TREATMENT AND SURVIVAL ANALYSIS FOR PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS – A SINGLE INSTITUTION REVIEW

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Introduction

Langerhans cell histiocytosis (LCH) is an inflammatory disease characterized by proliferation and accumulation of dendritic cells in a background of reactive macrophages, T lymphocytes and eosinophils. Historically it was described as three distinct clinical entities based on severity – eosinophilic granuloma, Hand-Schuller-Christian disease, Abt-Letterer-Siwe disease and histiocytosis X. Later these were unified under the term LCH as they were found to have similar underlying disease processes. LCH is a rare disease with annual incidence of about 3-9 cases per million in children.

The current classification of LCH is based on extent of organ systems involved at diagnosis. Single system disease (SS) LCH (involvement of one organ or system) most commonly involves skin and bone but can involve other organ systems. Single system involvement can be unifocal or multifocal in nature and usually carries an excellent prognosis. In contrast those patients who have multisystem (MS) or disseminated disease (>2 organ systems involved) have a less favorable prognosis.

LCH most commonly presents in infancy and early childhood. Patient frequently have some cutaneous manifestations which may mimic seborrheic dermatitis or eczematous lesions usually of the scalp especially in younger patients. Patients may have skin limited disease that can resolve spontaneously or with minimal therapy. In other cases, skin involvement can be a part of multisystem disease.

In patients with single system disease the most common presentation is bony lesions. These lesions can be unifocal or multifocal. In cases of solitary bone lesions the majorities are usually in the skull but can also present in vertebrae of any other long bone in the body. The X-ray appearance of bony lesions is that of a medullary lytic lesion. Vertebrae plana is another characteristic lesion in LCH, especially involving the thoracic region in children. Sclerosis may be present in the healing stage. MRI is used commonly to delineate marrow or soft tissue involvement in LCH of the bone.

There are lesions considered to be in critical anatomical sites, such as odontoid peg and vertebral lesions with intra spinal involvement that are not amenable to local control. These cases are considered to have disease in a “Special Site” due to the risk of disease progression and complications in attempting local control. There is also evidence that involvement of certain skull bones and lesions in the craniofacial area, referred to as ‘CNS Risk” lesions, predisposes the patients to development of endocrine dysfunction including diabetes insipidus. These include lesions in oral cavity, eye and ear involvement and craniofacial lesions. As a result, isolated disease in a “Special Site” or “CNS Risk” lesions can justify systemic therapy upfront.
There can be severe functional impairment in some patients when there are lesions noted within the cerebrum. The most common location involves the hypothalamic pituitary axis with granuloma presenting with diabetes insipidus and pituitary dysfunction. The second most common location is involvement of grey matter in the cerebellum, basal ganglia and brain stem. MRI findings in these cases represent so called "neurodegenerative LCH" (ND-LCH). It is a potentially devastating and long lasting often permanent complication of LCH. The clinical manifestations of ND-LCH are heterogeneous ranging from no or minimal neurological impairment, to very severe involvement in form of ataxia, intellectual and psychiatric issues and sometimes quadriplegia.

Another special consideration in patients with LCH is of risk organ (Liver, spleen, lung or bone marrow) involvement. Those patients with multisystem disease with risk organ involvement at presentation usually carry a worse prognosis and significant issues with morbidity and mortality. Another important prognostic factor is initial response to therapy. Other predictors of disease involvement, complications, recurrence, progression or survival are still under investigation9-10.

(Pictures 1-3) LCH Histology. Picture 1 shows H and E stain showing Histiocytic infiltration with reniform nuclei identified (arrow). Picture 2 with CD 1a staining and Picture 3 with CD207 staining which are characteristic for LCH.

(Picture 4-5) Skin LCH. Picture 4 with LCH rash mimicking diaper dermatitis and Picture 5 with LCH rash mimicking seborrheic dermatitis.
Because of the wide spectrum of clinical presentation usually seen in LCH, historically many different clinical approaches have been used. Single system LCH is usually treated with minimal and conservation approach to therapy. Those who present with small single skin lesions can sometimes be observed, others are treated with different dermatological approaches or minimal chemotherapy if needed.

The Histiocyte society initiated international randomized clinical trials using standard diagnostic strategies and disease monitoring methods. They used a treatment backbone of vinblastine and steroid. LCH I (1991-1995) compared vinblastine vs etoposide, together with pulse steroid for 6 month duration in patients with MS-LCH. Both the arms were equivalent in all criteria observed. In LCH II (1996-2001) patients were stratified based on risk factors i.e. < 2 years of age and/or risk organ involvement. Patients were randomized to receive Prednisone and vinblastine alone or intensified by adding etoposide to the combination. Also 6 Mercaptopurine was given during continuation phase in both groups. The total duration of therapy was 6 months. In both the arms, those patients with risk organ disease had higher survival rate than LCH I suggesting that intensification in therapy improved survival. In LCH III (2001-2008) those with risk organ disease received more intensive treatment by adding methotrexate and by increasing the duration to 12 months. In patients without risk organ disease, they were randomized to receive 6 or 12 month therapy12-16.

