**OUTCOME OF TREATING PEDIATRIC LANGERHANS HISTIOCYTOSIS WITH LCH III IN TERTIARY CENTER, SAUDI ARABIA.**

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**Abstract**

***Background:*** Langerhans cell histiocytosis (LCH) is a rare disease affecting any age and organ; its presentations and outcomes vary from self-healing lesions to life-threatening disseminated disease. This study evaluated the outcomes of treating children diagnosed with Langerhans cell histiocytosis (LCH) at the Oncology Center in Saudi Arabia.

***Methodology:*** Through a retrospective study design, the researchers reviewed the medical records and electronic files of all children (aged 0–14 years) who had been diagnosed with and treated for LCH at Princess Norah Oncology Center (PNOC), King Abdelaziz Medical City, Saudi Arabia, between January 2000 and December 2019 (n=33).

***Findings:*** Males constituted (66.7%), with a remarkable dominance of Saudis (93.9%). The median age at diagnosis was 28 months (interquartile range [IQR] =49 months), (42.4%) were diagnosed before their second birthday***.*** Fourteen patients (42.4%) had multisystem (MS-LCH) involvement, of which 13 patients were risk organ (RO) (+) and one patient was without risk organ (RO) (-). Most of the patients received the LCH III protocol. Reactivation occurred in 11 patients (33.3%), and two deaths (6.1%) occurred in patients with MS (RO) (+) progressive disease. The overall survival rate was 93.9%, with no statistically significant difference in event-free survival observed between patients with multisystem involvement and those with single system involvement.

***Conclusion and recommendations:*** excellent outcome of LCH is associated with single system involvement and worse outcome (reactivation or morality) is determined by multi-organ involvement, especially at a younger age (< 24 months). A better understanding of pathophysiology and genetic molecular background could lead to a striking transformation to novel therapies that warrant prospective clinical trials. High mortality in patients with progressive disease demands earlier aggressive salvage. Prospective clinical trials are required to improve treatment strategies in these subgroups.

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Keywords: Survival, Pediatric, Langerhans histiocytosis, Multi-system LCH, Single-system LCH

1. **Introduction**

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by reactive clonal proliferation and accumulation of dendritic cells, with a wide range of clinical presentations ranging from a self-healing unifocal single system involvement to a fatal multisystem disease involving the lungs, liver, spleen, and hematopoietic system (Abla et al., 2010; Nezelof & Basset, 2004). The etiology of LCH remains unclear. Consistent data on incidence are difficult to obtain, and only a few international and regional reports and studies on the disease have been reported (Cotterill et al., 2000; Kaatsch et al., 1995). For single bone lesions, biopsy, or curettage at the time of diagnosis is sufficient for treatment. If surgical excision is not feasible or there is multisystem disease involvement, other treatment modalities, such as chemotherapy or radiotherapy, are required (Broadbent et al., 1994).

Due to the heterogeneity of the clinical presentations of LCH among the pediatric age group and the need to determine the proper therapy to prevent recurrence and progression, we aimed to evaluate the clinical presentations, frequency of disease reactivation, prognostic factors, treatment outcomes, and sequelae of this disorder among Saudi children during a 20-year period.

1. ***Methodology***

Through a descriptive record-based study design, all pediatric patients aged 0–14 years who had been diagnosed and treated for LCH at the Princess Norah Oncology Center (PNOC), King Abdelaziz Medical City, Jeddah, between January 2000 and December 2019 were eligible for inclusion in the study (n=33). The researchers reviewed the medical records and electronic files of these patients. SPSS version 24 was used for data analysis, Chi square was used to test the significance of differences in the distribution of system involvement (categorical), and Kaplan Meier was used for testing the overall and event-free survival of the cases. Statistical significance was set at p<0.05.

