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## PICTORIAL ESSAY

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# An Institutional Audit and Pictorial Review of Langerhans' Cell Histiocytosis Presented with Intracranial Manifestations

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### ABSTRACT

**Objective:** To review the intracranial manifestations and role of imaging in Langerhans' cell histiocytosis.

**Methods:** This is a retrospective institutional review of clinical data and radiological findings of Langerhans' cell histiocytosis patients presenting to a tertiary Cancer Centre over the past 11 years. Of 23 patients with confirmed Langerhans' cell histiocytosis, 6 had central nervous system involvement (1 female, 5 male; age range, 2-59 years; mean age, 16 years). One of these patients only affected the hypothalamic-pituitary axis, while 5 had additional bone or multisystem involvement. All the patients underwent radiographic skeletal survey, chest radiography, and abdominal ultrasound. Brain computed tomography and magnetic resonance imaging limited to areas of suspected histiocytic infiltration were performed.

**Results:** Four patients had an absent T1 bright signal of the posterior pituitary gland and nodular enhancement of the infundibular stalk. After treatment, the latter feature resolved. One patient had an empty sella on long-term follow-up. Two patients had brain parenchymal involvement in the form of a focal lesion in the right temporal lobe with excessive perilesional white matter oedema and multiple small nodular-enhancing lesions involving both the cerebrum and brainstem. The patient with brainstem lesion endured a rapidly deteriorating clinical course and succumbed due to urosepsis and respiratory failure.

**Conclusions:** There was intracranial involvement in 26% of this patient cohort with Langerhans' cell histiocytosis, and manifested 2 extreme patterns of central nervous system involvement. The less severe form (67%) involved the hypothalamic-pituitary axis; the patient suffered chronic pituitary gland insufficiency despite radiological regression after treatment. The more severe pattern (33%) entailed brain parenchymal infiltration resulting in variable neurological deficits.

**Key Words:** Central nervous system; Histiocytosis, Langerhans-cell; Magnetic resonance imaging

## 中文摘要

### 根據一所機構的資料對顱內蘭格罕細胞組織球增生症進行審核及影像回顧

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**目的：**回顧蘭格罕細胞組織球增生症的顱內表現及影像學作用。

**方法：**回顧過去11年內就診於一所三級癌症中心的蘭格罕細胞組織球增生病人的臨床及影像學資料。23位確診患者中，6位中樞神經系統受累（5男1女；年齡介乎2至59歲，平均16歲）；其中1名患者只累及下丘腦—垂體軸，其餘5名還累及骨骼或多個系統。所有病人均接受全身骨骼及胸部X光檢查及腹部超聲波檢查，並對懷疑有組織細胞浸潤的部位進行腦部電腦斷層及磁力共振影像。

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**結果：**4名病人T1加權像垂體後葉高信號消失，漏斗柄呈結節狀強化。治療後，漏斗柄強化消失。其中1名病人長期隨訪時有空蝶鞍。兩名病人的右側顳葉局部腦實質內出現病灶伴週邊腦白質大量水腫，及大腦半球和腦幹多發小結節狀強化病灶。腦幹病變患者的病情急轉直下，最終因敗血症和呼吸衰竭死亡。

**結論：**本組蘭格罕細胞組織球增生症患者中，26%的病人有顳內侵犯，病情表現為中樞神經系統受累的兩種極端模式。輕者（67%）為下丘腦—垂體軸受累，雖然治療後影像學表現可改善，但仍有慢性腦垂體功能不全。重者（33%）腦實質浸潤，導致不同程度的神經功能缺損。

## INTRODUCTION

Langerhans' cell histiocytosis (LCH) describes a group of conditions (also referred to as histiocytosis X) affecting the reticuloendothelial system. It includes the subtypes of Letterer-Siwe disease, Hand-Schuller-Christian disease and eosinophilic granuloma, and usually affects children. Multisystem LCH presents most commonly in childhood<sup>1,2</sup> and has an annual incidence of 4 to 4.5 per million. Intracranial involvement in LCH is usually restricted to the hypothalamic-pituitary axis or involves extra-axial extension from skull vault lesions. Space-occupying supratentorial intracerebral lesions with mass effect and enhancement have rarely been described.

