**Original Paper, PET/CT.**

# Added Value of $^{18}$F-FDG PET/CT in Initial Evaluation of Osseous Lesions of Langerhans Cell Histiocytosis in Children.

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## ABSTRCAT:

**Objectives**: To demonstrate the value of FDG PET/CT in evaluation of childhood patient with osseous Langerhans cell histiocytosis (LCH). **Patients and Methods**: A prospective analysis of 24 pediatric patients with histopathologically proven LCH September 2016 till November 2018. All patients received specific therapy for LCH in the form of chemotherapy &/or surgical resection. Analysis criteria included the following: any focal FDG uptake was considered abnormal when it was greater than that of hepatic uptake or in presence of abnormal changes on CT with any degree of FDG uptake. **Results**: 17 patients (70.8%) presented with multi-system disease (bone as well as LNs &/or liver, lungs, soft tissue and skin), 5 patients (20.8%) had uni-focal osseous lesions and 2 patients (8.3%) presented by multi-focal bone lesions. FDG PET/CT revealed metabolic changes in osseous lesions detected by anatomical radiographic scan and revealed multiple other lesions as well. No statistically significant association could be detected between neither disease recurrence nor risk of mortality at diagnosis with age, sex, presenting organ, disease extent, risk of mortality, SUV max of leading lesion. **Conclusion**: PET/CT may be useful as additional imaging to assess known LCH lesions and rule out the presence of other organ infiltration and to provide a reference basis of staging, treatment plan.

FDG PET/CT provides the characteristics of lesions in CT scan, but also the lesions activity by FDG uptake. 18F-FDG PET/CT may be incorporated in patient management to facilitate disease stratification and avoid un-necessary interventions.

**Key words:** *Langerhans cell histiocytosis-F-18 FDG PET/CT.*

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# INTRODUCTION:

The histiocyte disorders are defined as disorders due to an abnormal accumulation of cells of the mononuclear phagocytic system historically known as histiocyte, consisting of dendritic cells and macrophages that can lead to organ damage and tumor formation [(1)].

Langerhans cell histiocytosis (LCH) occurs in a broad age range from the newborn to the elderly. The annual childhood incidence of LCH has been estimated to be 2.2 to 6 cases per million. The disease is more common and tends to be more severe in younger children with median age of presentation of about 24 months, for children under 1 year of age the annual incidence is 6 cases per million with slight predominance of cases in males yet male to female ratio is close to one [(2)].

70% of the overall pediatric age almost have single system disease with bones as the commonest system, however multisystem LCH usually occurs in children less than 2 years of age, multifocal single system in children between two and five years, while 50% of uni-focal bone disease occurs in children over the age of 5 years [(2)]. Evidence of familial clustering of LCH and higher concordance in monozygotic twins (80%) suggest that a genetic predisposition my exist for LCH [(3)].

Langerhans cell histiocytosis is a very diverse disease, ranging from a spontaneously regressing single lesion to a life-threatening extensive multi-system disorder with rapid progression and death.

The severity of the disease tends to be age-related, with extensive multi-system LCH with or without organ failure seen mostly in the young patients.

LCH commonly presents with a skin rash or a painful bone lesion. LCH may involve a single organ (single-system LCH), single site (uni-focal) or involve multiple sites (multi-focal), or may involve multiple organs (multisystem LCH) which may involve a limited number of organs or be disseminated. Involvement of specific organs such as the liver, spleen, and hematopoietic system separates multisystem LCH into a high-risk group and a low-risk group, where risk indicates the risk of death from disease [4, 5].

## MATERIALS AND METHODS:

**Study design**: This prospective study included twenty four children with osseous Langerhans cell histiocytosis were included. Data were prospectively collected in the period from 2013 till 2016. They were referred for FDG PET/CT for staging for pathologically proven Langerhans cell histiocytosis. Clinical information were extracted from the medical records, including age, sex, detailed pathology, disease extent at diagnosis, risk of mortality at diagnosis, imaging findings and disease status. Data were entered into a computerized database. Study endpoints included date of last follow-up or date of death. The age of patients encountered in the study ranged from 2.7 months to 9 years with a mean of 3.0 ± 2.3 years. They included 18 males (75%) and six females (25%). All patients were referred to the Oncology and Nuclear Medicine Department to perform F18-FDG PET/CT for initial staging or restaging.

