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Arch Dis Child 2009 94: 904-908 originally published online May 19, 2009
doi: 10.1136/adc.2007.125872

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Accepted 24 April 2009
Published Online First 19 May 2009

ABSTRACT

Langerhans cell histiocytosis is a rare disease. Depending on which organs are involved, the disease may prove rapidly fatal, develop a chronic reactivating but therapy-responsive pattern or resolve spontaneously. Understanding of the pathology of the disease is progressing rapidly, and while clinical trials of standard chemotherapy agents continue, it is likely that novel targeted therapy will become feasible in the next decade. Permanent consequences of the disease are more commoner than generally realised.

Langerhans cell histiocytosis (LCH) is characterised by aberrant proliferation of a cell type normally found as an epidermal histiocyte—the Langerhans cell (LC). This cell was first recognised by Paul Langerhans in 1868, when, owing to its dendritic processes, he described it as a neuronal cell but subsequently realised this was not the case.[1] It was not until much later, after the concept of the histiocyte as a tissue macrophage had emerged during the 1940s, that the immune function of the LC in antigen presentation was appreciated.[2] In 1953, having identified abnormal histiocytes in three related syndromes, eosiniphilic granuloma of bone, Letterer–Siwe disease and Schüller–Christian disease, Lichtenstein grouped them together as "Histiocytosis X (HX)—related manifestations of a single nosologic entity."[3] Over the ensuing decade, Basset and Nezelof investigated novel intracellular granules in histiocytes in HX lung and bone lesions which were subsequently recognised as similar to those described in normal skin LC by Birbeck's team.[4] Collaboration between these groups revealed that the "Birbeck" granules found in normal LC and histiocytes from skin, lung and bone in HX lesions were identical, leading to the gradual acceptance of the term LCH to replace HX.[4–6] The intriguing questions of what function Birbeck granules have and why a cell normally found in the epidermis should be involved in a disease with such diverse manifestations as LCH remain largely unanswered. Interestingly, however, recent reports from murine studies have described the finding of LC-like dendritic cell subsets in most non-lymphoid tissues.[7] Further studies may provide similar insights into the behaviour of human LCH cells.

Tissues characteristically involved in LCH are bone, skin, lung, liver, spleen, bone marrow, lymph nodes and the hypothalamic–pituitary region, although involvement of other organs such as the bowel can occur. Depending on organ involvement, staging distinguishes between single system (SS) and multisystem (MS) disease. In the context of MS disease, involvement of certain tissues—bone marrow, liver, spleen and lungs—so-called risk organ positivity (MS^{RO+}), is associated with a worse prognosis.[8] In cases of SS, bony or nodal disease several sites can be involved, which is then described as multifocal (MF) disease.

AETIOLOGY AND EPIDEMIOLOGY

Despite reports of clonality of LCH cells, there is still debate about whether the disease is malignant or reactive as the natural history ranges from rapidly progressive, fatal, multiorgan failure, through chronic reactivating disease to spontaneous remission.[9 10] It remains unclear whether the primary disorder is within the LCH cells or, given that they are found among a background of other activated immune cells, they are victims of a "cytokine storm."[11]

There are reports of LCH occurring in association with other malignancies. The Malignancy Registry of the International Histiocyte Society has identified in excess of 150 cases.[12] In some cases of LCH occurring in children previously treated for T cell acute lymphocytic leukaemia the cells share genetic rearrangements with the original leukaemic clone.[13] In other cases, disease develops after LCH has been treated, suggesting the possibility of therapy-induced second malignancy, such as acute myeloid leukaemia (AML) occurring after treatment with etoposide.[14]

LCH is a rare disease. A recent population-based French study has given an estimated annual incidence of 4.6 per million children (age 0–14 years).[15] Similarly, a British Paediatric Surveillance Unit (BPSU) study in conjunction with Newcastle University (NU) during 2003/5 revealed 94 cases, giving an annual incidence of four per million UK & Republic of Ireland children (age 0–15 years).[16] In this study, single system bony disease accounted for 63 cases, of which 10 had MF involvement. Of the 18 cases of MS disease without risk organ involvement (MS^{RO-}), 14 had bony disease compared with eight with skin involvement. By contrast, all of the seven with MS^{RO+} disease had skin involvement, but only one had bony disease. The median age at diagnosis in the MS^{RO+} group was 0.7 years compared with 3.2 years in the MS^{RO-} children and 6.7 years in the SS cases. There were three deaths reported, all in MS^{RO+} cases.

