

# Pituitary gland and bone involvement of Langerhans cell histiocytosis in a boy and brief review of the literature

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## Abstract

A 3 years old boy was hospitalized with a month's history of polydipsia, polyuria and low fever. There was no relevant family history. This is a rare case of Langerhans cell histiocytosis (LCH) with both bone and pituitary infiltration shown on the technetium-99m methylene diphosphonate (<sup>99m</sup>Tc-MDP) scan and brain magnetic resonance imaging (MRI). Sagittal and coronal T1-weighted images on MRI showed the typical lack of high signal intensity of the posterior pituitary which corresponded to the central signs of diabetes insipidus (DI). The diagnosis of LCH was suspected by <sup>99m</sup>Tc-MDP whole-body bone scan showing multiple bone lesions. The disease was further confirmed by pathology of the biopsy specimen from the right tibia. Brain MRI and bone scan are indicated for pediatric patients with DI. The high signal intensity of the posterior pituitary on MRI and the bone lytic lesions on scintigraphy suggested the diagnosis of LCH. This paper is original because it is the first full description of bone and pituitary involvement detected by bone scan and brain MRI in a pediatric LCH.

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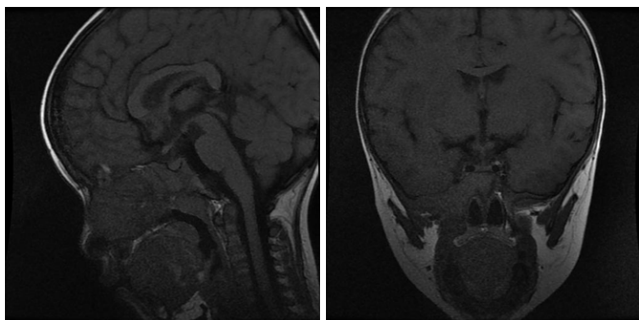
## Introduction

Langerhans cell histiocytosis (LCH) is a rare disease which is considered a reactive immune disorder or a neoplastic disorder [1]. The incidence of LCH is about 2.6-8.9 per million children (<15 years) each year. Langerhans cell histiocytosis is a group of disorders histologically characterized by the proliferation of LC, in multiple organs and systems [2]. Central nervous system (CNS) involvement, manifesting as diabetes insipidus (DI) secondary to pituitary involvement has been described [3]. This disease peaks between 1 and 3 years of age [4]. Although LCH may affect many organs [5], in 90% of the cases there is bone involvement which is solitary in one third of the cases [6]. Less frequently, lesions may be found in the lungs, liver, lymph nodes, skin and mucosae [2]. Lytic lesions may be found in the cranial dome [7] as showed by our case. Infiltrations by LCH of the thyroid, parathyroid, adrenal glands, ovaries, pancreas [8], orbit [7], scalp [9] and the oral cavity [2] have been rarely reported. The common affected areas in children are the cranial region, liver, spleen, lymph nodes and bone marrow. The organs most commonly involved in adults include extracranial organs such as the lungs, skin and bone [2, 10]. This report refers to a rare case of LCH with both bone and pituitary infiltration that on the technetium-99m methylene diphosphonate (<sup>99m</sup>Tc-MDP) bone scanning and brain magnetic resonance imaging (MRI).

## Case Report

A 3 years old boy was admitted in our hospital for polydipsia, polyuria and low fever of a month duration. He and his family medical history was nonsignificant. Physical examination findings were normal. The biochemical values before drinking water included serum sodium 135.2mmol/L (normal range, 135-146), potassium 4.11mmol/L (normal range, 3.5-5.1), chlorine 100mmol/L (normal range, 95-105), urine ketone 150mg/dL (normal range, <5), normal liver and kidney function. The urine specific gravity was 1.002 (normal range, 1.010-1.030) with a daily urine output 3280-4000mL and water intake 2990-3030mL. The pretreatment basal level of human growth hormone (hGH) was

0.821ng/mL. Insulin-like growth factor-1 was 28.00ng/mL, free thyroxine 18.79pmol/L (fT4, normal range, 6.6-24.8), thyroid stimulating hormone (TSH) was 1.33uIU/mL (normal range, 0.3-4.6uIU/mL), human chorionic gonadotropin (THCG) was <2.00mIU/mL and adrenocorticotrophic hormone (ACTH) 22.92pg/mL (5-60pg/mL). The child had brain MRI with a 1.5T MR unit (Twinspeed, GE Medical Systems, Milwaukee, WI, USA). The imaging protocol involved axial non-contrast T1-weighted (TR/TE, 2000-2202/9-10ms) and axial T2-weighted (TR/TE, 8000-8600/110-125ms). T1-weighted (w) images pre and post contrast MRI scans, T2-w fast spin-echo imaging mages (TR/TE, 2200-2500/90-95ms), fluid attenuated inversion recovery (FLAIR) were also performed. Diffusion-weighted MRI was acquired in the axial plane using a single-shot echo-planar imaging sequence (TR/TE effective range, 5000-5500/70-80). Sagittal and coronal T1-weighted images demonstrated the typical lack of high signal intensity of the posterior pituitary (arrow) (Figure 1a-b). Central DI was diagnosed and desmopressin acetate tablets (1/8# q12h-1/6# q12h-1/4#) were administered with no effect.



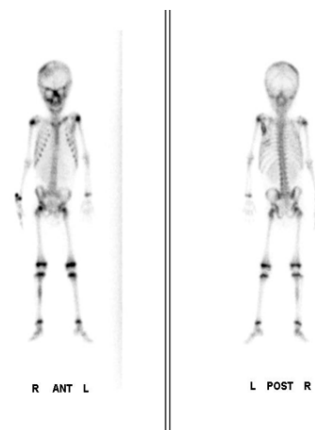
**Figure 1.** Sagittal and coronal T1-weighted images demonstrate the typical lack of high signal intensity of the posterior pituitary (arrow).

