Paediatric Manifestations of Langerhans Cell Histiocytosis: a Review of the Clinical and Radiological Findings

T. N. KILBORN *, J. TEH†, T. R. GOODMAN *

*Department of Radiology, John Radcliffe Hospital, Oxford and †Department of Radiology, Nuffield Orthopaedic Centre, Oxford, UK

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Langerhans cell histiocytosis is a rare disease in children. However, its ability to present in many ways, to mimic other conditions, and to manifest itself in many organs makes it a fascinating disease for radiologists. This article reviews the history of the disease, the features that are most useful in determining prognosis, and the various radiological findings seen in paediatric patients.

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INTRODUCTION

The disease complex formerly known as histiocytosis X, which included eosinophilic granuloma, Lettere–Siwe disease and Hand–Schuller–Christian disease, is now referred to as Langerhans cell histiocytosis (LCH) [1]. LCH can present in a variety of ways from a spontaneously regressing solitary lesion of bone to a multisystem life-threatening disorder. In all cases, the unifying pathological finding is proliferation of the Langerhans cell [2]. The diagnostic imaging findings in paediatric LCH are diverse and challenging. In the paediatric population, the differing radiological findings are highly dependent on age and clinical presentation.

BACKGROUND

The term histiocytosis refers to a group of disorders with proliferation of cells of the mononuclear phagocyte and dendritic cell system. LCH is classified as a class 1 disorder of the histiocytosis syndromes in children. This means that all lesions require the presence of Langerhans cells as components of the lesions, and definitive diagnosis requires the finding of Birbeck granules in cells of the lesion by electron microscopy [1]. The various manifestations of the disease were first recognized as having a common link by Lichtenstein in 1953 and given the name histiocytosis X [3]. The letter X referred to the unknown nature and cause of the disease. In 1973, the aetiology of the disease was identified as being due to an abnormal proliferation of Langerhans cells. The name LCH was, therefore, adopted in 1987 and is now the recommended term [1,2].

The Langerhans cell is an important component of the immune system. The cells originate in bone marrow and are derived from CD34 + stem cells. Cells depart from the marrow and travel via the blood to the skin, lung, thymus and lymph nodes. Langerhans cells function as antigen-presenting cells; they take up soluble antigen, which is then processed into immunogenic peptides that are presented to T lymphocytes so that an immune response may be elicited [4]. The unifying pathological feature of LCH is the inappropriate proliferation of these cells, which then infiltrate and accumulate in various tissues. The exact cause of this reaction is unknown although it has been postulated that infection plays a role [5]. Recent histological analyses have suggested the disease has a neoplastic aetiology due to the identification of clonal proliferation of Langerhans cells [6].

The clinical manifestations of LCH depend on the sites and extent of involvement. The disease may be focal or systemic and the most common sites of involvement include the bone
marrow, lung, thymus, liver, central nervous system, skin and lymph nodes.

CLINICAL AND RADIOLOGICAL FINDINGS

In children, LCH can present from the newborn period to 15 years with a peak incidence at 1–4 years of age [5]. The disease is rare, with a frequency of approximately 2–5 per million per year and is slightly more prevalent in boys [7]. After clinical assessment, imaging is used to determine the extent of disease. A skeletal survey is indicated once the diagnosis has been made (consisting of a chest radiograph, anteroposterior films of all long bones, anteroposterior pelvis and lateral cervical and thoracolumbar spine) [8]. This should be followed by a variety of diagnostic imaging investigations depending on individual symptoms and signs.

BONE

Bone lesions are commonly found in patients with LCH. They may be occult, but usually present with pain or swelling of less than 2 months duration [9]. In the first 6–12 months after diagnosis, additional lesions may develop or there may be progression of the original lesions. Any bone can be involved, but more than 50% of cases occur in the skull, spine, pelvis, ribs and mandible [10]. Of the long bones, the diaphysis of the femur, tibia and humerus are most often involved, with endosteal scalloping, cortical thinning and widening of the medullary cavity (Fig. 1a) [11]. Lesions may be monostotic or polyostotic with solitary lesions prevailing three to one over multiple lesions [9]. The bones of the hands and feet are rarely affected [11].