Twin studies and familial clustering suggest the possibility that a genetic predisposition may exist in some cases, but there is nothing to suggest that a single candidate gene may be involved.[17] There is no convincing evidence implicating specific environmental factors or infectious agents, although several studies have looked at the role of viruses in the aetiology of LCH. Cigarettes have been implicated in a particular form of lung LCH seen predominantly in young adults who smoke.[18]

PRESENTATION

The time interval between onset of symptoms and diagnosis is very variable. In the BPSU/NU study, intervals ranged from a few days to over 3 years for a patient with a single bony lesion (median 10 weeks).[16] The shortest time was for patients with MS^{RO+} disease (median 9, range 3.1 to 26.7 weeks).

The commonest form of LCH is SS unifocal bony disease, previously known as eosinophilic granuloma. The skull vault is a common site in younger children where it presents as a painless lump. On examination, the lesion is fluctuant, and the rim of the bony defect in the skull may be palpable. Lesions of the orbit may present with proptosis and the mastoid with swelling and chronic aural discharge. Disease may involve the mandible, giving rise to "floating" teeth. Vertebral, pelvic and long bone lesions may present with musculoskeletal pain. Rarely, a child may present with cervical pain or torticollis as a result of a lesion in the odontoid peg. Although this is an unusual site, we have included an illustration (fig 1) to emphasise the potential for disaster in this circumstance. The disease may rarely involve the bones of the hands and feet. Some 15% of children with SS bony disease may be found to have more than one site of involvement at the time of initial diagnosis.[16]

Cutaneous LCH typically presents as a widespread eczematous rash. In neonates, the lesions may present as vesicles with a weal and flare-like appearance (fig 2), which might not be recognised as LCH, as it is not the characteristic appearance reported in the literature. Umbilicated papules mimicking molluscum contagiosum and characteristic nail changes may be seen.[19] Skin disease varies from 3% of SS presentations in the UK and Ireland[16] to 10% in Sweden[20] and 23% in France.[15] A spontaneously regressing form can occur congenitally—so-called Hashimoto–Pritzker self-healing reticulohistiocytosis.[21] It is important to carefully follow infants with presumed isolated skin disease, as some may progress to multisystem involvement with time. Other SS presentations include localised lymphadenopathy and diabetes insipidus (DI) due to posterior pituitary involvement.

The majority of MS^{RO-} cases present with bony involvement. Less than half have skin disease, and posterior pituitary, lymph node and other rare site involvement make up the rest.[16] MS^{RO+} disease most commonly presents in infancy with an extensive skin rash and failure to thrive. Skin involvement predominates in MS disease under the age of 1 year, reflecting its strong association with risk organ involvement in this age group.[15] Up to half the cases may have bony disease. Specific risk organ involvement may result in cytopenias, liver dysfunction, hepatosplenomegaly and lung infiltration.

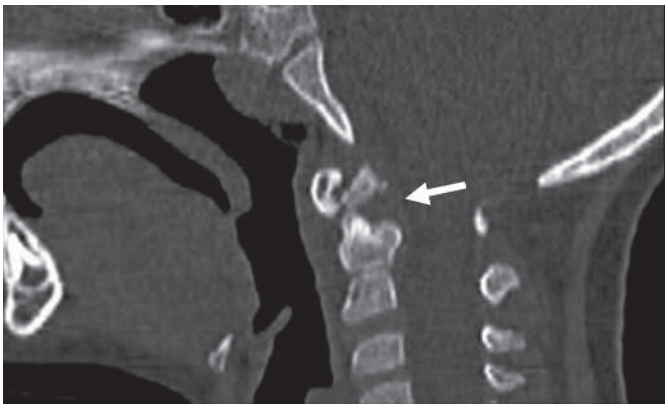

Figure 1 CT reconstruction of lytic lesion eroding odontoid peg.

LCH in adults

Adults can develop the same manifestations of LCH as children. The problem is that they tend to be seen in multiple clinics by subspecialty teams concentrating on whichever system is causing their predominant clinical problem. Efforts are ongoing to increase the awareness of the need for a multidisciplinary approach, including opening adult protocols and holding adult-orientated clinical meetings.[22 23] There is a form of isolated pulmonary involvement that occurs almost exclusively in young adults, in particular smokers. It is not clear at this time what treatment should be used to salvage cases, where, despite smoking cessation, the disease progresses to end-stage lung failure requiring transplantation.[24]