1. ***Results*:**

**Table 1: Characteristics of the patients (n=33).**

|  |  |  |
| --- | --- | --- |
| Characteristics | No. | Percentage |
| ***Gender:*** |  |  |
| Male | 22 | 66.7 |
| Female | 11 | 33.3 |
| ***Nationality:*** |  |  |
| Saudi | 31 | 93.9 |
| Non-Saudi | 2 | 6.1 |
| ***Age at diagnosis:*** |  |  |
| <24months | 14 | 42.4 |
| >24 months | 19 | 57.6 |
| ***Presenting clinical findings:*** |  |  |
| Swelling | 23 | 69.7 |
| Pain | 10 | 30.3 |
| Skin rash | 9 | 27.3 |
| Liver dysfunction | 5 | 15.2 |
| Ear dysfunction | 5 | 15.2 |
| Polyurea/Polydipsia | 5 | 15.2 |
| Diarrhea and failure to thrive | 3 | 9.1 |
| Others | 10 | 30.3 |
| ***Organ involved:*** |  |  |
| Bone unifocal | 20 | 60.6 |
| Bone multifocal | 14 | 42.4 |
| Soft tissue | 15 | 45.5 |
| Liver | 10 | 30.3 |
| Skin | 9 | 27.3 |
| Lymph nodes | 6 | 18.2 |
| Spleen | 5 | 15.2 |
| Lung | 4 | 12.1 |
| Pituitary gland | 1 | 3.0 |
| ***Special site involvement:*** |  |  |
| CNS | 15 | 45.5 |
| Vertebrae | 6 | 18.2 |
| Femur | 2 | 6.1 |
| ***Lab results at diagnosis:*** |  |  |
| ESR >20 | 21 | 63.6 |
| Hb <10 or infant < 9 | 8 | 24.2 |
| Bilirubin >18 | 5 | 15.2 |
| PLT <100 | 4 | 12.1 |
| ALT >2xULN | 4 | 12.1 |
| AST >2xULN | 4 | 12.1 |
| Albumin <25 | 2 | 6.1 |
| WBC <4000 | 1 | 3.0 |
| LDH >500 | 1 | 3.0 |
| ***Classification of the disease:*** |  |  |
| Multisystem RO (+) | 13 | 39.4 |
| Single system unifocal | 12 | 36.4 |
| Multifocal single system | 7 | 21.2 |
| Multisystem RO (-) | 1 | 3.0 |

Males constituted two-thirds of the patients (66.7%) (M:F ratio =2) with remarkable dominance of Saudis (93.9%). The median age at diagnosis was 28 months (IQR=49 months), and slightly less than half of the patients (42.4%) were diagnosed before their second birthday. The median follow-up time was 72.1 months (IQR=86.3). The most prominent clinical findings were swelling (69.7%), bone-related pain (30.3%), skin rash (27.3%), and polyurea/polydipsia (15.2%). The most involved organs were the bones, whether unifocal (60.6%) or multifocal (42.4%), skull bones (n = 12) most frequently affected bones, followed by the vertebrae (n = 6), and femur (n = 5). Other organs involved the soft tissue (45.5%) and liver (30.3%), with special site involvement of the CNS (45.5%) and vertebrae (18.2%). The laboratory results showed that almost two-thirds of the patients had ESR>20, and (24.2%) with lower Hb levels, and 15.2% had increased bilirubin levels >18. Fourteen patients (42.4%) had multisystem involvement, of which 13 patients (39.4%) had risk organ involvement (RO) (+) and one patient (3.0%) had no risk organ (RO) (-). Six patients (18.2%) with multisystem disease had 2 organs involvement, one patient (3.0%) had 3 organs, one patient (3.0%) had 4 organs, and six patients (33.3%) had 5 organs involvement. Twelve patients (36.4%) were staged as single system unifocal, while seven patients (21.2%) were classified as multifocal single systems **[Table 1]**.

Table 2: Comparing multisystem and single system involvement according to demographic characteristics and outcome.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | System involvement | | | |  |  |
| Characteristics | Multisystem  (n=14) | | Single system  (n=19) | | *X*2 | P\* |
|  | No | % | No | % |  |  |
| ***Gender***: |  |  |  |  | 0.992 | 0.319 |
| Male | 8 | 57.1% | 14 | 73.7% |
| Female | 6 | 42.9% | 5 | 26.3% |
| ***Age categories:*** |  |  |  |  | 8.375 | 0.004\*\* |
| <24 months | 10 | 71.4% | 4 | 21.1% |
| >24 months | 4 | 28.6% | 15 | 78.9% |
| ***Reactivation:*** |  |  |  |  | 3.039 | 0.086 |
| Yes | 7 | 50.0% | 4 | 21.1% |
| No | 7 | 50.0% | 15 | 78.9% |
| ***Outcome*** |  |  |  |  | NA | NA |
| Alive in CR | 12 | 85.7% | 16 | 84.2% |
| Alive with disease | 0 | 0.0% | 3 | 15.8% |
| Died | 2 | 14.3% | 0 | 0.0% |

*\* Based on Chi Square \*\* Statistically significant NA not applicable*

No statistically significant difference was detected between multisystem and single system patients according to sex (p>0.05) **[Table 2]**, yet multisystem risk organ involvement was significantly more common among patients aged < 24 months (71.4%) compared to patients with a single system (21.1%) (p<0.05). Although not statistically significant (p>0.086), half of the patients with multisystem involvement (50.0%) had more reactivation than 21.1% of single system patients. Two multisystem patients died, one of whom died after liver transplantation and the other during reactivation.

