

# Permanent Consequences in Langerhans Cell Histiocytosis Single Center Study

Arjmandi Rafsanjani Kh.,<sup>1</sup> Bahoush GR.,<sup>1</sup> Vossugh P.,<sup>2</sup> Hedayatiasl AA.,<sup>3</sup> Faranoush M.<sup>4</sup>

<sup>1</sup>Assistant professor of pediatric hematology and oncology, Iran University of Medical Sciences, Ali Asghar children's Hospital

<sup>2</sup>Professor of pediatric hematology and oncology, Iran University of Medical Sciences, Ali Asghar children's Hospital

<sup>3</sup>Fellowship of pediatric hematology and oncology, Iran University of Medical Sciences, Ali Asghar children's Hospital

<sup>4</sup>Assistant professor of hematology and oncology, Semnan University of Medical Sciences, Amir al Momenin Hospital

\*Corresponding Author

## Abstract

**Introduction:** Langerhans cell Histiocytosis (LCH) is a rare disease characterized by clonal proliferation of Histiocytosis in different tissues. Permanent consequences (PC) described among subjects with Langerhans cell histiocytosis (LCH). In this study we report the prevalence of permanent sequel among long – term survivors of LCH in our center.

**Methods:** We had 30 cases of LCH from 1989 – 2001 who came for at least 3 years after diagnosis. Information has been collected from their disease history, and on type and date of onset of any PC. The cumulative risks of developing a PC have been calculated from the date of LCH diagnosis using the Kaplan-Meier and non-parametric method.

**Results:** Among 30 patients 53.3% were female, 46.67% male, mean age at diagnosis 56.86%±7.79 months (range 7-156), median 42.5 months. 19 (63.33%) had single system (SS) and 11 (36.66%) multisystem (MS). Mean age at SS 5.97 ±1.03 yr, mean age of MS 7.59±1.05 yr. Mean age at follow up 11.3 ± 0.9 yr, median 11.5 yr, range 4.16-22 yr. Mean duration of follow up 6.57 ± 0.76 yr, median 5 yr, and range 3-18 yr. Nine of 30 cases (30%) had at least 1PC; in SS (26.3 %) and in MS (36.7%). The most frequent PC was diabetes insipidus (DI) 16.7%, in SS 5.26% , in MS 36.36%, the difference is significant P<0.05. Orthopedic abnormalities 10% which was only in SS (15.79 %), growth retardation (GR) 13.34%.

**Conclusion:** The prevalence of PC in our patients is low which could be due to a small sample and on the other hand as most of our patients had single system involvement, the exact prevalence of PC is not clear. Analysis of cumulative risk shows that some types of PC may become manifest many years from diagnosis and long term follow up is necessary for all patients.

**Key words:** LCH, long – term survivors, DI and other problems

Received: 5, Feb., 2005

Accepted: 20, Apr., 2005

## Introduction

Langerhans cell Histiocytosis (LCH) is a rare disease characterized by clonal proliferation of histiocytes in different tissues.<sup>(1)</sup> It is a complex disease that includes the syndromes originally described as Hand Schuller Christian disease.<sup>(2)</sup> Letterer Siwe disease<sup>(4,5)</sup>, and eosinophilic granuloma.<sup>(6)</sup> Hand–Schuller–Christian disease was first described in 1893 and includes the triad of lytic skull lesions, exophthalmos and diabetes insipidus.<sup>(2,3)</sup> Letterer–Siwe disease was described independently in 1924 and 1933.<sup>(4,5)</sup> The ratio of male to female incidence is 2:1. Most cases occur in children between 1 and 15 years of age. The patients were infants

with symptom included fever, diffuse purpura, purulent otitis media, lymphadenopathy and hepatosplenomegaly. The localized form of this syndrome eosinophilic granuloma or solitary bone, lung or lymphnode involvement ,was not described until 1940.<sup>(6)</sup> The annual incidence of LCH has been calculated to be between 3 and 7 cases per million people with males being more affected than females.<sup>(7,8)</sup> Patients develop the disease at all ages, with a peak occurrence at 1 to 4 years of age. Although the prognosis of LCH is good, late sequels are often described<sup>(9-13)</sup>. In this study we report the permanent consequences (PC) of our patients from 1989 to

2001 which referred to our ward for at least 3 years from diagnosis.