The radiographic appearance of lesions depends on the phase of the disease and the site of involvement. In the early stage, bony lesions may have an aggressive pattern of osteolysis and appear permeative with a wide zone of transition and a laminated periosteal reaction (Fig. 1b). The differential diagnosis includes osteomyelitis, Ewing’s sarcoma, leukaemia and lymphoma. In later stages, lesions have a more benign appearance with well-defined sclerotic margins, a narrow zone of transition and a mature or absent periosteal reaction [11]. The differential diagnosis includes healing metastases, intraosseous haemangioma, fibrous dysplasia, giant cell tumour, aneurysmal and simple bone cysts, enchondroma and non-ossifying fibroma.

Computed tomography (CT) is useful for determining cortical disruption and evaluating osseous destruction (Fig. 2a). Magnetic resonance imaging (MRI) is superior for depicting the extent of the lesion, evaluating marrow oedema and assessing soft tissue extent. High signal on T2-weighted images is seen within the lesion, marrow, periosteum and adjacent soft tissue with a soft tissue mass being seen in 30% of cases (Fig. 2c). The lesion is usually isointense to muscle on T1-weighted images. It should be noted that because of its sensitivity, MRI may lead to an overestimation of the lesions aggressiveness and should always be viewed in conjunction with plain films [10].

In the skull, the lesions are round and osteolytic with sharp borders and a “punched out” appearance (Fig. 2a and b). In the acute phase, the differential diagnosis includes metastases and leptomeningeal cysts. As the lesions start to heal and develop surrounding sclerosis, the differential includes fibrous dysplasia, epidermoid, meningocoele and chronic osteomyelitis. Involvement of both the outer and inner tables in varying degrees gives the characteristic bevelled edge appearance on tangential views (Fig. 2c). Residual bone within a skull lesion can form a “button” sequestrum. This is commonly demonstrated on both plain radiography and CT. An associated soft tissue mass on CT is usually of similar attenuation to grey matter and enhances after contrast media administration. On MRI the skull lesions are seen as sharply defined masses that return signal intensity comparable with skeletal muscle (Fig. 2d) and enhance markedly after contrast media administration [12]. Involvement of the orbital wall is a common manifestation and often results in proptosis (Fig. 2e).

When the mastoid is involved, features can mimic mastoiditis, and extension to the petrous bone and middle ear can cause destruction of the ossicles and deafness. It has been estimated that between 15 and 61% of patients with LCH have otologic involvement, although this is more common with associated multisystem involvement [13]. Diagnosis is often delayed in these cases because the clinical findings are similar to otomastoiditis. Involvement of cranial nerves can occur with disease involvement of the skull base.

Mandibular involvement gives the typical appearance of “floating teeth” within the lytic lesion and is often associated with soft tissue swelling (Fig. 3).

In the paediatric spine, the thoracic vertebrae are most often involved (54%), followed by lumbar (35%) and cervical vertebrae (11%) [10]. The body of the vertebra is more commonly affected than the posterior elements. Imaging often shows vertebral body collapse with the characteristic “vertebra plana” appearance (Fig. 4). Both CT and MRI may show abnormal soft tissue extending into the spinal canal that enhances with contrast media administration. LCH is the commonest cause of a vertebra plana in a child, however, the differential diagnosis includes metastases, lymphoma, trauma, Gaucher’s disease and haemangioma.

LUNG

Pulmonary involvement usually manifests itself as part of multisystem LCH, having been reported in 42% of cases [14]. It is not, however, associated with a poor outcome or prognosis [15]. Isolated pulmonary involvement is rare [7]. In children under 10 years old disease can regress spontaneously. In older children, pulmonary features are more like those of adults, and progress to a multicystic appearance (Fig. 5) [16].

Symptoms of pulmonary LCH include tachypnoea, dyspnoea and cough. Complications include spontaneous pneumothorax and pleural effusions not attributable to infection [7]. Initial investigation is usually with a chest radiograph, which shows reticular shadowing and in some cases nodules. The best way to assess pulmonary involvement, however, is with high-resolution CT (HRCT). The HRCT findings of LCH are those of reticular or reticulonodular opacities, which progress to form cysts, and ultimately honeycombing [16]. Features predominate in the upper and mid-zones with sparing...
Fig. 1 – Bone involvement in LCH. A 5 year-old boy with arm pain. Anteroposterior view of the humerus (a) showing LCH manifesting as a well-defined osteolytic expansile lesion of the proximal diaphysis with cortical thinning and endosteal scalloping. A 6 year-old girl with forearm pain. Lateral view of the forearm (b) showing an osteolytic, expansile lesion of the proximal radial diaphysis with a wide zone of transition and associated periosteal reaction. A coronal STIR MRI image of the same area (c) showing an intermediate signal intensity lesion with a cortical breech and surrounding soft tissue oedema. A 3 year-old girl with hip pain. Pelvic non-enhanced CT showing (d) an expansile, lytic lesion of the left iliac bone with cortical disruption and an associated soft tissue mass. The lesion was not visible on plain radiographs.
of the costophrenic angles [15]. Diagnosis is usually made on the basis of characteristic clinical and radiographic findings, but if the diagnosis is in doubt then bronchoalveolar lavage or lung biopsy may be necessary [14]. Histology of affected lung shows peribronchiolar inflammatory infiltrates, leading to fibrosis and cysts; lavage fluid shows Langerhans cells [5]. Knowledge of pulmonary involvement is important in the therapeutic management, as agents with known lung toxicity should be avoided [16].