This was a retrospective institutional review of all patients diagnosed with LCH in our hospital over an 11-year period between 1998 and 2009. Of 23 patients diagnosed with LCH, 6 who had central nervous system (CNS) involvement were reviewed for their radiological findings and clinical data.

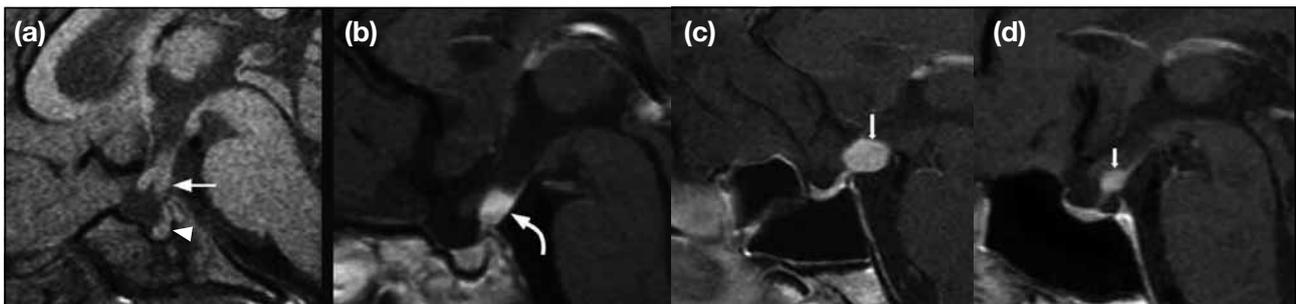
## METHODS

Subjects were retrospectively recruited from the insti-

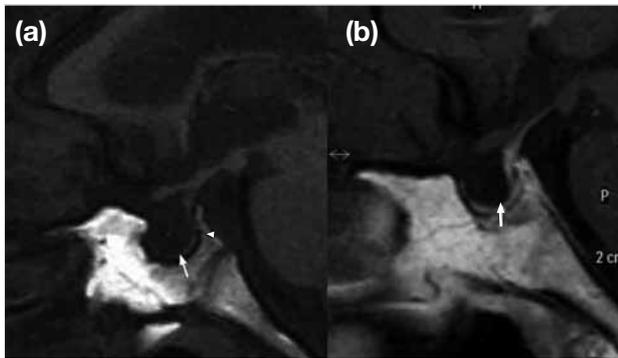
tutional database from 1998 to 2009 using the keyword "histiocytosis", "histiocytosis X", or "Langerhans' cell histiocytosis". Electronic patient records were retrieved and the following features were specifically looked for: age at the manifestation, gender, presenting complaints, type of imaging investigation (X-ray, ultrasound, or magnetic resonance imaging [MRI]), sites of involvement, initial lesion size, treatment given, treatment outcome, and any complications.

## RESULTS

Of 23 patients with confirmed LCH, 6 had CNS involvement. One was female, and the age range was 2 to 59 (mean, 16) years. Of the 6 patients with CNS involvement, 4 (67%) had hypothalamic pituitary involvement, in which one of them had hypothalamic axis as the sole site involved; 2 patients (33%) had brain parenchymal involvement; 5 (83%) had bone or multisystem involvement. All the patients underwent radiographic skeletal surveys, chest radiography, and abdominal ultrasound. Brain computed tomography (CT) and MRI was limited to areas of suspected histiocytic infiltration. Details of these 6 patients are given below.