DIAGNOSIS AND STAGING

A detailed history is important to ascertain past or current symptoms indicating involvement of a particular organ system. Areas on which to focus include odd rashes, atypical musculoskeletal pain, aural discharge and excessive thirst. Investigations are organ-system-based with the intention of establishing disease extent and obtaining diagnostic biopsy material. The diagnosis of LCH is confirmed by the characteristic morphology and the presence of CD1a or CD207 (Langerin) positive histiocytic cells. Nowadays, electron-microscopic confirmation of the presence of Birbeck granules is rarely used. Depending on the degree of involvement of each system, a prognostic score has been devised, which may subsequently be used to monitor response and modify therapy.[25]

Bone

Plain *x* ray of the majority of bone lesions will demonstrate the characteristic punched out, radiolucent appearance. However, lesions in the skull base may not be obvious, and vertebral involvement may appear as a crush fracture. Rarely bone lesions may present with a more atypical "tumour-like" appearance. Having found a lesion, CT or MR imaging may help ascertain the extent and character of the lesion prior to biopsy. If the lesion is in a site which is difficult to biopsy, further screening *x* rays may be performed to find a more amenable site. Once the diagnosis is established, the rest of the skeleton should be imaged for other lesions. This is traditionally done by performing an age-appropriate skeletal survey rather than a less sensitive isotope bone scan.[26] Recently, whole-body PET CT and MRI have been proposed as more sensitive modalities.[27 28]

Skin

The extent of skin involvement should be documented, and the mouth and perineum carefully inspected. The axillae, groins and skin creases may be severely affected, and ulcerated lesions may occur. A punch biopsy should be obtained from an area of clearly active disease.

Lymph nodes

Lymph nodes draining involved bone or skin may be affected, but occasionally LCH may occur in isolated nodes. This usually comes to light after a suspicious node has been biopsied to exclude a diagnosis of malignancy. In the context of MS disease, it is not necessary to confirm nodal involvement, unless there are no other areas suitable for biopsy.

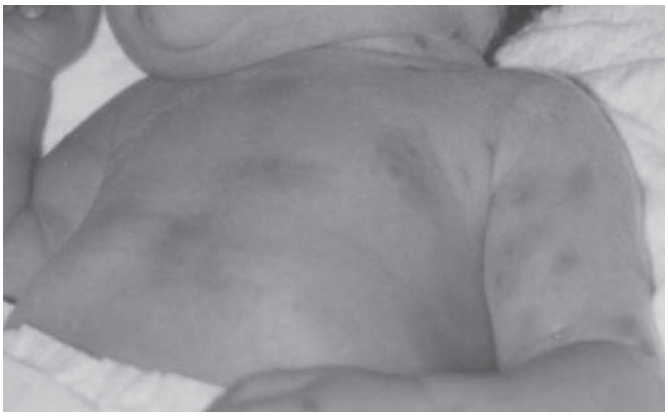

Figure 2 Neonatal cutaneous Langerhans cell histiocytosis showing vesicles with surrounding inflammatory weals.

Hypothalamic–pituitary region

In the absence of symptoms, a normally concentrated early morning urine is adequate to exclude DI in a child with LCH; otherwise a formal water deprivation test is necessary. Occasionally, a child presents with isolated DI, and LCH is included in the differential diagnosis. If screening tests for other manifestations of LCH and germ-cell tumour markers are negative, it may be necessary to make a presumptive diagnosis of LCH rather than attempt a pituitary biopsy. In these circumstances, MRI features compatible with pituitary LCH should be seen (absence of the posterior bright spot and thickening of the stalk) and regular follow-up examinations performed to confirm a non-progressive lesion. Rarely, LCH may present as a hypothalamic or other intracranial mass, which should normally be confirmed by stereotactic biopsy.

Gastrointestinal tract

While bowel disturbances are common in children with widespread LCH, pathological histiocytic infiltration of bowel is rare.[29] Involvement should only be diagnosed on the basis of positive endoscopic biopsies.

Bone marrow

Cytopenias suggesting bone marrow involvement in LCH are an ominous finding associated with a poor prognosis but are not necessarily always due to direct marrow infiltration by LCH.[30] CD1a positive cells may be found in relatively low numbers in bone marrow, and it is possible that any cytopenia may be due to concurrent macrophage activation or secondary haemophagocytosis.[31] Consequently, for staging purposes, haematopoietic involvement is defined according to specified levels of cytopenia.[32]