The findings of the PET/CT were compared with skeletal survey, computed tomography (CT) and/or magnetic resonance imaging (MRI) findings within time interval of less than 6weeks. The choice of methods depended on tumor location. All procedures were approved by the institutional review board.

### $^{18}$F-FDG PET/CT:

$^{18}$F-FDG PET/CT study was done using a dedicated PET/CT scanner (GE Healthcare). This machine integrates a PET scanner with a dual-section helical CT scanner and allows the acquisition of co-registered CT and PET images in one session.

### Patient Preparation and Imaging Technique:

All patients fasted for at least 4 h before the injection of 0.1-0.15mCi/kg (3.7-5.5 MBq /kg) $^{18}$F-FDG. Blood glucose levels did not exceed 150 mg/dL. Scanning started 45-60 min after tracer injection (acquisition time: 1-2 min/bed position).

Intravenous contrast agent was administered in most patients. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans were acquired during breath holding within the normal expiration position and reached caudally to the mid thighs. PET over the same region was performed immediately after acquisition of the CT. Attenuation correction of PET images was performed by using attenuation data from the low dose CT component of the examination.

Images were interpreted at a workstation equipped with fusion software (GE) that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Focal FDG uptake was considered abnormal when it was greater than that of hepatic uptake or in presence of abnormal changes on CT with any degree of FDG uptake. Interpretation was accomplished by 2 experienced nuclear medicine physicians.

Maximum standardized uptake value (SUV max) of each involved site was determined for semi-quantitative analysis using a spherical region of interest at site of focal FDG uptake.

### Statistical Analysis:

Data were statistically described in terms of mean, standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. Correlation between various variables was done using Pearson moment correlation equation. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft Windows.

## RESULTS:

**Age and sex:** In our twenty four children with osseous Langerhans cell histiocytosis the mean age of onset was 3.0 ± 2.3 years ranging from 2.7 months to 9 years and median of 27.4 months. The majority of children were males, 18 patients (75%) and six female patients (25%) with male to female ratio 3:1. **Disease extent:** Seventeen patients (70.8%) presented with multi-system disease from the start. While five patients (20.8%) had uni-focal lesions and only two patients (8.3%) presented by multi-focal lesions.

**Quantification of osseous lesions with metabolic activity in 24 patients with Langerhans cell histiocytosis:**

Among twenty four patients with LCH, the highest SUV max and mean value were seen in skull, pelvic and long bones and vertebrae, with mean SUV max of 4.4(±2.1 SD), 3.5 (±2.4 SD), 3.4 (±2.5 SD), 3.4 (±0.8 SD), respectively as seen in ***Table (1) & Figure (1, 2)***.

**Table 1:** Quantification of osseous lesions in 24 patients with osseous LCH.

| Site | Number of cases | Percent | Mean SUV max | Minimum SUV max | Maximum SUV max |
|---|---|---|---|---|---|
| **Skull** | 21 | 87.5% | 4.4 (±2.1 SD) | 1.2 | 9.1 |
| **Pelvic bones** | 7 | 29.2% | 3.5 (±2.4 SD) | 1.8 | 7.3 |
| **Long bones** | 6 | 25% | 3.4 (±2.5 SD) | 1.2 | 8.4 |
| **Vertebrae** | 4 | 16.6% | 3.4 (±0.8 SD) | 2.5 | 4.5 |
| **Scapular** | 5 | 20.8% | 3.2 (±3.3 SD) | 1.0 | 9.0 |
| **Ribs** | 8 | 33.3% | 2.4 (±1.0 SD) | 1.7 | 4.7 |
| **Sternum** | 2 | 8.3% | 2.0 (±0.7 SD) | 1.5 | 2.5 |

In our twenty four patients, the highest SUV max and mean value were seen in mediastinal LNs, abdominal LNs, axillary and cervical LNs and only one patient had hepatic focal lesion with mean SUV max of 5.9(±3.2 SD), 4.9, 2.7, 2.1(±0.6 SD) and 0.9 respectively as seen in ***Table (2)***.

