# Langerhans cell histiocytosis in Turkish children

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**SUMMARY: Tokuç G, Boran P, Öktem S. Langerhans cell histiocytosis in Turkish children. Turk J Pediatr 2009; 51: 344-349.**

**Langerhans cell histiocytosis (LCH) is a rare disorder with diverse forms of clinical presentation ranging from a benign course to diffuse progressive disease, and descriptions of LCH generally have been limited to single case reports and small case series.**

**Since the condition is uncommon, we aimed in this study to describe our own experience and discuss the findings, treatment and outcome in our patients with LCH in light of the current literature.**

**The eight patients (5 boys, 3 girls) ranged in age from 2 months to 3 years (mean 18±10.8 months). Multiple organ involvement was noted in 3, isolated bone involvement in 3, orbital involvement in 1, and pituitary gland involvement with rash in 1 patient. Treatment modalities used varied from simple observation to chemotherapy. Outcome results of our study demonstrated resolution of lesions in 5 patients and death in 2 patients. One patient with pituitary gland involvement developed diabetes insipidus and is receiving intranasal desmopressin acetate.**

**Based on our results and a review of the literature, we recommend that any child with suspected solitary LCH undergo a full diagnostic investigation to rule out multiple lesions. A biopsy is recommended for a diagnosis at the time of presentation and should be attempted in any suspicious lesion. Chemotherapy is reserved for multiple systemic lesions and central nervous system (CNS) risk lesions. Follow-up investigations should be individualized but should consist of radiography and magnetic resonance imaging (MRI). Studies suggest that follow-up of at least four years is required.**

***Key words: histiocytosis X, diabetes insipidus, Langerhans cell histiocytosis.***

Langerhans cell histiocytosis (LCH) is a rare disorder, characterized by clonal proliferation of abnormal bone marrow-derived Langerhans cells that may affect any age group[1-4]. In 1987, the Writing Group of the Histiocyte Society suggested the term LCH to encompass disorders previously known as Hand-Schüller-Christian disease, Abt-Letterer-Siwe disease, histiocytosis X, and eosinophilic granuloma[1].

The clinical manifestations usually depend upon the number and site of involvement, in addition to the general symptoms such as fever, weakness and failure to thrive. The outcome is variable, ranging from spontaneous regression to rapid progression and death or recurrence. Solitary LCH with bone involvement is the most common presentation and has the best prognosis[2-4]. In contrast, multiple organ involvement (involvement of the lungs, hematopoietic system, spleen, liver or the digestive tract), young age (less than 2 years) and presence of organ dysfunction carry the risk of a poor outcome[2-4]. Other common sites of involvement include skin, lungs, gastrointestinal system, hematological system and the nervous system.

Although definitive diagnosis of LCH is made by tissue biopsy, computed tomography (CT) and magnetic resonance imaging (MRI), skeletal survey and laboratory investigations help to confirm the diagnosis[5]. Histopathological diagnostic criteria modified according to the Writing Group of the Histiocyte Society[1] require the demonstration of CD1a antigenic determinants on the surface of lesional cells by immunohistology or the finding of Birbeck granules in lesional cells by electron microscopy.

Over the last 15 years, several new drugs and/or procedures have been reported as being useful in the treatment of patients with LCH[6-9]. Treatment options include conservative approach, chemotherapy and radiotherapy. Since the early 1990's, trials organized under the Histiocyte Society have helped to standardize the investigations and therapy. Patients with localized disease are felt to need minimum or even no treatment, and chemotherapy is usually given for multiple lesions or involved visceral organs. New therapeutic modalities with cyclosporin A, interferon alpha and 2-chlorodeoxyadenosine and stem cell transplantation have not yet been clearly shown as effective procedures and further trials are needed[10].

Since the condition is uncommon and descriptions of LCH have been generally limited to single case reports and small case series, we aimed in this study to describe our own experience and discuss the findings, treatment and outcome in our patients with LCH in light of the current literature.

## Material and Methods

Retrospective evaluation of eight patients with biopsy-proven diagnosis of LCH admitted to our pediatric oncology clinic between December 1995 and December 2005 was performed. Data collected from the charts included demographic characteristics, age, sex, symptoms, physical examination findings, site of involvement, imaging techniques used for diagnosis, procedure applied, pathological and laboratory investigation findings, treatment modality used, and outcome. Among the inclusion criteria were those for "definitive diagnosis" of LCH proposed by the Writing Group of the Histiocyte Society: the immunohistochemical demonstration of characteristic surface antigens (i.e., CD1a) and/or the electron microscopic demonstration of Birbeck (Langerhans) granules[1].

