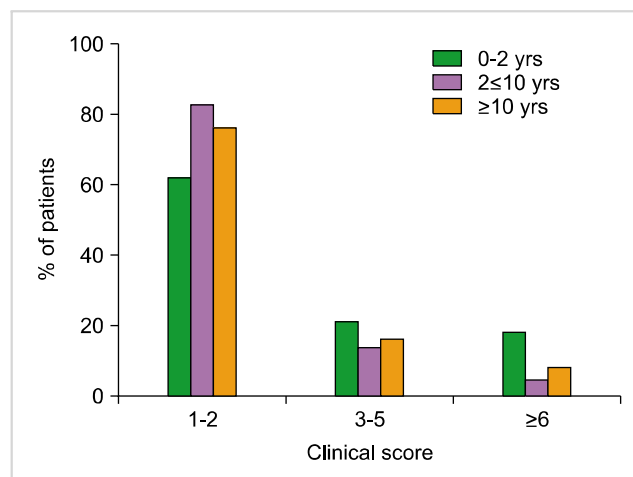


Fig. 2. The age distribution of 3 clinical score categories. In the group with scores of 1 or 2, the number of patients who were less than 2 years of age was higher than in the group with scores higher than 3. However, this difference did not reach statistical significance.

were not regarded as “CNS risk” lesions, and 7) lymphadenopathy. Scoring was done according to the contribution of each factor to the clinical course. Risk organ involvement was regarded as high risk and most important. The final scoring system is described in Table 1.

3. Statistical analysis

The SPSS 13.0 (SPSS, Chicago, IL) statistical software package was used for all statistical analyses. Scores of different groups at diagnosis were compared using the Kruskal-Wallis test. The reactivation-free survival rate was estimated using the Kaplan-Meier method. Differences in survival rates according to the scores were compared using the log-rank test. A P -value < 0.05 was regarded statistically significant.

RESULTS

1. Patients characteristics

One hundred fifty-one patients (69 female, 82 males) were available, but only 133 patients (59 female, 74 male) were included in this study. The data from 18 patients were not suitable for evaluation, because their complete data was not available. The median age of the 133 patients was 52 months (range, 0.1-178 months) and median follow-up duration was 125 months (range, 6-236 months).

2. Comparisons of the clinical courses according to the clinical scores

The score distribution at initial diagnosis was highly asymmetrical and is shown in Fig. 1. The score was between 1 and 2 in 75.9% (N=101) of cases, 3-6 in 15.8% (N=21) and more than 6 in 8.3% (N=11). The number of patients with a score of 1 or 2 was significantly higher than the other groups. In the groups with a score of 1 or 2, the number of patients who were less than 2 years of age was

Table 2. Therapeutic approach according to the new clinical scores.

	1-2 (N=101)	3-5 (N=21)	≥6 (N=11)
Wait and see, n (%)	6 (5.9%)	0 (0%)	0 (0%)
Local therapy, n (%)	39 (49.5%)	0 (0%)	0 (0%)
Systemic therapy, n (%)	56 (55.4%)	21 (100%)	11 (100%)

higher than in the groups whose scores were more than 3, but this did not reach statistical significance (Fig. 2). Six patients (4.5%) were not treated and follow-up studies revealed resolutions of the lesions; 39 patients (29.3%) had single bone involvement at diagnosis and received local therapy, such as curettage. All the patients who were not treated or received only local therapy were patients in the groups with a score of 1 or 2. Patients who had a score of more than 3 were all treated with systemic chemotherapy, whereas only 55.5% (56/101) of patients in score 1 or 2 groups received systemic chemotherapy (Table 2). When we compared the treatment response at 6 weeks, 93.1% (94/101) of the patients with scores of 1 or 2 had relevant to better responses (complete resolution, 43.6%; regression, 49.5%), whereas only 4 cases (4.0%) in this group had a worse response. In the group with scores of 3 to 5, 76.2% (16/21) of the patients fit the criteria for better response (complete resolution, 38.1%; regression, 38.1%), and the rest of the patients (5/21) proved to be stable. In the group with scores above 6, 27.3% of the patients (3/11) had a better response (regression, 27.3%) and none of the patients had complete resolution, whereas 36.3% of the patients (4/11) were observed to have a worse response (Table 3). The reactivation-free survival curves (Fig. 3) differed among these 3 score categories, with significantly higher number of reactivations occurring in

Table 3. Treatment response at 6 weeks according to the new clinical scores.