**Figure 1.** (a) T1-weighted sagittal image of pituitary-hypothalamic region in a 4-year-old boy (case 1) presenting with 3 months of polyuria and polydipsia. There is absence of normal bright signal in the posterior pituitary gland (arrowhead) and thickening of the pituitary stalk (arrow). (b) Contrast-enhanced T1-weighted sagittal image of the same patient showing thickening and enhancement of the pituitary stalk (curved arrow). (c) Contrast-enhanced T1-weighted sagittal image of a 26-year-old man presenting with progressive bilateral gynecomastia associated with loss of libido for 6 months (case 2). There is globular enhancement of the pituitary stalk and hypothalamus (arrow). (d) Contrast-enhanced T1-weighted sagittal image of an 18-year-old girl presented with oligomenorrhoea, increase in body weight, and symptoms of diabetes insipidus (case 3). There is nodular enhancement in the mid-pituitary stalk (arrow).



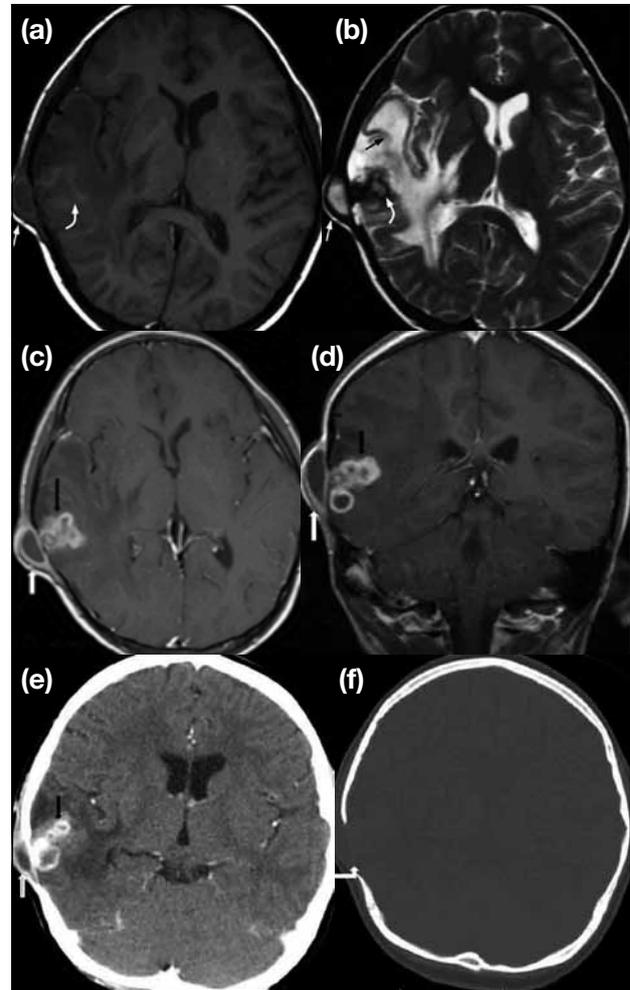
**Figure 2.** Follow-up magnetic resonance study in a 17-year-old boy after completing treatment of Langerhans' cell histiocytosis. He presented with diabetes insipidus at the age of 7 years (case 4). (a) A T1-weighted sagittal image through the pituitary fossa shows absent normal bright signal in the posterior pituitary (arrowhead) and an empty sella (arrow). (b) Contrast-enhanced sagittal image: the delayed nature of enhancement (arrow) was demonstrated on a dynamic series (not shown).

### Cases 1 to 4

Cases 1 to 4 had similar radiological findings, although their ages at presentation and clinical symptoms were different.