**Purpose of this study**

The main objective of this study is to determine the incidence of LCH patients diagnosed at Children’s hospital New Orleans during the time period (2005-2014) and to compare our treatment and outcome data and results to national and international data reported through the Histiocyte society.

**Methods**

A retrospective analysis of the medical records of subjects diagnosed with Langerhans Cell Histiocytosis treated at Children’s Hospital New Orleans (CHNOLA) from 2005-2014 was performed after appropriate Institutional Review Board approval was obtained. The number of cases diagnosed during the study period was abstracted from the institutional tumor registry after obtaining approval from the Cancer Committee Chair. Internal Classification of Diseases (ICD-9) codes were also used to facilitate the identification of the LCH cases. During the study period, 41 subjects were identified with the diagnosis of Langerhans Cell Histiocytosis at Children’s Hospital New Orleans.
Information was collected through the medical records here at Children's Hospital New Orleans. The age, date of diagnosis, date of symptom onset, location of LCH involvement, presence and absence of Risk organ involvement. Presence or absence of CNS special site involvement, type and duration of therapy used (including observation), response to therapy, and time to recurrence or disease progression and mortality data were recorded.

The incidence and location of progression and recurrence were recorded as counts and proportions using categorical variables, and age of symptom onset, age at diagnosis, and time to disease progression were recorded as means and ranges.

Results

A total of 41 patients were diagnosed and treated for Langerhans cell histiocytosis at Children's Hospital New Orleans during 2005 - 2014. Figure 1 shows the distribution of LCH by year during that time period. The distribution by year of diagnosis at certain timeframes are even throughout the 10 year duration.

Figure 2 shows the classification of LCH at diagnosis. Out of the total 41 patients, 20 (49%) presented with single system involvement and 21 (51%) presented with multisystem disease. Of those with single system involvement, 17 (42%) presented with bony involvement and 3 (7%) presented with only skin manifestations. Of those 17 patients who had bony disease, 13 (76%) presented with unifocal bone involvement and 4 (24%) presented with multifocal bony lesions.

21 patients presented with multisystem disease at presentation. 13 (62 %) presented with risk organ involvement and 8 (38%) patients did not have risk organ involvement. Of the patients with risk organ involvement, the most common site was liver (11 patients), spleen (7 patients) and bone marrow disease (4 patients).

Figure 3 shows the baseline demographic characteristics of our patients. Out of 41 total patients 22 patients (54 %) were male and 19 patients (46%) were female. The Age of diagnosis ranged from 0.2 years to 16 years with a mean age of presentation of 2.1 years. 22 (54%) of our patients were younger than 2 years at presentation.

Figure 4 shows the treatment used for patients with single system disease. Of the 13 patients with unifocal bone disease, 9 patients were treated by orthopedic service with curettage only. 4 of these patients received chemotherapy as part of their treatment. Those patients receiving chemotherapy had either “Special Site involvement or “CNS risk” lesions at presentation. All 4 patients with single system - multifocal bone lesions were treated with chemotherapy. All of these patients had either “Special Site” or “CNS risk ” lesion involvement. Of the 3 patients who presented with skin lesions only, 2 were treated with chemotherapy and one received treated local treatment.
Figure 4 shows data regarding treatment response in our patients. Of the 20 patients with single system disease, 4 (20%) had either progression or reactivation. There was no mortality in any of these patients. In those with unifocal bone disease, 1/13 (8%) patient had either reactivation / progression. This patient had special site involvement at presentation. In those with multiple bony lesions 2/4 (50%) patients had reactivation/progression. Both of these patients had either special site or CNS risk lesion involvement. Of those with skin only disease 1/3 (33%) had reactivation. This patient had extensive skin involvement at presentation. For patients with Single system disease there was no comparative LCH III data but historically these patients do very well with usually no mortalities but documented morbidities.

In patients with multisystem disease, all patients received systemic chemotherapy. The duration of therapy differed in some patients treated earlier as new emerging data suggested prolonging therapy in these patients. 10/21(48%) patients with Multisystem disease had reactivation / progression. The mean duration of follow up for these patients was 3.2 years.

Of the 8 patients without risk organ disease at presentation, 4 patient (50%) had reactivation / progression (Figure 5). The mean duration for follow up for these patients was 2.7 years. Five of these 8 patients were treated with therapy duration of 6 months or less and 3 of these 5 patients had reactivations or progression (60%). This was comparable to LCH III data as they reported a 5 year reactivation rate of 52 %. Three
patients were treated for duration of 6 to 12 months. Only 1 of these 3 (33%) patients had reactivation/progression which was also comparable with LCH data. They reported a 5 year reactivation rate of 37%.