**Table 3: Treatment protocols and outcomes (n=33).**

|  |  |  |
| --- | --- | --- |
| Treatment protocols and outcome | No. | Percentage |
| ***Treatment provided:*** |  |  |
| Surgery | 6 | 18.2 |
| Radiotherapy | 1 | 3.0 |
| Observation | 1 | 3.0 |
| **Chemotherapy** | 26 | 78.8 |
| *Chemotherapy protocol name* |  |  |
|  |  |  |
| LCHIII Arm A\* | 25 | 75.7 |
| LCHIII Arm B\* | 1 | 3.0 |
| *Initial therapy* |  |  |
| VBL/PDN\* | 26 | 78.8 |
| *6 MP Given* | 17 | 51.5 |
| *Salvage* | 4 | 12.1 |
| ***Duration of initial therapy (n=26):*** |  |  |
| 6 months | 2 | 7.7 |
| 12 months | 22 | 84.6 |
| 24 months | 2 | 7.7 |
| ***Response after 6 weeks:*** |  |  |
| Active disease better | 15 | 45.5 |
| Active disease intermediate | 10 | 30.3 |
| Active disease worse | 1 | 3.0 |
| NA | 7 | 21.2 |
| ***Response after 12 weeks:*** |  |  |
| Active disease better | 20 | 60.6 |
| Active disease intermediate | 2 | 6.1 |
| Active disease worse | 1 | 3.0 |
| NA | 10 | 30.3 |
| ***Response at the end of therapy:*** |  |  |
| Complete remission | 25 | 75.8 |
| Active disease | 5 | 15.1 |
| NA | 3 | 9.1 |
| ***Duration till complete remission:*** |  |  |
| End of therapy | 20 | 60.6 |
| After 12 weeks | 3 | 9.1 |
| After surgical resection | 3 | 9.1 |
| Postradiotherapy | 1 | 3.0 |
| NA | 6 | 18.2 |
| ***Reactivation (n=11):*** |  |  |
| *Number of reactivations* |  |  |
| Once | 9 | 81.8 |
| Twice | 1 | 0.9 |
| Thrice | 1 | 0.9 |
| *Duration from remission to reactivations* |  |  |
| Between 3-6 months | 6 | 54.5 |
| >6 months | 5 | 45.5 |

*\*VBL: Vinblastine. PDN: Prednisone. LCH III: Langerhans Cell Histiocytosis protocol III*

**Table 3** illustrates the treatment modalities provided to the patients, with the majority of patients receiving chemotherapy (78.8%) with a six-week initial therapy of Vinblastine and Prednisone (VBL/PDN), according to LCH III protocol arm A **[Appendix]** Only one patient (3%) received LCH III Arm B (with addition of methotrexate 500 mg/m2) protocols. The initial therapy was administered for an average of 12 months for the overwhelming majority of the patients (84.6%), while only two patients (7.7%) received treatment for a shorter duration (6 months), and the other two received it for a longer duration (24 months). In contrast, six patients (18.2%) underwent surgery, and only one patient (3.0%) received radiotherapy, while only one patient was set under observation. After six weeks of treatment, slightly less than one-half of the patients (45.5%) achieved active disease improvement, while in one-third (30.3%) of the patients, the active disease was intermediate, and only one patient became worse. Moreover, after 12 weeks, there was an increase in the proportion of patients who achieved disease improvement (up to 60.6%). At the end of therapy, complete remission was observed three in of the four treated patients (75.8%). By estimating the duration between starting treatment and complete remission, it was found that it was achieved after 12 weeks in 9.1% of the patients and at the end of therapy in 60.6% of the patients. Reactivation occurred in 11 patients (33.3%); slightly more than half (54.5%) had reactivation in the first six months after remission, while the rest (45.4%) had reactivation after six months of remission. Most patients (81.8%) had reactivations once, while one patient had two episodes, and another patient had three episodes of reactivation.