## Results

Eight patients (5 boys, 3 girls) ranging in age from 2 months to 3 years (mean: 18±10.8 months) were included in the study. Follow-up varied from 1 to 10 years (mean 3.5 years). The most common presenting symptom was lump in the involved area and skin rash. Findings of lymphadenopathy, swelling on the involved site, exophthalmus, rash and hepatosplenomegaly were noted on physical examination. The clinical data in 8 cases of LCH are presented in Table I.

Multiple organ involvement was noted in 3, isolated bone involvement in 3, orbital involvement in 1, and pituitary gland involvement with rash in 1 patient. Radiological imaging consisted of plain radiography, bone scanning and CT or MRI in all patients. Biopsy was performed in all cases and positive results were obtained in all. Among the 8 histopathologically confirmed cases, 4 were additionally verified through demonstration of CD1a antigen and 2 for staining with S100. Laboratory investigations

**Table I.** Clinical Data of Eight Cases of Langerhans Cell Histiocytosis

| Case | Age (mo) | Sex | Symptoms | Sites of involvement | Procedure | Tx | Outcome | Follow up (mo) |
|---|---|---|---|---|---|---|---|---|
| 1 | 10 | M | LAP in the neck | LN, LIVER, SPLEEN, LUNG | BIOPSY | C | REMISSION IN 4 MONTHS | 12 |
| 2 | 36 | F | Lump on the head | SKULL | BIOPSY | N | REMISSION IN 1 YEAR | 24 |
| 3 | 13 | F | Lump on the leg, leg pain | BONE | CURETTAGE | N | REMISSION | 120 |
| 4 | 18 | M | Rash | SKIN, pituitary gland | BIOPSY | N | REMISSION | 40 |
| 5 | 17 | M | Rash | SKIN, LIVER | BIOPSY | C | EXITUS | 4 |
| 6 | 2 | M | Rash, LAP | SKIN, LIVER, LUNG, BONE | BIOPSY | C | EXITUS | 23 |
| 7 | 20 | M | Unsteady gait | BONE (PELVIS) | CURETTAGE | C | REMISSION IN 3 MONTHS | 71 |
| 8 | 30 | F | Proptosis in the right eye, lump on the head | ORBITA, SKULL (frontal, parietal, occipital, sphenoid) | BIOPSY | C | REMISSION IN 7 MONTHS | 41 |

mo: Months. M: Male. F: Female. LAP: Lymphadenopathy. LN: Lymph node. Tx: Treatment. C: Chemotherapy. N: No treatment.

include complete blood count and blood chemistry and other evaluations varied according to site of involvement.

Treatment modalities used varied from simple observation to chemotherapy (in the initial therapy, oral prednisone at a dose of 40 mg/m$^2$ daily as a 4-week course, followed by a tapering dose over a period of 2 weeks and 6 weekly doses of vinblastine 6 mg/m$^2$ intravenously [i.v.]). Continuation treatment included 5 days of oral prednisone at a dose of 40 mg/m$^2$ daily (for 3 weeks) and vinblastine 6 mg/m$^2$ every 3 weeks, continued until the end of 24 weeks. Patients who did not respond at the end of 6 weeks received an additional course of oral prednisone 40 mg/m$^2$ daily for 3 days each week and 6 weekly doses of vinblastine at a dose of 6 mg/m$^2$. If etoposide was added as a third drug, it was given at a dose of 150 mg/m$^2$ i.v. infusion weekly).

Two (patients 5 and 6) of the three patients with multiple organ involvement presented with signs of organ dysfunction, and died due to respiratory insufficiency and sepsis despite receiving chemotherapy.

Patient 5 presented with rash and hepatosplenomegaly at 17 months of age and then developed icterus. His past medical history was remarkable for history of recurrent otitis media. The laboratory tests revealed hepatic dysfunction and marked anemia. The thorax CT showed diffuse interstitial involvement with cysts and nodules. Bone scintigraphy was normal. He received chemotherapy with intravenous vinblastine and oral prednisolone and etoposide was also added as a third drug. He died due to respiratory insufficiency in three months.

Patient 6 presented with rash and hepatosplenomegaly. He received chemotherapy with vinblastine and steroid and a rapid response was noted, and one month after the start of the chemotherapy, his rash and lymphadenopathy disappeared. However, within 21 months, his condition deteriorated suddenly and he was admitted to the hospital with tachypnea, respiratory distress and hepatic dysfunction. He required a repeat course of chemotherapy with vinblastine, steroid and an addition of a third drug, etoposide. He died due to respiratory insufficiency in three months after the second admission.