Whole body  $^{99m}\text{Tc}$ -MDP scintigraphy was performed by a double head single photon emission tomography (SPET) gamma camera equipped with low energy high resolution parallel hole collimator. After intravenous administration of 185MBq  $^{99m}\text{Tc}$ -MDP and waiting period of 2-3 hours, routine whole body scans were obtained. Bone scintigraphy showed multiple increased activity in the right cranium, left scapula, left ribs, and right tibia (Figure 2) which further suggested the diagnosis of LCH. Finally, the pathology of the biopsy specimen from the right tibia confirmed the diagnosis of LCH by showing a lot of oval cells among a large number of neutrophils, eosinophils and lymphocytes (Figure 3a). Immunohistochemical analysis revealed positivity of CD1a (Figure 3b). Finally, the boy underwent chemotherapy with improvement of DI.

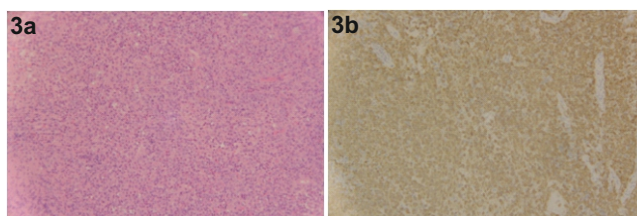
## Discussion

Central nervous system (CNS) involvement in LCH is rare and can be fatal [4, 11]. The prevalence of CNS involvement in

LCH ranges from 3.4% to 57% [1]. The hypothalamic-pituitary (HPA) axis involvement was about 5%-50% in autopsy cases in children with LCH [4]. The other most common type of hormone deficiency in children and adults with LCH is growth hormone (GH) deficiency [4]. Furthermore, ACTH deficiency was reported in 41.6% [12] and corticotropin releasing hormone (CRH/ACTH deficiency in 57.1% of patients studied [13]. All above statistics are rather poor because they use small series of patient [14]. The most common pituitary infiltration with LCH induces DI and may precede or follow other manifestations of the disease [3-5]. In our case the initial complaint was DI. Pituitary involvement is a common feature of LCH, and therefore all LCH patients should undergo a thorough endocrine evaluation, periodically [13].



**Figure 2.** Bone scintigraphy, anterior and posterior view demonstrates multiple increased activity in the right cranium, left scapula, left ribs and right tibia.



**Figure 3.** 3a, Pathology of tibia bone lesion showed a lot of oval cells among a large number of neutrophils, eosinophils and lymphocytes. 3b, Immunohistochemical analysis was positive for Cd1a.

Etiology of LCH remains unknown but environmental, infectious, immunologic, genetic causes, and a neoplastic processes have been suggested [2]. Immunological abnormalities may result from suppressor cells deficiency. New data suggest that abnormal immunological response may be the result of viral infection of lymphocytes, with special reference to HHV-6 [2].

The standard evaluation of multisystem LCH includes a clinical evaluation, laboratory tests and a skeleton/skull X-ray survey, with chest high-resolution computed tomography (HRCT) in the case of pulmonary involvement [15], bone scan for bone involvement and the use of MRI for brain infiltration of LCH [16]. The clinical presentation varies, ranging from the appearance of a single bone lesion to multisystemic

involvement. The minimum criteria of brain MRI include T2w, FLAIR, T1w images before/after contrast in at least two different section planes and thin post contrast sagittal slices T1w through the sella [17]. In children, DI due to a pituitary lesion poses the differential diagnosis of germ cell tumor, hypophysitis and lymphoma [18]. Testing  $\alpha$ -fetoprotein (AFP) and human chorionic gonadotrophin (HCG) in cerebrospinal fluid (CSF) and in the peripheral blood may confirm the diagnosis of germinoma [19, 20]. Cytological evaluation of CSF may also be able to identify pleocytosis or lymphoma. Our case had normal HCG. The bone and pituitary involvement suggested LCH confirmed by pathology.

Bone scintigraphy, although very useful for the diagnosis of LCH disease may show poor sensitivity in the pelvis, sacrum, ribs, sternum, clavicles, scapula and vertebral lesions [6]. Since normal bone scan appearance varies dramatically with age it is crucial that the interpreting physician be well experienced [21-24]. Fluorine-18 FDG PET/CT studies show all dissemination of the disease [6, 25, 26] and may replace the standard evaluation for staging of adult patients with multisystem LCH [15].

Pathophysiology of LCH involves histiocytes, cells derived from monocytes of granulocyte/macrophage series after extravascular diapedesis [2]. The disease is histologically characterized by the clonal proliferation of CD1a and myeloid dendritic cells associated with a significant inflammatory component [7] also as shown by lot of neutrophils in the specimen of our case. The LCH diagnosis is confirmed by the presence of Birbeck granules using electron microscopy or by positive immunohistochemical staining for the protein markers S100 and CD1a [2, 4].

The primary treatment for LCH includes local excision of the lesion, chemotherapy, steroid therapy, radiation, the use of anti-CD1a monoclonal antibodies and in patients with hormone deficiencies, hormone replacement therapy [27], even without a biopsy provided that germ cell tumor and lymphoma have been excluded [28]. The LCH IV is an international collaborative treatment protocol that is expected to be completed by 2018 which aims to reduce mortality and reactivation rates by intensification and prolongation of treatment especially in multisystem LCH and also expected to use treatment strategies with no side effects [5].

*The authors of this study declare no conflicts of interest*

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