**Figure 1: Classification of the disease (n=33).**

The survival function at the last follow-up of the patients showed that the overwhelming majority (84.8%) were alive in complete recession, while only three patients (9.1%) were alive with the disease and two patients (6.1%) died **[Figure 1]**.

**Figure 2:** *Fate of the patient at last follow up.*

The Kaplan-Meier survival analysis showed that there was no statistically significant difference in the survival of the patients according to age at diagnosis (p>0.05) **[Figure 2]**.

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**Figure 3: Overall and event free survival of LCH patients.**

The overall survival of all studied patients was 93.9% and was comparable in patients with multisystem involvement compared to those with single system involvement (85.7% versus 100%, respectively, p=0.168). Meanwhile, there was no statistically significant difference in event-free survival between the two groups (50.0% vs. 79.9%, p=0.114) **[Figure 3]**.

1. ***Discussion:***

LCH has been considered an immune dysregulation disorder; however, with advances in molecular biology and genetics, 50-60% of LCH patients were found to have a proto-oncogene mutation in BRAF-V60E, and almost 100% had cellular signal transduction phosphorylation defects of MEK/ERC. This led to the consideration of LCH as a dendritic cell neoplasm with a strong inflammatory component (Abla & Weitzman, 2015). The course of the disease is unpredictable, varying from self-limited disease to rapid progression and death or frequent recurrence and reactivation, with the risk of permanent, predictable, and often irreversible sequelae (Donadieu, 1996). The exact incidence of LCH in Saudi Arabia is uncertain; however, data from the National Cancer Registry, Saudi Arabia (SA-NCR) for pediatric patients (age 0-14 years) diagnosed between 2005 and 2009 reported an incidence of 0.12% (Belgaumi et al., 2019). Al-Mulhim et al. reported the outcome of 21 Saudi children with Histiocytosis-X. At the median of 3 years follow, three patients died, three had recurrences, and eight patients had various disabilities (38%). The overall disease-free survival rate was 84.2% (Al-Mulhim et al., 1991). The paucity of confirmed LCH cases may suggest a degree of under-reporting or under-diagnosis in these previous studies, or cases that may be treated without chemotherapy are not included in SA-NCR. LCH has a wide clinical variety and outcomes. Localized disease is usually observed in older patients, whereas a more aggressive form of disease with organ dysfunction is typical in children younger than 24 months of age (Broadbent et al., 1994). The data support this, with more patients younger than two years presenting with MS-LCH than older patients. The distribution between sexes in patients is in accordance with most previous studies that showed ratios from 1.1 to 2 boys to every girl. Age is an important prognostic factor for MS-LCH patients. The majority of our younger (<2 years) patients (71.4%) presented with MS-LCH (P<0.004). Due to the small number of patients in our series, age at diagnosis was not associated with the outcome. Skin rash may be the first sign of LCH (Howarth et al., 1999). In the current study, of the nine children who had initial skin lesions, three received previous treatments for other pathologies that could have resulted in a diagnostic deferral.