Patient 1 was admitted with cervical lymphadenopathy and hepatosplenomegaly. Chest X-ray and skeletal survey were normal. He was started on vinblastine and steroid. Although laboratory tests revealed hepatic dysfunction and anemia, a rapid response was noted, and he went into remission in four months. He was lost to follow-up after one year.

Patient 8 presented with exophthalmus in the right eye and soft swelling measuring 3×2 cm over the frontal region. Ocular examination including fundus and ocular movements were normal. Vision was 6/6 in both eyes and fields were normal. CT scan showed a peripherally enhancing soft tissue mass in the superolateral aspect of the right orbit, extending posteriorly along the lateral wall with lytic destruction of the orbital roof (Fig. 1). The mass had intra- and extraorbital soft tissue components with infiltration of the lateral rectus, superior rectus and intraconal fat, extending up to the optic canal with intracranial extension into the right frontal lobe consequent to erosion of the greater wing of the sphenoid. Skull X-ray and bone scintigraphy revealed multiple lytic defects in the temporal, frontal and occipital bones. The patient, after incisional biopsy, responded very well to chemotherapy with vinblastine and steroid in seven months and no local recurrence or additional focus was noted in three years of follow-up.

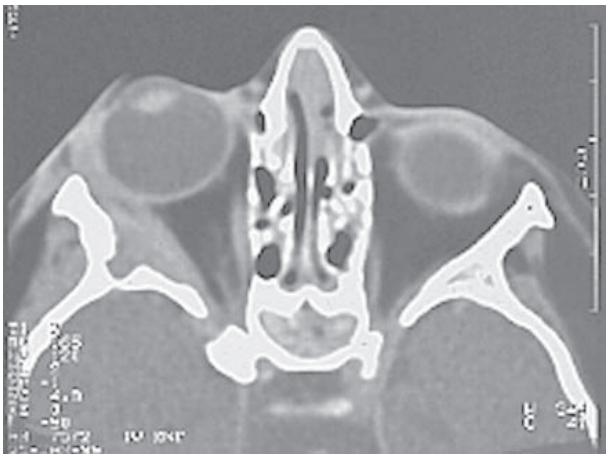

**Fig. 1.** Patient 8: Soft tissue mass in the superolateral aspect of the right orbit, extending posteriorly along the lateral wall.

Patient 4 presented with prolonged perianal dermatitis despite aggressive local treatment when she was two months old and systemic evaluation revealed no other focus. She presented with polyuria and polydipsia when she was four years old and diabetes insipidus was detected. No findings on cranial MRI

were noted. She is still under follow-up and receiving replacement therapy with intranasal desmopressin acetate.

In our series, two of the three patients with isolated bone involvement underwent curettage only and no additional focus or relapse was noted during follow-up. Lesions of the other patient with isolated bone involvement resolved spontaneously without treatment. Patient 2 was presented with a swelling on the head. Her physical examination was normal except for a lump on the head. Skull X-ray revealed frontal 2×2 cm and left temporal 2×0.5 cm lytic bone defects on the skull. Cranial tomography showed left frontotemporal cystic mass (6×3×7.5 cm) and parietal lytic bone defect. Bone scintigraphy showed increased uptake limited to the left frontoparietal and temporal regions on the cranium. It was decided to follow this patient with observation only and skull X-ray was normal after two years of follow-up and there were no other symptoms. Patient 7 was presented with leg pain. On pelvic X-ray and CT, destructive lesion on the left femoral head was detected and a biopsy was taken with curettage. Systemic evaluation was unremarkable. She was followed up by observation and remained asymptomatic.

Outcome results of our study showed resolution of lesions in five patients and death in two patients. The last patient with pituitary gland involvement is under replacement therapy with intranasal desmopressin.

**Discussion**

Langerhans cell histiocytosis is a rare disease with diverse forms of clinical presentation ranging from a benign course to diffuse progressive disease. The disease seems to particularly affect young children between one and four years, with a male preponderance[1-4].

Our study revealed a male preponderance (M/F: 5/3), in parallel with the other studies.

Although diagnoses of our patients enrolled in the study were confirmed by biopsy, immunohistochemical identification of the presence of Langerhans cells by cell surface CD1a were made in only four of them, which is a criterion needed for the definitive diagnosis according to the Histiocyte Society[1].