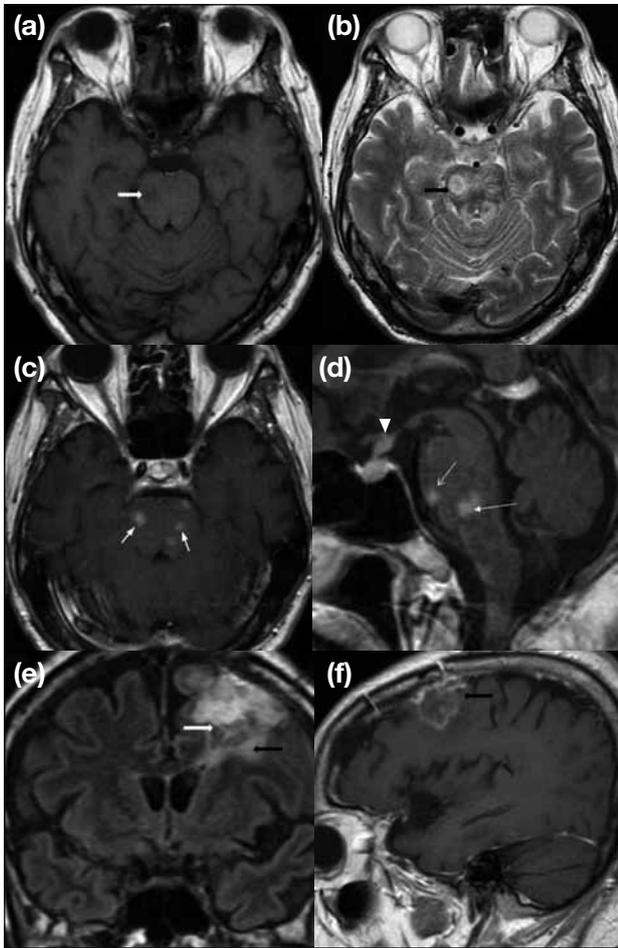
Case 1 was a previously healthy 4-year-old boy, who presented with polyuria and polydypsia for 3 months. Case 2 was a 26-year-old man who was a chronic smoker, and presented with a 6-month history of progressive bilateral gynaecomastia and loss of libido. Case 3 was an 18-year-old girl presented with oligomenorrhoea, increase in body weight, and with symptoms of diabetes insipidus (DI). Case 4 was a 7-year-old boy presenting with symptoms of DI.

In the above 4 cases, cranial MRI showed absence of normal bright signal characteristic of the posterior pituitary gland. There was nodular enhancement along the hypothalamic pituitary axis (Figure 1). Findings were compatible with LCH. Skeletal survey showed characteristic bone involvement in all patients (except case 4), which also supported the diagnosis. All patients were given standardised medical treatment with intranasal desmopressin / 1-deamino-8-D-arginine-vasopressin (DDAVP) [Minirin; Ferring Pharmaceuticals Pty Ltd, Australia] 50 µg twice daily and low-dose steroid, hydrocortisone 10-15 mg/m<sup>2</sup>/day orally as maintenance therapy. On follow-up MRI studies, the abnormal enhancement along the hypothalamic pituitary axis resolved in all patients, but the loss of the hyperintense T1 signal from the posterior pituitary persisted (consist-



**Figure 3.** A 2-year-old boy presented with scalp masses over left occipital and right temporal region. (a) T1-weighted and (b) T2-weighted axial images of the brain showing an irregular T1-hypointense and T2-hyperintense right temporal lobe lesion (curved arrow) with excessive perifocal white matter oedema (black arrow) causing compression of the right lateral ventricle and mild leftward midline shift. Note the small extraosseous component crossing the adjacent temporal bone (white arrow). (c) Axial and (d) coronal T1-weighted contrast-enhanced images showing multiple conglomerated ring-enhancing lesions in the right temporal lobe (black arrow) and an associated rim-enhancing extraosseous necrotic component (white arrow). (e) Contrast-enhanced axial computed tomographic image and (f) image at the same level displayed at bone window settings, taken 1 week post-treatment. There are residual ring-enhancing lesions in the right temporal lobe (black arrow) with an extraosseous component (white arrow). The mass effect and midline shift have resolved. A bony defect (curved arrow) is present at the right temporal bone.

ent with chronic clinical pituitary gland insufficiency). Furthermore in case 4, the residual anterior pituitary tissue formed a very thin peripheral band, giving an empty sella appearance (Figure 2). Dynamic scan showed delayed enhancement of the pituitary stalk and of the thin residual pituitary tissue. The above features are frequently present in LCH patients with central DI.