As discussed previously, one of the most significant prognostic factor for multisystem LCH with risk organ disease is response to therapy. LCH III measured response at 6 weeks, 3 months and 12 months of therapy. All patients in LCH III with risk organ disease were treated for duration of 12 months. Again, due to the time period of our study (2005-2014), some of the patients received 6 months therapy and others 12 months therapy. Out of 13 patients with risk organ positive disease, 5 patients received therapy for 6 months and 8 patients received therapy for duration of 12 months. 1 patient was disease free after 6 weeks (8%), 3 patients after 3 months (23%) and 9 patients after 12 months (69%). All of the patients with risk organ disease received 12 month therapy. Comparison to LCH III is shown in figure 6. The response is comparable at all time points with the exception of the response at 12 months showing higher response rate than LCH III results.

Of the 13 patients with risk organ disease, 6 patients (46%) had either reactivation/progression. The mean age of follow up for these patients was 3.5 years. When further analyzing it by duration of therapy, 3/5 (60%) patients who received 6 months therapy had reactivation/progression. In contrast, only 3/8 (38%) who received therapy for 12 months had reactivation/progression. In this group LCH III reported a 5 year reactivation rate of 27%.

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Discussion

The data from this study clearly confirms the known facts that most of the patients with Single system LCH have a very good response rate. In the long term, some of these patient are at risk for progression or reactivation. In contrast those patients with multisystem disease are divided into two broad categories based on the involvement of risk organs. In those patients without risk organ involvement the survival is usually very good with mortality rates reported to be less than 1%. These patients are still at risk of reactivations and morbidities associated with the disease and treatment offered. Patients with multisystem risk organ disease have the highest risk for disease related mortality and morbidity. These are the patients who are sometimes resistant to therapy therefore the initial response to therapy is an important prognostic factor. These patients have historically been known to have reactivations and progression of disease and as such newer therapeutic approaches have included treatment intensification and therapy prolongation for these patients. These patients may become resistant to first line therapy and may require second, third line or even eventually salvage therapy.

Recently there has been much interest in the role of BRAF V600E mutations in LCH. This mutation has been found in the dendritic cells of 60% of LCH patients. The specificity of finding LCH in the LCH dendritic cells compared to surrounding cells has sparked a new discussion about the pathophysiology of LCH suggesting that LCH may be a clonal process rather than a reactive inflammatory process as thought previously.

As noted earlier, patients with involvement of "Special Sites" or "CNS risk" lesions have more treatment resistance and are prone to reactivations/progressions. Also, these patients are at increased risk of neurodegenerative syndrome with endocrine dysfunction or other behavioral and learning problems associated with this syndrome.

In our study, most of the reactivations in those patients with single system involvement occurred in those with "Special Site" or "CNS risk" lesions solidifying that these lesions have increased risk of reactivation/progression and treatment resistance requiring intensive systemic therapy upfront. Patients with multisystem disease even without risk organ involvement will also require this systemic therapy.

Patients with multisystem risk organ disease are now uniformly treated with intensive therapy for 12 month duration. In our study, patients who received 12 months therapy had less reactivations irrespective of whether risk organ was involved or not. In the subgroup of patients who also had "Special Site" or "CNS risk" lesions, they were at a higher risk of reactivation.

Our data represents a relatively small sample size as collected from a single institution retrospectively over duration of 10 years. There was no mortality noted in patients with single system disease and 80 % of these patients were event free with a mean follow up of 3.7 years. Patients with multisystem disease had overall even free survival of 52 % with mean duration of follow up of 3.2 years.

In patients without risk organ disease, there was a 50% event free survival with mean duration of follow up of 2.7 years. The major prognostic factors for reactivation were involvement of Special sites, CNS risk lesions and duration of therapy. There was no mortality in this patient group. Those with Multisystem risk organ disease had a 54 % event free survival with mean age of follow up of 3.5 years. Again, the main prognostic factor was duration of therapy. There was one mortality noted in this patient group. This patient passed away with invasive fungal disease. Although our sample size was small, most of our treatment and outcome data as discussed above are comparable with the national data from LCH III study.

In conclusion during the past decade, our institution has continued to accomplish the same advances in the diagnosis, treatment, and ultimate cure of children with LCH. When we compare our overall treatment and
outcome data with the latest national data from the histiocyte society, it was comparable in every aspect. This data confirmed that the care provided for children with LCH here at Children’s Hospital New Orleans produces the same results in terms of outcome and survival as other institutions in the country.

References