Lungs

As it is often asymptomatic, lung involvement should be considered in all cases of MS disease. Pulmonary function tests may be abnormal, and interstitial infiltrates may be visible on plain *x* ray in the early stages. With progression, reticulonodular changes appear followed by cyst formation giving the classical honeycomb lung appearance. If there are any suspicious changes, these should be investigated further with high-resolution CT. Bronchoalveolar lavage might not provide diagnostic material unless accompanied by transbronchial biopsy but may be useful in excluding opportunistic infection in severely ill patients.[33] Lung biopsy is indicated when the presence or absence of pulmonary involvement will influence treatment, for example in the rare situation where lung is the only potential risk organ. Even in such cases, it is not entirely clear that lung involvement without another risk organ involved has a poor prognosis.[34 35] All patients with suspected or proven LCH should have a chest *x* ray prior to general anaesthesia to exclude any cystic changes which may predispose to pneumothorax occurring during assisted ventilation.[36]

Liver and spleen

For staging purposes, involvement is diagnosed in the presence of hepatosplenomegaly or abnormal liver function tests.[32] In some cases, ultrasound, cholangiography and liver biopsy may be indicated to distinguish between sclerosing cholangitis due to bile-duct infiltration by LCH cells and the indirect effects of an accompanying macrophage activation syndrome leading to hypoalbuminaemia and hepatomegaly.[37]

TREATMENT

Children with SS or MS^{RO-} disease do not die from LCH. In these children, it does not behave as a malignancy, and the goal of treatment is to preserve normal activity and prevent long-term sequelae.

Single system

Treatment of isolated skin disease depends on the sites and extent of involvement, which dictate whether local therapy may be tried. Sometimes minimal therapy with topical emollients may be all that is needed. In more severe cases, topical mustine is very effective and can safely be used in extensive and severe skin disease.[38] There are anecdotal reports of the effectiveness of other topical agents including steroids, ciclosporin and tacrolimus. Oral steroids alone are generally disappointing in this situation, and additional intravenous vinblastine may be necessary if topical therapy fails or is impractical.

A single bony lesion may heal spontaneously after biopsy or respond to recurettage and injection of methylprednisolone acetate. In some children, indometacin is very effective in promoting regression of disease.[39] Bony lesions are generally exquisitely sensitive to oral prednisolone, but tend to recur on withdrawal of treatment. This can result in a "reactivation" pattern which may lead to prolonged use of high-dose steroids, especially in MF disease. There are several other reasons why chronic reactivation is undesirable. Each episode of reactivation may cause short-term functional problems and in the long term contribute to permanent deformity in a facial or long bone. Alternatively, the lesion may be in a critical anatomical site such as the odontoid peg (fig 1) where severe consequences may occur if rapid and complete healing is not ensured. In these situations, it is better to commit early to treatment with vinblastine and prednisolone, and continue with relatively low-dose maintenance for up to 12 months.

A lesion in a base of skull or facial bone with significant intracranial extension or proptosis is designated "special site" disease. Although there may be only a single lesion amenable to local therapy, it has been advocated that if special site lesions are not adequately treated with prolonged systemic therapy, the chances of developing DI are increased.[40] Pamidronate has been proposed for refractory cases and appears to be particularly helpful when pain is an issue.[41]

Multisystem

From its foundation in 1985, the Histiocyte Society (HS) has been responsible for clarifying the diagnostic and staging criteria

for LCH and developing a common language for treatment evaluation. Three randomised therapeutic trials for MS disease have been consecutively administered by the HS, initially using data from Italian and German, Austrian and Dutch trials opened during the 1980s.[42 43]

LCH I (1991–5) confirmed MS^{RO+} disease and a poor response to the first 6 weeks of treatment were associated with a bad prognosis. Therapy randomisation failed to show any advantage of etoposide over vinblastine.[8] Subsequently, LCH II (1996–2000) did not demonstrate any benefit of combining etoposide and vinblastine compared with vinblastine alone. The prognostic significance of a poor early response in MS^{RO+} patients was confirmed, and it established that age <2 years was not an independent predictor of poor outcome.[44] Although not reported at the time, a recently published historical comparison of LCH I and LCH II has suggested that children who received both drugs may have fared better.[45] LCH III (2001–8), investigated adding methotrexate to vinblastine for MS^{RO+} disease, and whether 6 months is as efficacious as 12 months' therapy in terms of preventing reactivations in MS^{RO-} children. The study is now closed, and a final analysis is under way. It will be interesting to see if this trial shows results similar to the DAL-HX study with lower reactivation rates and incidence of diabetes insipidus in those treated for longer periods.[43]