## Methods

After the report on PC in LCH patients in Pediatric Blood and Cancer 2004, 42.438-444, we decided to evaluate our LCH patients for PC. In the period of 1989-2001, 40 LCH patients referred to our unit, among these 30 patients came at least 3 years after diagnosis. For each patient data was collected on demographic, method of diagnosis, system involvement at diagnosis according to criteria proposed by the HS<sup>(14)</sup>, date of diagnosis, date of last information, and type of PC. PC was defined as any irreversible clinical condition developed at any time during the course of the disease or related to treatment. For this study subjects were stratified according to system involvement. The prevalence of PC was calculated overall by system involvement. The cumulative risks of developing a PC were calculated from date of LCH diagnosis using the Kaplan Meier.<sup>(15)</sup> Statistical tests were non-parametric methods and tests were considered significant when  $P < 0.05$ .

## Results

Among 30 patients, 16 (53.3%) were female and 14 (46.7%) were male. Mean age at diagnosis was  $56.86 \pm 7.7$  months, range 7-156 months median 42.5 months. 11 (36.7%) had multisystem (MS) and 19 (63.3%) had single system (SS). Mean age at SS.  $5.97 \pm 1.03$ yr, mean age of MS.  $7.59 \pm 1.05$  yr. Age at follow up  $11.3 \pm 0.9$  yr, median 11.5 yr, range 4.16-22 yr. Mean duration of follow up  $6.57 \pm 0.76$  yr, median 5 yr, and range 3-18 yr. At least one PC was detected in 9 cases (30%), 4 (36.36 %) in MS and 5 (26.31%) in SS. Five (16.7 %) patients had DI, one (5.26%) in SS and four (36.36%) in MS. Two patients had DI at diagnosis, one during the treatment and two after treatment. Four cases (16.7%) had growth retardation (GR), three in SS and one in MS. Three had orthopedic problem only in SS, in one case mild kyphosis with fusion in L1, L2 and T12, in the other scoliosis in vertebra column and in the last one depression of occipital bone. Table 1 shows percentage of LCH cases with PC and system involvement, figures 1, 2, 3 and 4 show estimated cumulative risk for developing PC, DI, GR, orthopedic abnormality

and table 2 shows correlation between selected PC and LCH localizations.

## Discussion

The prevalence of PC in this study is 30%, in single system 26.3% and in multisystem 36.36%, most of our cases had single system disease. Willis et al<sup>(16)</sup> reporting 51 LCH cases with more than 3 years follow up, with an overall prevalence of PC was 71%. They described at least 1 PC among all their 21 multisystem cases. Nanduri et al<sup>(17)</sup> found 75% prevalence of PC among 40 multiple cases that followed for more than 5 years after the end of treatment. In pilot study from The Histiocyte Society, late effect study group among 182 subjects, 95 (52%) had at least 1 PC, MS 71%, SS 24%.<sup>(18)</sup> DI was the most reported PC of long-term survivors of LCH 23%<sup>(18)</sup>, the last case was diagnosed more than 8 years after LCH, this percentage is the highest reported in the literature,<sup>(17,19)</sup>. In our 30 patients the prevalence of DI was 16.7%, SS 5.26 % and MS 36.36 %, the difference was significant  $P < 0.05$ . Risk factors for DI correlated with localization of LCH to skull, CNS, ears. It was previously confirmed by Grois et al.<sup>(20)</sup> In our patients, 40 % of primary site were in skull, 20% in CNS, 20% in ear (table 2). Evidence of growth retardation was significantly associated with the risk of DI. Growth retardation was seen in our patients 13.36%, their primary sites were 25 % in skull and 40 % of GR had DI. We had 3 cases (10 %) orthopedic abnormalities, but all of the patients had SS, as sequel of primary site, so the prevalence in SS was 15.79%. Orthopedic abnormality had been reported by 42% in Willis et al<sup>(15)</sup> and 2.5% by the French LCH study group.<sup>(11)</sup> Discrepancies are most probably due to the different length of follow up.<sup>(18)</sup> We don't have neurological PC among our patients, it was 11% in Histiocyte Society study<sup>(18)</sup> and 14% by Willis.<sup>(16)</sup> Our patients don't have any other problems, such as loss of teeth, hepatic or pulmonary involvement and hearing loss. Second cancer was reported in LCH cases<sup>(19-21)</sup> but not among our patients. In conclusion, among 30 patients of LCH that we studied, 30 % had at least 1 PC, the low percentage is probably due to small number of patients in the study and few with ms disease in our center and long term follow up is necessary for all patients with LCH.