	1-2 (N=101)	3-5 (N=21)	≥6 (N=11)
Better			
Complete resolution	44 (43.6%)	8 (38.1%)	0 (0%)
Regression	50 (49.5%)	8 (38.1%)	3 (27.3%)
Intermediate			
Mixed	1 (0.9%)	0 (0%)	2 (18.2%)
Stable	2 (2.0%)	5 (23.8%)	2 (18.2%)
Worse			
	4 (4.0%)	0 (0%)	4 (36.3%)

Table 4. Late sequelae according to the new clinical scores.

	1-2 (N=101)	3-5 (N=21)	≥6 (N=11)
DI	3 (3.0%)	1 (4.8%)	0 (0%)
Endocrinopathy	0 (0%)	1 (4.8%)	2 (18.2%)
Neurologic disorder	0 (0%)	0 (0%)	3 (27.3%)
Pulmonary sequelae	0 (0%)	1 (4.8%)	1 (9.1%)
Orthopedic sequelae	5 (5.0%)	0 (0%)	0 (0%)
Hearing impairment	0 (0%)	1 (4.8%)	1 (9.1%)

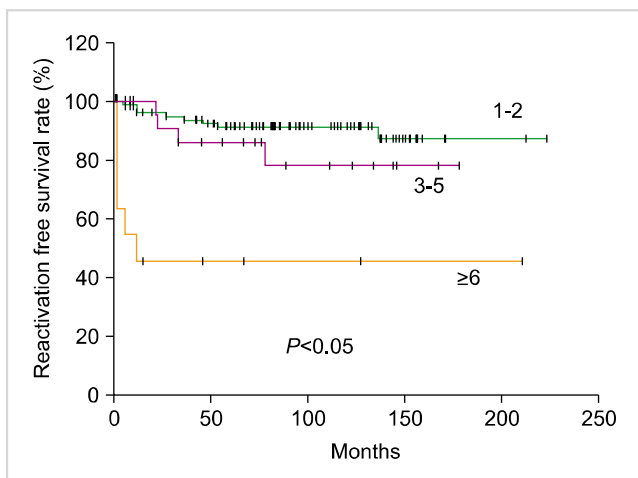


Fig. 3. The curve of reactivation free survival rate. The reactivation-free survival curves during follow-up in the high score group (>6) was significantly lower than in groups with lower scores.

the high score group (>6) than in the groups with lower scores during follow-up. In terms of late sequelae, orthopedic sequelae occurred more frequently in lower score groups (scores 1 and 2) and was associated with bone involvement (Table 4).

DISCUSSION

LCH has a variable clinical spectrum, and the course of the disease is unpredictable, varying from spontaneous regression and resolution to rapid progression and death or recurrence [1-3]. Patients with localized disease generally have a good prognosis and need minimal or even no treatment. Bone involvement with or without other associated sites is the most common manifestation of LCH and has been observed in 80-100% of cases [7]. The bones most frequently involved in LCH patients, in a study of 503 osseous lesions, were the skull (27%), femur (13%), mandible/maxilla (11%), pelvis (10%), vertebral bodies (8%), ribs (8%), humerus (5%), and tibia (3%) [8]. The prognosis is dependent on the number of organs involved, as well as the presence of organ dysfunction, and to a lesser degree, the age of the

patient at the onset of the disease [1-3]. Involvement of the spleen, lung, liver, or hematopoietic system also contributes to a poor prognosis [1]. In one large study of 101 children with LCH, the overall survival rate for all was 79% at 1 year, 74% at 3 years, and 71% at 5 years; however, in patients with liver or spleen involvement, the 1-year survival was 33% and 5-year survival was just 25% [9].

