



Outcome of Langerhans Cell Histiocytosis Among Children in Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh

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ABSTRACT

Background: To analyze the spectrum of challenges faced in the treatment of Langerhans Cell Histiocytosis resource limited settings lacking salvage therapy.

Methods: In this observational study, 30 patients of Langerhans cell histiocytosis were enrolled. Risk organ involvement, treatment course and outcome were analyzed. The patients were treated with vinblastine(iv) weekly, prednisolone(po) daily and MTX (iv) in 1st, 3rd and 5th week for 6 weeks and then 6 MP daily, MTX weekly, vinblastine every 3 weekly for 6 to 12 months according to risk group. Intravenous Cytarabine pulses used for 5 days 3-weekly apart and Japanese Protocol used for refractory cases. The salvage therapy available in developed countries in the form of 2-CdA (2-chlorodeoxyadenosine) and RIC SCT reduced-intensity conditioning stem cell transplantation not available in our center. **Results:** Age of the patients range from < 1 to 10 years (19% <2 yrs). M: F Ratio was 2:1. Majority (72%) of the patients presented with multisystem-LCH (MS-LCH) with 100% mortality in MS-LCH group (p-value=0.045) and 18/42 (43%) had risk organ involvement with 72% mortality. Twenty-nine (70%) had bone lesions and 12(29%) had central nervous system involvement. Fifty five percent completed treatment, 2/42 (5%) are on treatment, 9/42 (21%) abandoned treatment and 8/42 (19%) expired due to progressive disease and worsening infection. Sixteen (38%) had reactivations of disease requiring therapy for more than one year. Twenty four percent of cases received two cycles of initiation therapy before continuation therapy started. The treatment initiated >6 months after the onset of symptoms in 30/42 (72%) of cases with 100% expiries in this group and 89% of abandonment. The children presenting at younger age had risk of having MS-LCH 75% as compared to 36% in age >2years. **Conclusion:** Treatment abandonment, delayed diagnosis and poor social support are major challenges in treating LCH in developing countries. Early diagnosis and timely treatment with effective infection control measures and strong social support are of utmost importance to improve long term overall survival.

Keywords: Langerhans Cell Histiocytosis, Multiorgan, Chemotherapy.

INTRODUCTION

Langerhans Cell Histiocytosis (LCH) is a relatively rare disease accounting for about 1% of new cases each year enrolled in Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh. LCH previously termed as histiocytosis X occurs primarily in childhood and is a rare clonal disorder of Langerhans cell proliferation, the antigen presenting immature dendritic cells that originate in bone marrow.¹ The clinical manifestations vary widely from a self-limiting unifocal bone lesion to a multi-system disease including rapidly fatal organ dysfunction. Currently LCH is classified as single-system (SS) and multisystem (MS) disease again divided in two groups depending on risk organ (RO), namely, liver, spleen and bone marrow involvement, RO-negative MS and RO-positive MS disease.^{2,3} The incidence of LCH is 4-5 cases per million per year in children less than 15 years with peak at less than 3 years of age. It is more common in boys than girls (1.2-2:1). LCH is usually sporadic though genetic predisposition may play a role as it is reported in twins and 1% of patients have relatives with LCH.⁴ For LCH diagnosis, histopathological examination is essential with histiocytes positive for CD1a or Langerin (CD207) on immunohistochemistry. Langerin is a cell surface receptor that triggers the formation of the Birbeck granules which are Langerhans cell-specific tennis racquet-shaped organelle detected by electron

microscopy. Active LCH lesions contain LCH cells aggregates forming granulomas along with several inflammatory cells predominantly macrophages in later stages. When CD1a-positive cells show dysmorphic features and mitotic figures, Langerhans cell sarcoma should be excluded.^{5,6} The etiology of LCH has been debatable whether it is reactive based on the fact that these lesions sometimes show spontaneous regression and some virus DNA sequences have been found in blood and tissues of LCH patients.^{7,8} However, many facts support it as a neoplasm such as LCH cells are monoclonal and they also sometimes depict chromosomal deletion or gain more than 50% LCH patients, oncogenic BRAF V600E mutations are found associated with higher reactivation rate though present in equal frequency in SS and MS LCH.⁹⁻¹² Treatment course of LCH is quite variable depending on the extent and risk organ involvement. The mortality is less in SS LCH or without risk organ involvement is <5% and upto 10-50% in MS LCH and RO positive disease.¹³

PATIENTS AND METHODS

In this observational study, conducted at the department of Paediatric Haematology & Oncology of Bangladesh Shishu Hospital & Institute, Dhaka. Total 30 patients of Langerhans Cell histiocytosis were enrolled, from January 2020 to December 2024. Data regarding their age, sex, classification, Risk organ involvement, treatment course and outcome analyzed. The patients were treated with vinblastine(iv) weekly, prednisolone(po) daily and MTX (iv) in 1st, 3rd and 5th week for 6 weeks and then 6 MP daily, MTX weekly, vinblastine every 3 weekly for 6 to 12 months according to risk group. Intravenous Cytarabine pulses used for 5 days 3-weekly apart and Japanese Protocol used for refractory cases. The salvage therapy available in developed countries in the form of 2-CdA (2-chlorodeoxyadenosine) and RIC SCT reduced-intensity conditioning stem cell transplantation not available in our center.