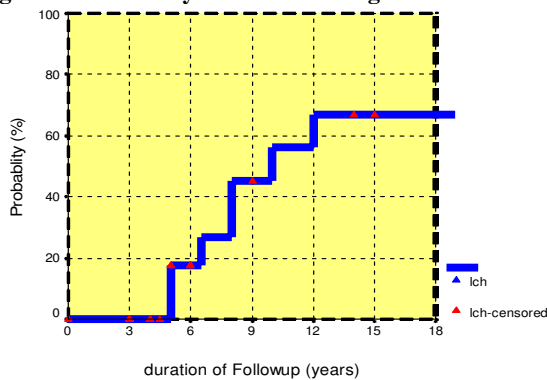
**Table 1: Percentage of LCH Subjects Reported With PC Overall and by system involvement % with sequel**

	Single system (n=19)	Multisystem (n=11)	Total (n=30)
Permanent consequence	Yes	Yes	
Diabetes insipid us	1	4	5
Growth retardation	3	1	4
Orthopedic problems	3	0	3

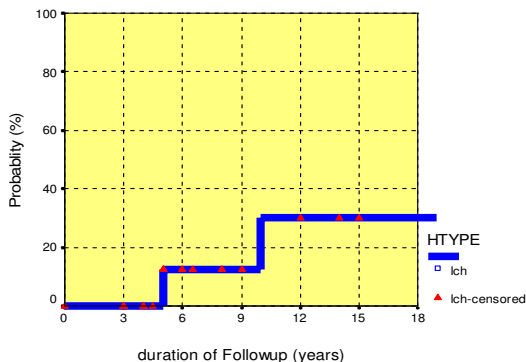
**Table 2: Correlation between Selected Permanent Consequences and LCH Localizations.**

	SKULL		CNS		Growth Retardation		Ear	
	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
<b>DI</b>								
Yes	2 (40)	3 (60)	1 (20)	4 (80)	2 (40)	3 (60)	1 (20)	4 (80)
No	12 (48)	13 (52)	1 (4)	24 (96)	2 (40)	20 (90)	2 (8)	23 (92)
<b>Growth Retardation</b>								
Yes	1 (25)	3 (75)	0 (0)	4 (100)				
No	11 (47.8)	12 (52.2)	1 (4.3)	22 (95.7)				

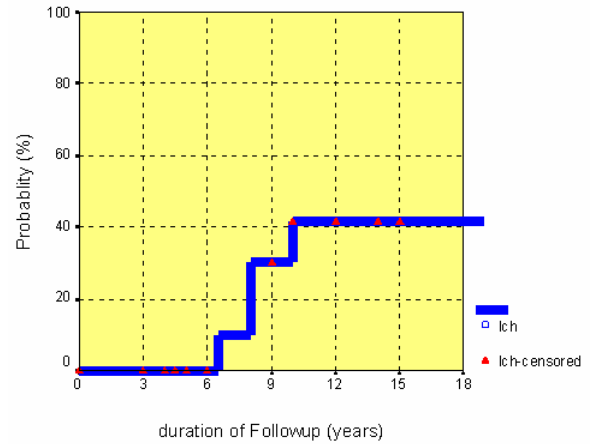
**Figure 1: Probability of P.C. following to LCH.**



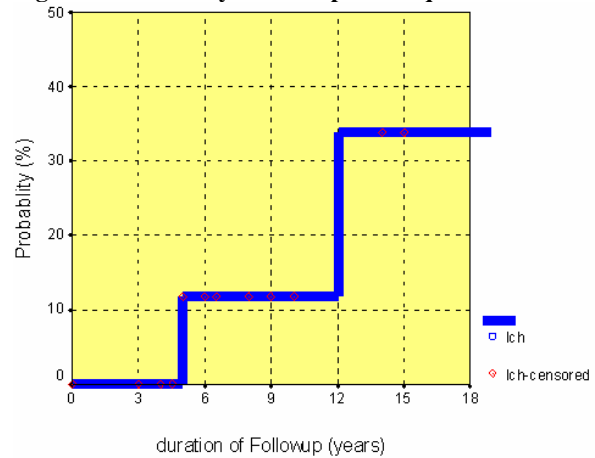
**Figure 2: Probability of Growth Retardation after LCH.**