**LYMPH NODES, SKIN AND SOFT TISSUES**

Cutaneous lesions are often the first manifestation of LCH, and consist of scaly erythematous red or brown papules. When the skin is the only organ involved, the patient is usually a male infant less than 1 year of age [16]. Skin lesions may be the only manifestation, but further investigation, including a skeletal...
survey is needed in order to determine that there is not more extensive disease.

Lymph node involvement usually affects the cervical chain and may reach a massive size with resultant local pressure effects such as airway compromise (Fig. 6) [17]. The differential diagnosis includes reactive lymphadenopathy, lymphoma and cervical adenitis.

Isolated soft tissue masses may be found without associated bone disease. Masses have been reported in the cavernous sinus, neck, mediastinum, limbs and face [8]. CT and MRI are useful imaging techniques for defining soft tissue masses [18]. On MRI masses often have signals comparable with muscle and strongly enhance after intravenous contrast media administra-

Fig. 5 – Lung appearances of LCH. A 2 year-old boy with tachypnoea. Unenhanced CT of the chest showing multicystic areas at both bases. Reproduced with permission from Radiology Now. 2001;16:3–17.

Fig. 6 – Soft tissue appearances of LCH. A 5 year-old boy with neck swelling. Coronal STIR MRI of the neck showing a large right-sided cervical lymph node mass. Small left-sided nodes were also present.

THYMUS

The thymus gland is commonly involved in LCH, especially in multisystem disease. Radiologically the gland is enlarged, may contain multiple cysts and has a heterogeneous contrast media enhancement pattern (Fig. 8) [19]. Small areas of

Fig. 7 – Soft tissue appearances of LCH. A 13 year-old boy with proptosis. Coronal unenhanced CT of the orbits (a) showing a soft tissue mass (arrow) superior to the left globe, which is destroying the roof of the orbit. Coronal T1 MRI of the same patient post-contrast (b) demonstrating the enhancing nature of the soft tissue mass (arrow).

(a)

(b)
Punctate calcification have also been described within the gland, which may be visible on CT. This may be useful in differentiating LCH from teratomas, where the calcification is larger and more discrete [16]. The finding of punctate calcification in an enlarged thymus of an infant with skin, bone or lung disease is highly suggestive of LCH [20].

Liver involvement is usually seen as a manifestation of extensive LCH. Typically, it is seen in patients less than 1 year of age with the formerly named Letterer–Siwe disease. Patients usually present with hepatomegaly, abnormal liver enzymes, or jaundice. Jaundice may be due to hepatic infiltration or due to enlarged nodes causing compression at the porta [5]. The pathological pattern ranges from mild cholestasis to more severe periportal infiltration with consequent hepatocellular injury. Bile duct involvement can progress to a sclerosing cholangitis type picture, fibrosis and eventually to liver failure. The liver lesions are predominantly periportal and have been staged histologically into four different phases; proliferative, granulomatous, xanthomatous and fibrous [21].

Early imaging is usually by ultrasound, which shows periportal well-defined hypoechoic lesions in the proliferative, granulomatous and fibrous phases and hyperechoic lesions in the xanthomatous phase, relative to normal liver (Fig. 9a) [21]. There is corresponding low attenuation on CT with enhancement after contrast media administration [21]. MRI shows the periportal distribution of lesions, which are of low signal intensity in the proliferative and granulomatous phases and of high signal intensity in the xanthomatous or fatty phase on T1-weighted images. T2-weighted images are ideal for demonstrating the dilatation and distortion of the intrahepatic bile ducts seen with the sclerosing cholangitis type appearance (Fig. 9b). Lesions have been shown to improve after chemotherapy [22].