RESULTS

Total 30 patients with age ranging from < 1 to 10 years (20% <2 yrs) were included. M: F Ratio was 2:1. Table 1 shows majority patients in both age group presented with multisystem disease, < 2 years age group 5(83.33%) and < 2 years age group 5(83.33%). P value 0.033 which is significant. In Table 2 all 12 patients in group A (Multi system risk patient) either expired 7(58.33%) or LAMA 5(41.67%) and P value is significant (0.042). In group B (Multi system low risk patients) among 10 patients 5 expired (50%) and 2 LAMA (20%) P value is significant (0.034). In group C among 8 patients 2 expired and 1 LAMA and P value is significant (0.041). Table 3 shows majority patients either expired (14) or leave hospital against medical advice (8) and only 7 patients out of 30 completed treatment and 1 on treatment. Among LAMA group majority abandoned treatment due to financial constrain. Etiology of our 14 death either due to progressive disease or worsening infection.

Table-1: Histiocytosis according to age of presentation

Group A: <2 Years: 6	MS-LCH: 5/6 (83.33%)	RO+: 4/6 (66.67%)
	SS-LCH: 1/6(16.67)	RO-: 2/6(33.33%)
Group B: >2 Years: 24	MS-LCH: 17/24(70.83%)	RO+: 18/24 (75%)
	SS-LCH: 7/24(29.17%)	RO-: 6/24(25%)
p-value: 0.033		

Majority patients are more than 2 years of age

Table-2: Outcome of Histiocytosis according to Risk Group

Group	Histiocytosis type	Patient number	Outcome		P value
Group A	Multi system risk patient	12	Expired: 7	58.33%	0.042
			LAMA*: 5	41.67%	
Group B	Multi system low risk patients	10	Expired: 5	50%	0.034
			LAMA: 2	20%	
Group C	Single system	8	Expired: 2	25%	0.041
			LAMA: 1	12.5%	

*Left against medical advice

Table-3: Langerhan Cell Histiocytosis overall Treatment Outcome in all risk group (n=30)

Parameter	Number	%
Treatment completed	7	23.33
On treatment	1	3.33
LAMA	8	26.67

Expired at home	9	30
Expired in hospital	5	16.67

Majority patients either expired or leave hospital against medical advice

DISCUSSION

LCH can involve any organ or system with clinical manifestations in skin, CNS, bone, lung, liver, lymph nodes and haematological system with wide differential diagnoses confirmed by histological and immunophenotypic examination of the lesions in the form of positive CD1a and or CD207 (Langerin) for a definitive diagnosis.¹⁴If the risk of biopsy is more than the need of definitive diagnosis, then effort should be made to exclude other conditions with similar radiological features and should be on close follow up.¹⁵In our study 72% cases had their symptoms for more than six months before their diagnosis of LCH was made and definitive treatment started. The combination of Vinblastine and prednisolone is being used in LCH since 1966 and alone or with other chemotherapeutic agents these have been used in different prospective trials in MS-LCH in over 1000 patients with excellent tolerability with overall success of at least 60%.¹⁶Therefore this combination can be used effectively in resource limited settings with success as it is cost effective and well tolerated as evidenced by LCH-III trials with 70% and 86% initial response in RO+ and RO-MS-LCH patients.¹⁷In LCH-IV, a large prospective trial, one of the focuses is to evaluate the role of second-line chemotherapeutic agents including cytarabine which minimize reactivations and permanent sequelae of LCH, a protocol which induces complete response and effective in neurodegenerative CNS-LCH. In refractory cases in risk –organ involvement it is suggested to be treated in specialized centers with a combination of cladribine (2-CdA and cytarabine (Ara-C) and in non-risk organ cases 2-CdA can be used as a monotherapy or further courses of standard vinblastine and prednisolone combination, but 2CdA and RIC-SCT is not available in our center so few cases expired due to progression of disease not responded to standard therapy.¹⁸⁻²⁰LCH can be cured with standard chemotherapy in low income countries as described in Guatemala, El Salvador, Honduras, and Nicaragua with 57% well in remission, 16% on treatment, 24% abandonment and 3% expiries as compared to our study showing 21% abandonment and 19% expiries due to progressive disease, advanced stages and superimposed infections. So, the focus should be on minimizing the abandonment in LCH patients in low-income countries.²¹Reactivation is common in MS-LCH up to 50% cases with spontaneous recovery in some and requiring treatment in others with resolution. This reactivation is more common in first two years of disease onset and bone is more frequently involved than risk organs. It results in permanent sequelae also requiring close follow up and monitoring.^{22,23}In our study 38% of cases had reactivation of LCH and 62% among MS-LCH requiring further treatment. These children need follow up and monitoring of permanent sequelae of different tissues like endocrinopathy (Diabetes Insipidus, Growth hormone deficiency, pubertal delay), orthopedic complications like scoliosis, hearing deficits requiring hearing aids, neuropsychological impairment (cerebellar ataxia, learning difficulties) and associated malignancies.²⁴These facilities are available in our center so these children are encouraged for long follow up and monitoring.

CONCLUSION

Delayed diagnosis, treatment abandonment and poor social support are major challenges in treating LCH in developing countries like Bangladesh.

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