More detailed clinical information will help delineate the different entities of LCH clearly and may facilitate the development of an advanced classification system as a basis for selecting the appropriate therapeutic approach. Therefore, factors influencing the outcome of LCH must be identified to prevent or facilitate the treatment of disease progression and relapse. A quantitative disease activity score can help therapeutic decision-making, especially in complex situations such as multi-organ involvement. We developed a new quantitative scoring system for LCH disease activity, which is easy to practice and can help therapeutic decision-making in this disease. It may also serve to standardize the management of patients with very severe forms of LCH, who need more effective treatments.

According to our new clinical score, most of the patients were assigned scores of 1 and 2 (75.9%). The patients with low scores (1-2) did not have life-threatening disease, and the reactivation rate was lower in this group than in the higher score groups (Fig. 3). Most of the patients in this group were diagnosed with single or multiple bone involvement. Of these patients, only 55.4% received systemic chemotherapy, and 4.0% of the patients had a worse response at the 6-week evaluation. On the basis of these data, the treatment plan of these patients has to be simplified, and more attention may be needed to prevent functional sequelae. All the patients with moderate scores (3-6) received chemotherapy, and none of them showed progression at the 6-week evaluation. This group of patients showed reactivation-free survival rates comparable to the lower score group (1-2) (86.5% vs. 77.9%). Patients with high scores (>6) showed a poor short-term outlook: 36.3% of the patients progressed at 6 weeks and the reactivation-free survival rate was 45.5%. These results are much worse than for other groups. Such patients may therefore qualify for aggressive chemotherapy or even stem cell transplantation (Table 2, 3).

Comparing our scoring system with that of Donadieu et al. [5], their scoring system does not take bone involvement

into account, even though this is the most frequent manifestation. In addition, only bone pain was taken into account, and this is a subjective symptom and responds very rapidly to various treatments, including non-steroidal anti-inflammatory drugs. Radiological outcome was poorly characterized and was not used to assess disease activity or progression. Further, the score did not evaluate endocrine or neurological sequelae. Our new clinical scoring system accounts for all these factors and uses a simplified protocol.

The etiology and pathogenesis of LCH have remained an enigma [10-12]. The mechanisms of LCH cell development are still not completely understood. However, several mechanisms might play important roles, including multiple chromosomal alterations that have been found in LCH cells [13-15], and clonal proliferation of LCH cells [16-19]. Although definitive and consistent molecular events leading to clonal proliferation are unclear, high levels of cytokines are secreted by LCH cells, as well as by bystander cells in LCH lesions [20-22]. These cytokines could contribute to the proliferation and differentiation of LCH cell progenitors and could play a role in preventing LCH cells from maturing. The clinical course of LCH is quite variable, and we divided the LCH patients into 3 groups according to the new clinical scores. With this classification, we observed differences in clinical courses and outcomes among these 3 groups. Roughly, most of the patients with scores 1 and 2 have single system disease, especially bone involvement, and those with scores 3-5 have multisystem disease, without risk organ involvement, whereas patients with scores >6 have multisystem disease, with risk organ involvement. We pinpoint correlations between the clinical variability and different pathogeneses, albeit with caution.

The major limitation of this scoring system is that it has been applied to only a small patient dataset, in a retrospective fashion. In particular, a precise evaluation of late sequelae was not possible. We stress that it needs to be validated prospectively in larger patient populations. Future studies on the biology of LCH should enable us to better understand the pathology and mechanisms responsible for the development of LCH and its variable clinical course.

Despite these limitations, our new clinical score has the merit of being able to quantify LCH disease activity at diagnosis. We expect that this new clinical score can help therapeutic decision-making and formulation of improved follow-up plans in this variable disease. It may also serve to standardize the treatment of patients with severe forms of LCH, who need more intensive treatments.