**Table 2**: Quantification of soft tissue lesions in 24 patients with osseous LCH.

| Site | Number of cases | Percent | Mean SUV max | Minimum SUV max | Maximum SUV max |
|---|---|---|---|---|---|
| **Mediastinal LNs** | 3 | 12.5% | 5.9 (±3.2 SD) | 2.5 | 8.9 |
| **Abdominal LNs** | 1 | 4.2% | 4.9 | 4.9 | 4.9 |
| **Axillary LNs** | 1 | 4.2% | 2.7 | 2.7 | 2.7 |
| **Cervical LNs** | 16 | 66.7% | 2.1 (±0.6 SD) | 1.2 | 3.1 |
| **Liver** | 1 | 4.2% | 0.9 | 0.9 | 0.9 |

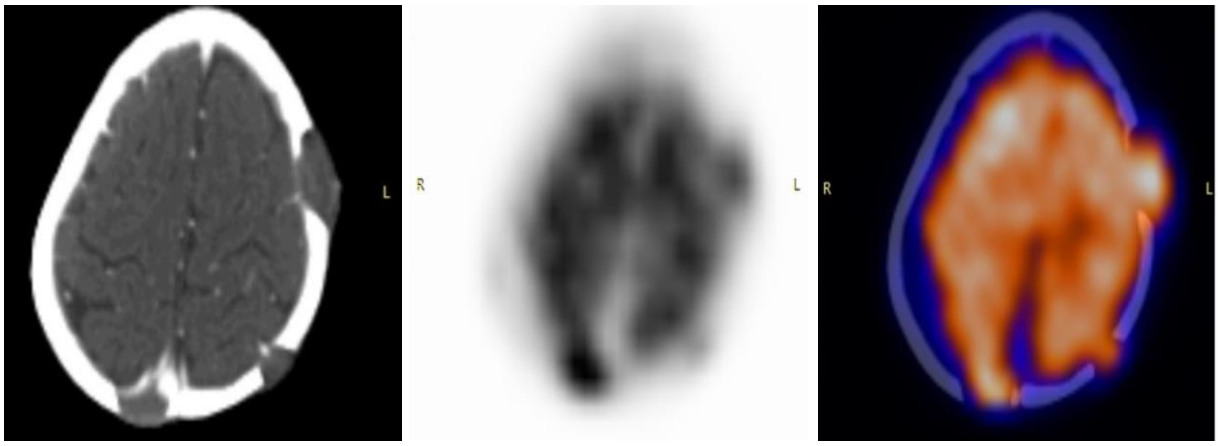


**Fig. 1:** Axial CT-FDG PET and fused PET/CT of Skull shows FDG avid lytic bone lesions**.**

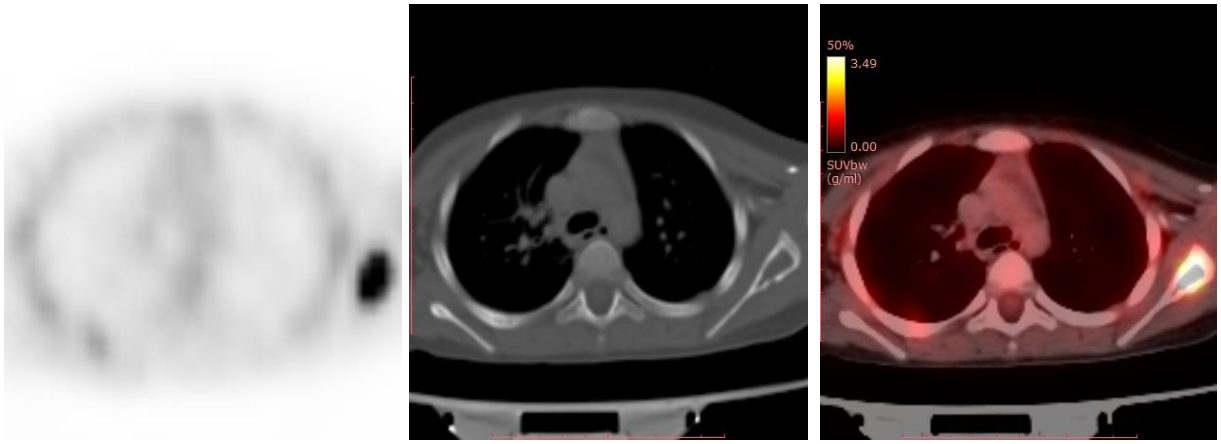


**Fig. 2**: Axial CT-FDG PET and fused PET/CT of the chest shows FDG avid left scapular lytic bone lesions.

**Correlation with radiological imaging at initial staging:** When comparing FDG PET/CT with diagnostic CT, FDG PET/CT showed additional lesions in 7 patients (46.7%) and was confirmatory in 8 patients (53.3%).