**Figure 3: Probability of DI following to LCH.**



**Figure 4: Probability of Orthopedic Sequel after LCH.**



**References**

1. Willman C, Busque L, Griffith BB, et al. Langerhans, cell histiocytosis ( histiocytosis X ), a clonal proliferative disease. N Engl j Med 1994; 331: 154–160.
2. Schuller A: Ueber eigenartige schadefekte im jugendalter. Fortschr rontgenstr. 1915; 16(23): 12.
3. Christian HA: Defects in membranous bones, exophthalmos and diabetes insipidus, an unusual syndrome of dyspituitarism. Med Clin North Am. 1920; 3: 849.
4. Letterer E: Aleukamische retikulose (ein be tag zu den proliferativen erkankungen des retikuloendothelialapates). Frank pathol Z. 1924; 30: 377.
5. Siwe SA: Die rieticuloendotheliose–ein never krankheitsbild unter den hepatosplenomegalien. Z kinderh 1933; 35: 212.
6. Lichtenstein L, jaffee HL: Eosinophilic granuloma of bone with report of a case. Am J pathol 1940; 16: 95.
7. Nicholson HS, Egeler RM, Nesbit ME. The epidemiology of Langerhans cell histiocytosis. In egeler RM, D, Angio GJ, eds. Hematology / Oncology Clinics of North America 12. Philadelphia, W.B.Saunders, 1998; 379–384.
8. Hamre M, Hedberg J, Buckley J , et al Langerhans cell histiocytosis : an exploratory epidemiologic study of 177 cases .Med ped Oncol 1997; 28: 92-97.

9. Ceci A, De Terlizzi M, Colella R, et al. Langerhans cell Histiocytosis in childhood: Results from the Italian cooperative AIEOP–CNR–HX, 83 Study. *med padiatr oncol* 1993; 21 : 259–264 .
10. Gardner H, Heitger A, Grois N, et al. Treatment strategy for disseminated Langerhans cell histiocytosis. *Med padiatr oncol* 1994; 23: 72- 80.
11. The French Langerhans, cell histiocytosis study group. A multicenter retrospective survey of Langerhans, cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996; 75: 17 – 24.
12. Minkov M , Grois N, Heitger A , et al Treatment of multisystem Langerhans cell histiocytosis results of the DAL – HX 83 and DAL – HX90 studies . DAL – HX study group. *Klin padiatr* 2000; 212: 139-144.
13. Gardner H. Grois N, Arico M, et al. Arandomized trial of treatment for multisystem Langerhans, cell histiocytosis. *J padiatr* 2001; 138: 728 – 734.
14. Lahey E. Histiocytosis X- An analysis of prognostic factors .*J padiatr* 1975; 87: 184 – 189.
15. Kaplan EL, Meier p, Nonparametric estimation for incomplete observations *J Am Stat Assoc* 1958; 53: 457-481.
16. Willis B, Ablin A, Weinberg V, et al. Disease course and late sequelae of Lngerhan,s cell histiocytosis : 25 – year experience at the university of California , San Francisco .*J Clin Oncol* 1996; 14: 2073 – 2082 .
17. Nanduri V, Levitt G, Stanhope R, et al. prevalence of late sequelae of multisystem langerhans , cell histiocytosis – A single institution study [ abstr ] .*Med padiatr Oncol* 1999; 32: 235.
18. Riccardo Haupt, MD, Vasanta Nanduri, MRCPCH , Maria Grazia Calevo, PhD, Cecilia Bernstrand , MD, JorgeL.Braier , MD , et al . Permanent consequences in langerhans cell histiocytosis patient.
19. Dunger DB, Broadbent V , Yeoman E, et al . The frequency and natural history of diabetes inspidus in childrens with Langerhans – cell histiocytosis. *N Engl J Med* 1989; 321: 1157 – 1162.
20. Broadbent V, pritchard J. Diabetes inspidus associated with Langerhans cell histiocytosis: Is it reversible *Med Padiatr Oncol* 1997; 28: 289 – 293.
21. Haupt R, Fears TR, Heise A, et al. Risk of secondary leukemia after treatment with etoposide ( VP-16 ) for Langerhans cell histiocytosis in the Italian and Austrian – German populations . *Int J Cancer* 1997; 719–13.
22. Egeler RM, Neglia JP, Arico M, et al, The relation of Langerhans cell histiocytosis to acute leukemia, lymphomas, and other solid tumors. The LCH – Malignancy Study Group of the Histiocyte Society. *Hematol Oncol Clin North Am* 1998; 12; 369 – 378.
23. Streubel, B, Ye, H, Du, MQ, et al. Translocation t(11;18)(q21;q21) is not predictive of response to chemotherapy with 2CdA in patients with gastric MALT lymphoma. *Oncology* 2004; 66:476.