REFERENCES

- Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008;25:291-5.
- Amir G, Weintraub M. Association of cell cycle-related gene products and NF-kappaB with clinical parameters in Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2008;50:304-7.
- Weitzman S, Egeler RM. Langerhans cell histiocytosis: update for the pediatrician. *Curr Opin Pediatr* 2008;20:23-9.
- Gadner H, Grois N, Arico M, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; 138:728-34.
- Donadieu J, Piguat C, Bernard F, et al. A new clinical score for disease activity in Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2004;43:770-6.
- Jubran RF, Marachelian A, Dorey F, Malogolowkin M. Predictors of outcome in children with Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2005;45:37-42.
- Glotzbecker MP, Carpentieri DF, Dormans JP. Langerhans cell histiocytosis: clinical presentation, pathogenesis, and treatment from the LCH etiology research group at the Children's Hospital of Philadelphia. *UPOJ* 2002;15:67-73.
- Kilpatrick SE, Wenger DE, Gilchrist GS, Shives TC, Wollan PC, Unni KK. Langerhans' cell histiocytosis (histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. *Cancer* 1995;76:2471-84.
- Alston RD, Tatevossian RG, McNally RJ, Kelsey A, Birch JM, Eden TO. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. *Pediatr Blood Cancer* 2007;48:555-60.
- Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008;25:291-5.
- Weitzman S, Egeler RM. Langerhans cell histiocytosis: update for the pediatrician. *Curr Opin Pediatr* 2008;20:23-9.
- Bechan GI, Egeler RM, Arceci RJ. Biology of Langerhans cells and Langerhans cell histiocytosis. *Int Rev Cytol* 2006;254:1-43.
- Chikwava KR, Hunt JL, Mantha GS, Murphy JE, Jaffe R. Analysis of loss of heterozygosity in single-system and multisystem Langerhans' cell histiocytosis. *Pediatr Dev Pathol* 2007;10:18-24.
- Betts DR, Leibundgut KE, Feldges A, Plüss HJ, Niggli FK. Cytogenetic abnormalities in Langerhans cell histiocytosis. *Br J Cancer* 1998;77:552-5.
- Scappaticci S, Danesino C, Rossi E, et al. Cytogenetic abnormalities in PHA-stimulated lymphocytes from patients with Langerhans cell histiocytosis. AIEOP-Istiocitosis Group. *Br J Haematol* 2000;111:258-62.
- Schouten B, Egeler RM, Leenen PJ, Taminiau AH, van den Broek LJ, Hogendoorn PC. Expression of cell cycle-related gene products in Langerhans cell histiocytosis. *J Pediatr Hematol Oncol* 2002;24:727-32.
- Bank MI, Rengtved P, Carstensen H, Petersen BL. p53 expression in biopsies from children with Langerhans cell histiocytosis. *J Pediatr Hematol Oncol* 2002;24:733-6.
- Petersen BL, Rengtved P, Bank MI, Carstensen H. High expression of markers of apoptosis in Langerhans cell histiocytosis. *Histopathology* 2003;42:186-93.
- Weintraub M, Bhatia KG, Chandra RS, Magrath IT, Ladisch S. p53 expression in Langerhans cell histiocytosis. *J Pediatr Hematol Oncol* 1998;20:12-7.
- Egeler RM, Favara BE, van Meurs M, Laman JD, Claassen E. Differential in situ cytokine profiles of Langerhans-like cells and T cells in Langerhans cell histiocytosis: abundant expression of cytokines relevant to disease and treatment. *Blood* 1999;94:

- 4195-201.
21. Annels NE, Da Costa CE, Prins FA, Willemze A, Hogendoorn PC, Egeler RM. Aberrant chemokine receptor expression and chemokine production by Langerhans cells underlies the pathogenesis of Langerhans cell histiocytosis. *J Exp Med* 2003; 197:1385-90.
22. Andersson By U, Tani E, Andersson U, Henter JI. Tumor necrosis factor, interleukin 11, and leukemia inhibitory factor produced by Langerhans cells in Langerhans cell histiocytosis. *J Pediatr Hematol Oncol* 2004;26:706-11.

Filler Photo



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