While in comparison with skeletal survey, FDG PET/CT showed additional lesions in 8 patients (47.1%) and was confirmatory in 9 patients (52.9%). PET/CT was confirmatory to MRI in all eight patients as shown in ***Table (3)***.

**Table 3:** Comparison between FDG PET/CT, skeletal survey, diagnostic CT and MRI at initial staging of osseous LCH.

| | Number | PET/CT | |
|---|---|---|---|
| | | Confirmatory | Additional lesions |
| **Skeletal survey** | 17 | 9 (52.9%) | 8 (47.1%) |
| **CT** | 15 | 8 (53.3%) | 7 (46.7%) |
| **MRI** | 8 | 8 (100%) | |

**Disease outcome:** At the end of study 18 patients (75%) were disease free with marked metabolic regression, while six patients (25%) had mild metabolic regression indicating residual disease. No statistically significant correlation could be found between disease outcome and either of risk of mortality (P value=0.9), initial number of osseous sites involvement per patient (P value=0.09) and initial SUV max (P value=0.8) ***(Table 4).***

**Table 4**: Correlation between Disease outcomes with risk of mortality, number of lesions and SUV max as identified by initial PET/CT.

| Disease Outcome | P Value |
|---|---|
| **Risk of mortality** | (P value=0.9) |
| **Number of lesions** | (P value=0.09) |
| **Initial SUV max** | (P value=0.8) |

# DISCUSSION:

Langerhans cell histiocytosis (LCH) is the most common of the histiocyte disorders, it is agranulomatous disorder characterized by clonal proliferation of cells that share phenotypic characteristics with the primary antigen presenting cells of the epidermis known as Langerhans cell. Its clinical manifestations are highly variable, extending from very benign forms to a disseminated, aggressive disease that causes significant mortality. Langerhans cell histiocytosis commonly presents with a skin rash or a painful bone lesion. Systemic symptoms of fever, weight loss, diarrhea, edema, dyspnea, polydipsia, and polyuria relate to specific organ involvement or multisystem disease presentation [(4)].

$^{18}$F-flourodeoxyglucose (FDG) is glucose analog. Just as glucose, FDG is actively transported into the cell mediated by glucose transport proteins (GLUT). Once intracellular, FDG are phosphorylated by hexokinase however it cannot enter glycolysis and becomes effectively trapped intracellularly as FDG-6-Phosphate. Tumor cells display increased number of glucose transporters, as well as higher levels of hexokinase. Tumor cells are highly metabolically active (high mitotic rates) and favor the more inefficient anaerobic pathway adding to the already increased glucose demands. These combined mechanisms allow for tumor cells to uptake and retain higher levels of FDG when compared to normal tissues. When looking at large numbers of patients with many different tumors, initial results from the National Oncologic PET Registry showed that PET changed management 36.5% of patients [(5)].

The present work was designed to evaluate the role of 18F-FDG PET/CT in evaluation of children with osseous Langerhans cell histiocytosis in relation to clinical data and radiological imaging. In our study, the mean age of onset was 3.0 years ± 2.3 years with a range of 2.7 months to 9 years and median of 27.4 months (2.3 years).

These results confirm previous results of ***Antoneli et al,*** who analyzed 145 cases of disseminated LCH registered by the National Cancer Institute during 2000–2009 from 18 series. The Median age at diagnosis was 12 months and most of patients were between one and four years old at diagnosis [(6)].

Also ***Guyot-Goubin et al***, analyzed 255 patients of LCH registered by the French National Registry of Childhood Hematopoietic Malignancies from 2000 to 2004. Age at diagnosis ranged from 1 day to 14.6 years, with a median of 3.5 years [(7)].

In this study, there was male predominance as the majority of our patients were males, eighteen (75%) with only six females (25%) with over all male to female ration 3:1. Higher ratio observed below one year of age 4:1. and lower ratio above one year 2.1:1.