**Figure 4.** A 59-year-old man presenting with quadriplegia, bulbar palsy and dysphasia (case 6). He developed diabetes insipidus during hospitalisation. (a) T1-weighted and (b) T2-weighted axial images of his brain showing T1-hypointense and T2-hyperintense nodular lesions in the brainstem (arrows). (c) Axial and (d) sagittal T1 contrast-enhanced images showing multiple nodular-enhancing lesions in the brainstem (white arrows), also there is nodular enhancement of the pituitary stalk (white arrowhead). (e) Coronal fluid-attenuated inversion-recovery image shows left frontal irregular hypointense lesion (white arrow) with perifocal hyperintense white matter oedema (black arrow). (f) T1-weighted post-contrast sagittal image shows irregular ring enhancement of the left frontal lesion (black arrow).

### Case 5

A 2-year-old boy presented with a 6-month history of scalp masses over the left occipital and right temporal region. Clinically the masses were accompanied by seborrhoeic dermatitis. Skull X-ray incidentally found osteolytic lesions in the corresponding regions. CT brain showed the presence of multiple soft tissue masses over the skull vault. Excisional biopsies by curettage confirmed the diagnosis of LCH. No other systems were involved. The patient was treated with vinblastine and prednisolone for 1 year. Five years later, he developed central DI and started DDAVP treatment. He subse-

quently complained of a painful swelling over the right temporal scalp, confirmed by MRI (Figure 3a to d) and subsequent CT (Figure 3e and f) to be an aggressively enhancing soft tissue lesion with both extracranial and intracranial components. The lesion was associated with a bony defect at the right temporal region. The intracranial component involved the brain parenchyma, with nodular ring enhancement and was associated with marked vasogenic oedema. The features were compatible with LCH recurrence. The patient started treatment with vinblastine and prednisolone. After 6 months of chemotherapy, the scalp lesion became softer while imaging revealed overall regression of the intracranial lesion. The patient remains in remission to date.

### Case 6

A 59-year-old man presented with bilateral lower limb weakness, slurring of speech and choking over a few months. His initial MRI performed in a private hospital (not shown) showed abnormal high T2-signal intensities in the brainstem, left frontal lobe and pituitary stalk with no significant mass effect. Positron emission tomography-CT showed these lesions to be hypermetabolic (not shown). The patient's condition continued to deteriorate clinically and imaging revealed lesions in the brainstem had progressed. Brain biopsy of the left frontal lobe lesion yielded aggregates of histiocytes with patchy perivascular lymphocytic infiltration, but no granuloma or necrosis. With these inconclusive findings, the patient was referred to our hospital for further investigation. On physical examination, the patient was dysarthric with reduced lower limb power (grade 4/5). The heel-shin test was clumsy. During hospitalisation, he developed cranial DI and started DDAVP treatment. Brain biopsy slides were reviewed (with special immunocytochemistry performed using a biotin-avidin technique). This revealed numerous CD1a+ histiocytes, of which many also reacted to S-100 protein, thus confirming the diagnosis of LCH. Polymerase chain reaction for tuberculosis was negative.

In our centre, his first MRI showed multiple T1-hypointense and T2-hyperintense nodular lesions with avid homogeneous contrast enhancement in the midbrain, pons, and medulla (Figure 4a to d). An additional irregular ring-enhancing lesion was present in the left frontal lobe (Figure 4e and f). The pituitary infundibulum was also involved (Figure 4d). The patient was initially planned for chemotherapy, which was withheld due to his rapidly deteriorating clinical course. He developed increasing brainstem signs, aspiration pneumonia and urosepsis

(associated with urinary tract obstruction from retroperitoneal involvement). The patient urgently received palliative whole brain irradiation and dexamethasone to halt the progressive brainstem lesions, but succumbed.