Gastrointestinal involvement occurs in fewer than 5% of children [5]. Frequency of involvement is often underestimated because clinical manifestations are not prominent. The most common sign is failure to thrive caused by malabsorption, but vomiting and diarrhoea may also be present. Imaging is rarely performed as the diagnosis is usually made clinically and after endoscopic biopsy. Enteric involvement has been described on barium studies as showing alternating segments of dilated and stenotic small and large bowel. However, as the findings are non-specific, biopsies are often needed for diagnosis [6].

Endocrine glands

Diabetes insipidus is more common in extensive disease. It
is present in 5% of patients at the time of diagnosis, and presents with polydipsia and polyuria [12]. Approximately, 40% of children with multisystem disease develop diabetes insipidus, and in those with associated organ dysfunction mortality is 50% [5]. Other risk factors for the development of diabetes insipidus include bony involvement of the skull and proptosis. Growth retardation resulting from anterior pituitary involvement has been described, but growth hormone deficiency is seen in less than 1% of patients [5]. Growth failure per se in children with LCH is common but is, in most cases is multifactorial. The imaging method of choice to assess the hypothalamus and pituitary stalk is MRI. Features include thickening of the pituitary stalk (>2.5 mm), which is best appreciated in either the coronal or sagittal plane. The thickened stalk enhances avidly after intravenous contrast media (Fig. 10a). In addition there is loss of the bright signal seen in the posterior pituitary on T1-weighted images (Fig. 10b) [12]. The differential diagnosis includes germ cell tumours and granulomatous diseases.

**CENTRAL NERVOUS SYSTEM**

Disease in the central nervous system (excluding diabetes insipidus) is seen in approximately 4% of cases. It is usually found in association with extensive disease and multiple bone lesions, is rarely a feature at diagnosis, and typically presents approximately 5 years after diagnosis [5]. Typical presentations include ataxia, dysarthria, nystagmus and cranial nerve palsies [12]. Several patterns of involvement have been described with all patterns best demonstrated on MRI [23]. These include: (1) symmetrical, poorly defined white matter change involving predominantly the cerebellum and brainstem, which return low signal on T1-weighted images and high signal on T2-weighted images (Fig. 11). (2) Well-defined high-signal changes on T2-weighted images in white and grey matter. (3) Extrarenchymal dural-based masses that are isointense to brain on T1-weighted images, hypointense on T2-weighted images and show contrast enhancement [23]. On biopsy these lesions have been shown to contain Langerhans cells [23].
D’Angio GJ, guarded with a mortality of 10–15% [5]. Spontaneous remissions are common. In extensive disease, prognosis as the clinical course is usually benign and regressing completely. Restricted disease carries a good prognosis of LCH. Prognosis is excellent, with some lesions curable with systemic therapy. In some cases the lymph node mass may have regressed completely, with systemic treatment reserved for those with organ dysfunction. Pain, systemic symptoms or failure to thrive. In restricted disease, single bone lesions tend to resolve spontaneously over a period of months to years. Biopsy of the lesion may initiate healing without the need for curettage. Criteria for additional treatment in single lesions include pain or the threat of unacceptable deformity due to the disease itself or secondary to pathological fractures. In these cases formal curettage, intralesional steroids or low-dose radiation have been used. When only lymph nodes are involved, prognosis is favourable and most patients recover without the need for systemic therapy. In some cases the lymph node mass may have to be surgically removed to alleviate pressure effects. Children with extensive disease may be managed conservatively, with systemic treatment reserved for those with organ dysfunction, pain, systemic symptoms or failure to thrive. In most cases a combination of corticosteroids and chemotherapeutic agents (usually cyclosporin) are used. This regime has been shown to be effective in 50–60% of cases [18]. Unfortunately, malignancy secondary to treatment in the form of lymphoma, acute leukaemia or solid tumours arising in the radiation field have been described in 1–5% of long-term survivors. Treatments involving a combination of chemotherapy and radiotherapy have been reported to carry the greatest risk [5].

This article reviews the clinicoradiological features of LCH in children. Initial imaging is directed at determining extent of disease. Further imaging is performed to identify other organ involvement, the treatment of which will alter prognosis. Awareness of the variety of ways that the disease can manifest itself and the wide spectrum of possible organ involvement is vital for paediatricians and radiologists who encounter this disease.

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