Similar data were reported by ***Bernstrand et al,*** they analyzed 84 Nordic children with LCH and found male to female ratio of 2:1 among the Danish group (30 patients) [(8)].

On the other hand, ***Antoneli et al,*** reported that the male to female ratio was close to 1 and the incidence rate was higher in female children <1 year.

Also ***Guyot-Goubin et al***, showed male to female ratio was 1.2 also with the incidence rate higher in female children <1 year [(6,7)].

This difference in incidence of male to female ratio is related to different number of patients in different series**.**

**Disease extent and Risk of mortality at diagnosis:** In our study, seventeen (70.8%) patients presented with multi-system disease, most of them were below five years old. While seven (29.2%) patients had single system involvement. Five (20.8%) patients had unifocal lesions and only two (8.3%) patients presented by multi-focal lesions. Twenty patients (83.3%) had low risk of mortality and only four patients (16.7%) had high risk organ involvement, all were below five years old. Also ***Huang and Arceci,*** found that multisystem LCH usually occurs in children less than 2 years of age.

Also our results concur with ***Bernstrand et al***, they analyzed 84 Nordic children with LCH and found similar presentation rate between extent categories among the Danish group (30 patients) [8,9].

On the controversy to ***Riguad et al,*** who analyzed 1478 patients over 30 years from the French national cohort of children with Langerhans cell histiocytosis (LCH). They found predominant single system involvement with tendency to decrease in disease severity with time during enrollment [10].

Also ***Guyot-Goubin et al***, found the majority of patients had unifocal involvement [7]. Although our study had smaller population with high risk patients.

However other studies as ***Riguad et al***, reported only 219 patients out of 1478 patients (15%) presented with high risk.

Also ***Kotecha et al***, reported 11 patients out of 69 patients (15.9%) presented by risk organ involvement [10,11].

**Organ involvement:** In our study, eighteen patients (75%) had bone lesions with multiple system involvement, another four patients (16.7%) presented by only single bone lesion or multiple bone lesions in two patients. By far the skull was the most common site of involvement, seen in twenty one patients (87.5%). Three patients had vertebral, rib, scapula, pelvic bones &/or long bone lesions. Four patients (16.6%) had vertebral lesions, eight patients (33.3%) had rib lesions, five patients (20.8%) had scapular lesions, six patients (25%) had long bone lesions, two patients (8.3%) had sternal lesions and seven patients (29.2%) had pelvic bone lesions.

***Rigaud et al***, showed that 1213 patients of 1478 patients (82%) had bone lesions and more than half were single system involvement.

Also ***Morimoto et al***, found that 68 patients out of 91 patients (74.8%) had bone lesions [10,12].

Similar data were stated by ***Phillips et al***, who evaluated children with LCH from August 2004 to April 2007 and found that skull was the most common site of involvement, they counted seventy skull lesion and followed by fifty two vertebral lesions, fifty one long bone lesions, forty two pelvic lesions, seven rib lesions and twenty one other none osseous lesions (brain, liver, lungs, lymph nodes and soft tissue). Also they found that PET was confirmatory or superior in 236/256 (92%) of lesions. PET detected additional lesions leading to significant change in treatment in 10 (22.7%) patients [13]. Also in this study, FDG PET/CT found additional lesions when compared to skeletal surveys in 8 patients (47.1%) and Computed Tomography in 7 patients (46.7%).

Also ***Zhou et al***, who evaluated patients with LCH from December 2004 to April 2013. They found that bone was the commonest site of involvement including thirty one of forty five lesions (68.9%) with mean SUV max 6.30±2.87. F-18-FDG PET/CT was sensitive in detecting LCH lesions with a true positive detection rate of 92.9%. All of the LCH lesions were F-18-FDG avid with overall mean SUV max was 7.13±4.91 [14]. In the present work, mean SUV was higher in skull, pelvic, vertebrae and long bones.

# CONCLUSIONS:

18 FDG PET/CT as a useful tool in identification of metabolically active lesions not detected by other imaging modalities, detection of disease activity in LCH patients. However Skeletal Survey remains the standard modalities for initial evaluation, however further multi-center studies are required to evaluate impact of FDG PET/CT in patient management.

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