Ear involvement was described in five patients, which was often misdiagnosed as otitis infection. It is more common among younger children with multisystem disease; therefore, the presence of persistent otitis that does not respond to common treatments should increase the suspicion of LCH (Surico et al., 2000). Bony lesions were the most common initial manifestation of the disease, and almost 70% of patients had bone-related swelling and pain. This is consistent with the literature data (Arico & Egeler, 1998; Azouz et al., 2005; Broadbent et al., 1994; Del Río et al., 2007). The reported two deaths occurred in patients with liver dysfunction, one of which died after liver transplantation, which asserts what had been documented before that liver dysfunction is associated with the worst outcome (Donadieu, 1996; Gadner et al., 1994; Kilpatrick et al., 1995; Lahey, 1975). Grois et al. (1995) pointed out that diabetes insipidus (DI) is a common manifestation of LCH due to infiltration of the hypothalamic-pituitary axis, which may precede the disease or manifest itself later during the disease course (N. Grois et al., 1995). DI varies considerably, with rates between 5% and 50% (N. Grois et al., 1995; Salotti et al., 2009). In our patient population, five (15%) patients had a long duration of diabetes insipidus before the diagnosis was made, mostly associated with multiple system involvement. Previous studies have claimed that MS-LCH patients, especially those with craniofacial involvement at diagnosis are 4-6 times more at risk of developing DI than those with a single-system disease (N. Grois et al., 1995; Nicole Grois et al., 2010). The clinical outcomes of LCH have improved markedly over the past few decades through cooperative randomized national and international clinical trials (Cotterill et al., 2000). In the current study, the overall survival was 93.9% and was comparable in patients with multisystem involvement compared to those with single system involvement (85.7% versus 100%, respectively, p=0.168). Excellent survival rate (100%) was observed in the SSD group. However, the probability of EFS at 16 years in this group of patients (50%) showed some predilection for disease relapse. Reactivation is a potential challenge encountered in the management of LCH. In our study, recurrence occurred in nearly one-third of the patients; however, the majority attained remission after second-line therapies. The two patients who received treatment for six months had a shorter duration of CR, emphasizing the importance of a prolonged duration of treatment course; they responded to second-line therapies and survived. As reported by others, recurrence is not a predictive factor of the worst outcome (Gadner et al., 1994). Among those patients with single system disease, only three (23%) had one reactivation episode, which is comparable to other reported studies (N. Grois et al., 1995; Histiocyte Society, 2002; Titgemeyer et al., 2001). No cases of secondary neoplasms were observed after a long follow-up period, presumably after the use of etoposide, as described in a few cases (Histiocyte Society, 2002).

**Conclusion:**

The excellent outcome of LCH is associated with single-system involvement and probably in the older age group. On the other hand, worse outcomes (reactivation or morality) of LCH are determined by multi-organ involvement, especially at younger ages (< 24 months). Single-system LCH patients may benefit only from an observational approach. A better understanding of the pathophysiology and genetic molecular background could lead to a striking transformation to novel therapy that warrants a prospective clinical trial to solve the challenges of high mortality in younger age groups with organ dysfunction, high relapse rates, especially among MS-LCH patients, and disease-associated complications.

**Conflict of interest:**

The authors declare that there is no conflict of interest.

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**Appendix**

**Summary of treatment components of LCH III protocol**

|  |  |  |
| --- | --- | --- |
|  | Treatment A | Treatment B |
| COURSE I | 1. Prednisone (PDN): 40mg/m2 daily in 3 doses as a 4-week course, tapering over a period of 2 weeks 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 1, 2, 3, 4, 5, 6. | 1. Prednisone (PDN): 40mg/m2 daily in 3 doses as a 4-week course, tapering over a period of 2 weeks 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 1, 2, 3, 4, 5, 6. 3. Methotrexate 500 mg/m2 24 hours-infusion with Folinic acid (leucovorin) rescue. 4. Folinic acid 12mg/m2 orally is given 24 hours and 30 hours after the stop of the MTX infusion. |
| \*COURSE II | 1. Prednisone (PDN): 40mg/m2 in 3 divided doses for 3 days every week, from week 7-12. 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 7, 8, 9, 10, 11, 12. | 1. Prednisone (PDN): 40mg/m2 in 3 divided doses for 3 days every week, from week 7-12. 2. Vinblastine (VBL) 6 mg/m2 IV day 1 of week 7, 8, 9, 10, 11, 12. 3. Methotrexate 500 mg/m2 24 hours-infusion with folinic acid (leucovorin) rescue. 4. Folinic acid 12mg/m2 orally is given 24 hours and 30 hours after the stop of the MTX infusion |
| Continuation treatment: | 1. Oral 6-mercaptopurine (6-MP) 50mg/m2 daily until the end of month 12 from therapy start. 2. Pulses of oral prednisone PDN 40mg/m2 in 3 doses, day 1-5 q 3 weeks. 3. Vinblastine (VBL) 6mg/m2 IV bolus, day 1 q 3 weeks. | 1. Oral 6-mercaptopurine (6-MP) 50mg/m2 daily until the end of month 12 from therapy start. 2. Pulses of oral prednisone PDN 40mg/m2 in 3 doses, day 1-5 q 3 weeks. 3. Vinblastine (VBL) 6mg/m2 IV bolus, day 1 q 3 weeks. 4. Methotrexate 20mg/m2 orally, once weekly until the end of month 12 |

\* Starting without delay after course 1 for patients who are Active Disease (AD) better or intermediate after course 1. Patients who are Non-Active Disease (NAD) after course 1 proceed to continuation treatment