## DISCUSSION

LCH is a rare disease of unknown aetiology. At present some hypotheses favour a primarily reactive, immunologically mediated pathogenesis, rather than a neoplastic process, but there is no evidence of a viral stimulus or strong genetic component.<sup>3,4</sup>

The classical manifestation of LCH in CNS is DI starting in childhood and persisting into adulthood, so patients with isolated DI should be observed for other associated symptoms classical for systemic LCH (bone pains, skin rash, dyspnoea, lymphadenopathy, organomegaly). DI, which is the most common clinical feature, occurred in all of our 4 patients with pituitary involvement. Some of our patients also developed a scalp mass over the right temporal region, oligomenorrhoea, increased body weight, and progressive bulbar palsy. Most of the patients received Minirin and intranasal DDAVP tablets (desmopressin acetate, a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin [ADH]) and low-dose steroids. Chronic pituitary gland insufficiency ensued in all 4 patients, although radiological features regressed. The patient with brainstem and left frontal lesions died due to respiratory failure. The other with temporal lobe involvement appeared to have responded partially to vinblastine and prednisolone treatment.

During the course of disease, involvement of the CNS is noted in 25 to 35% of patients, mostly in those with multisystem LCH.<sup>5,6</sup> Grois et al<sup>7</sup> and Prayer et al<sup>8</sup> studied the MR appearances in a series of patients with intracranial manifestations. In LCH, the hypothalamic-pituitary axis is, by far, the most frequently involved intracranial region, and the resulting DI is a clinical hallmark. Radiological findings correlate with the clinical symptoms of DI. Typically, they are characterised by a lack of the normal T1-weighted image shortening (bright signal) in the posterior pituitary, frequently in association with a thickened (>3 mm) and gradually enhancing pituitary stalk without wash-out. One of our patients also had an empty sella associated with an absent bright signal in the neurohypophyses.

Other CNS manifestations described are diffuse or localised atrophy (e.g. in the pons or cerebellum), white or

grey matter lesions which may demonstrate enhancement, pineal gland changes and extra-axial dural, arachnoidal or choroidal lesions. In the first series by Grois et al,<sup>7</sup> the grey matter lesions in the cerebellum or pons demonstrated enhancement and mass effect, but no supratentorial lesions with mass effect and enhancement were described. In the second series by Prayer et al,<sup>8</sup> imaging of involved grey matter indicated a neurodegenerative pattern. Namely, there was initial hyperintensity on T1-weighted image followed by hypointensity or hyperintensity on T2-weighted image, with subsequent extension of T2 hyperintensity to the perinuclear white matter over months or years. Some of the small supratentorial white matter lesions followed a vascular pattern showing symmetrical enhancement and mass effect and the remainder manifested leukoencephalopathy pattern (low signal intensity on T1-weighted image and high signal intensity on T2-weighted image).<sup>8</sup>

Space-occupying sizable cerebral lesions exerting a mass effect and enhancement are rare and only a few case reports exist in the literature. Graif and Pennock<sup>9</sup> described a frontoparietal mass with surrounding oedema in a 12-year-old boy with multisystem LCH, while Gunny et al<sup>10</sup> documented 2 space-occupying enhancing temporal lobe lesions in a 34-year-old patient who have spontaneous resolution. Very rarely, nodular meningeal thickening, spinal cord<sup>11</sup> or nerve root infiltration<sup>12</sup> can be seen, and there has been 1 biopsy-proven case of histiocytic granuloma of the choroid plexus.<sup>13</sup> Pathologically, proliferation of the adventitial cells of blood vessels initially creates perivascular foci of Langerhans' cells. They later coalesce to granulomatous masses,<sup>14</sup> which can be identified radiologically as cerebral, meningeal, or spinal cord lesions. Involvement of the brain stem (particularly the pons) with intraparenchymal LCH was associated with poor prognosis,<sup>15</sup> which was also noted in our patient who died with neurological disability and cranial nerve involvement.

Although intracranial manifestations of LCH have been described in radiology textbooks, the purpose of this audit was to illustrate an institutional review of both typical and atypical examples. The cranial manifestations can present as the typical hypothalamic-pituitary pattern with or without other radiographic features that are diagnostic of LCH. In some cases, even without histological proof, imaging is helpful to suggest the diagnosis based on radiological features and related signs and symptom. In atypical lesions, imaging is useful as a guide to the appropriate site for biopsy. In such cases,

imaging is also helpful in follow-up and monitor treatment response.

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