Langerhans cell histiocytosis can involve any bone, but the skull (especially the calvaria and temporal bones), pelvis, spine, mandible, ribs, and tubular bones are the commonly involved sites[1-4]. In our patients with bone involvement, the skull was involved in two, femur in one and pelvis in another. In the majority of cases, especially in those with localized osseous lesions, LCH is considered a benign process and single bone lesions are known to resolve spontaneously[2-4]. Our results support the concept of osseous LCH even if multifocal as a benign self-limiting disorder. Two of the three patients with isolated bone involvement underwent curettage only and no additional focus or relapse was noted during the follow-up. Lesions of the other patient with isolated bone involvement resolved spontaneously without treatment.

In contrast, multisystem LCH, especially with lung, liver or other visceral organ involvement, is usually associated with poorer prognosis and a fulminant disease process. In patients with multisystem LCH, a poor response to the initial standard chemotherapy with vinblastine and corticosteroid prednisolone has been shown to be the most important single prognostic factor, defining a group of patients with a less than 30% survival rate at two years from diagnosis[11]. Many of the patients die from sepsis or bleeding. In our series, two of the three patients with multiple organ involvement died due to respiratory insufficiency and sepsis despite receiving chemotherapy. The course of the disease may show extreme case to case variation, and the third patient with multiple organ involvement responded very quickly to therapy. Although it is known that bone involvement is almost always present, bone survey of the three patients with multiple organ involvement was normal.

In our patients with multiple organ involvement, two of the three patients also had lung involvement. Pulmonary LCH (PLCH) is seen in less than 10% of childhood LCH, but in more than 30% of multisystem LCH. PLCH is an isolated form of LCH that primarily affects cigarette smokers[12-14]. It is characterized by peribronchiolar proliferation of Langerhans cell infiltrates that form stellate nodules. The nodular lesions frequently cavitate and form thick- and thin-walled cysts, which are thought to represent enlarged airway lumina. In advanced cases, fibrotic scars are surrounded by enlarged, distorted air spaces. The characteristic radiographic features of

PLCH are bilateral nodular and reticulonodular areas of opacity that predominantly involve the upper and middle lung zones with relative sparing of the lung bases[12-14]. In typical cases, a predominantly nodular pattern is seen on CT scans in early phases of the disease, whereas a cystic pattern predominates in later phases. The radiologic abnormalities may regress, resolve completely, become stable, or progress to advanced cystic changes[12-14]. The clinical course is unpredictable. In our patients, bilateral nodular and reticulonodular pattern was seen on thorax CT scans. One patient died due to respiratory failure, but the other patient recovered clinically although reticulonodular pattern did not regress completely.

Although orbital involvement in LCH generally represents unifocal disease, in our case, multiple involvements of the cranial bones were present[15-18]. Orbital involvement in a series of 76 children with LCH was 23%[19]. In our patient, as in others[19], the site of predilection was the anterolateral aspect of the superior orbit[16]. LCH of the orbit has been reported to resolve after low-dose irradiation, intralesional corticosteroid injection, and simple biopsy or subtotal curettage[15-18]. Ophthalmic literature indicates that unifocal LCH of the orbit is usually responsive to local intervention, with systemic treatment reserved for incomplete response, local reactivation or the appearance of lesions elsewhere[15-18]. Current international oncologic protocols identify involvement of the facial bones or anterior or middle cranial fossa (temporal, sphenoidal, ethmoidal, zygomatic bone, orbital bones) with intracranial tumor extension as a central nervous system (CNS) risk lesion (3-fold risk for delayed onset diabetes insipidus [DI]) and mandate a six-month course of chemotherapy[16,20]. Data from the DALHX study indicate that chemotherapy may be associated with a reduced frequency of DI[8].

Our patient had multiple lytic lesions in the skull in addition to orbit, so six months of chemotherapy was administered in addition to subtotal curettage of the orbit, based on the International Histiocyte Society protocol.

The hypothalamic-pituitary axis is, by far, the most frequently involved intracranial region in LCH, and the resulting DI is a clinical hallmark of LCH. DI is the most frequent CNS-related permanent consequence in LCH, which mostly requires life-long hormone replacement therapy. In our case, LCH was detected when the patient was two months old and she developed DI at 4 years of age and is still under follow-up and receiving replacement therapy with intranasal desmopressin acetate.

It should be kept in mind that LCH has diverse clinical presentations that can bring it before all physicians; acute awareness is required in making the diagnosis. Based on our results and a review of the literature, we recommend that any child with suspected solitary LCH undergo full diagnostic investigation to rule out multiple lesions. A biopsy is recommended for a diagnosis at the time of presentation and should be attempted in any suspicious lesion. Chemotherapy is reserved for multiple systemic lesions and CNS risk lesions. Follow-up investigations should be individualized but should consist of radiography and MRI. Studies suggest that a follow-up of at least four years is required.

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