Refractory disease

Although the majority of patients with MS $^{RO+ve}$ disease respond to the therapy as above, some may progress quite rapidly and require a change to more aggressive treatment. Close monitoring during the first few weeks of therapy helps to identify these poor responders early. To salvage these patients who progress on protocol and have a potential mortality of 66%, strategies have been designed using high-dose AML type therapy with a pilot study showing good results with or without allogeneic stem cell transplantation.[30] This therapy has been further developed via international HS protocols LCH-S-98 and LCH-S-2005, but unfortunately, owing to the extremely small number of eligible children, and the difficulty in obtaining regulatory approval for therapeutic studies in orphan diseases, patient accrual has been disappointing. A sustained effort needs to be made by centres to open such studies and recruit more patients. More recently, low-intensity conditioning transplants have been successfully performed, an important advance in the treatment of children who are often desperately unwell.[46]

PERMANENT CONSEQUENCES

Permanent consequences resulting from destruction and scarring of tissue are common in LCH. Damage may have occurred by the time LCH is diagnosed or may not manifest until years later. Owing to wide differences in ascertainment methodology and patient populations studied, there is considerable variation in the apparent prevalence of sequelae, but residual abnormalities have been reported in 20–70% of survivors.[12] As LCH can result in permanent disability and significantly affect survivors' health-related quality of life, it is important to develop uniform criteria to define late effects and facilitate selection of patients who need specific, standardised investigation.[47]

Skeletal

The skeleton is the most common site of involvement of LCH, and sequelae have been reported in 3–42%.[12] As children grow, bones may remodel to an extent, but damage to a growing skeleton can cause disability. Chronic reactivations or treatments such as radiation or surgery may result in permanent damage. LCH of the spine can result in vertebra plana or scoliosis. Limb deformities are relatively infrequent but can occasionally lead to significant morbidity. Abnormalities of the facial bones may persist, and residual asymmetrical proptosis is common. Facial asymmetry may become more obvious as the child grows and may require reconstructive surgery. Orthodontic surgery may be needed for loss of teeth or abnormal growth of the jaw.

Aural

Mastoid lesions can result in permanent damage and hearing loss. Although conductive deafness is the most common problem, permanent sensorineural hearing loss may result from damage to the inner ear and bony labyrinth.[48] Involvement of the vestibular region is rare but presents with loss of balance in addition to hearing loss. Children with ear involvement should be followed up with regular audiometry and assessment, as early diagnosis of hearing loss and the use of hearing aids can significantly improve outcome.

Cutaneous

Depending on the severity and extent of involvement, scarring can result in up to 30% of children who have had skin disease, whether treated topically or systemically.[38]

Endocrine

LCH has a predilection for involving the posterior pituitary gland with up to 40% of MS cases being affected.[49] DI may occur before or several years after the diagnosis of LCH. As discussed earlier, involvement of the craniofacial bones, especially the orbit and base of the skull, has been associated with an increased risk of developing irreversible DI. Growth-hormone deficiency is the next most common endocrine abnormality, occurring in around 20% of MS cases, with other hormone deficiencies such as secondary hypothyroidism, gonadotrophin and corticotrophin deficiency occurring less frequently.[49] Pituitary irradiation, if used in patients with DI, does not ameliorate the condition, may cause anterior pituitary failure and should therefore be avoided. All children with DI, short stature, poor growth or delayed puberty should have anterior pituitary stimulation tests. Other factors which may contribute to poor growth include bony destruction, chronic steroid therapy and the effects of chronic disease.

Neurological

There is increasing awareness of the long-term sequelae of LCH affecting the brain, including neuropsychological problems (intellectual loss, memory impairment, learning deficit, poor school performance, emotional disturbance and significant cognitive impairment) and cerebellar degeneration in 12–20%.[12] Characteristically, this may manifest many years after diagnosis with bilateral cerebellar signal changes on MRI. The pathophysiology and natural history of neurological disease in LCH remain unclear, and abnormalities may plateau or progress resulting in severe disability. Although there is no proven therapy, it is recommended that patients who have had MS disease, craniofacial bone lesions or DI are carefully followed up with neuropsychometric studies, with a low threshold for performing cerebral MRI studies, to facilitate early supportive intervention.

Pulmonary

Although lung involvement has been reported to be present in up to 50% of children with MS disease at diagnosis, permanent lung damage is uncommon, with reports ranging between 1 and 8%.[12] This is probably due to the ability of the young child's lungs to repair and replace damaged alveoli. Irreversible lung damage predominantly occurs in young adult smokers, who may develop endstage disease necessitating lung transplantation. All patients with LCH should be strongly recommended to refrain from smoking.

Hepatic

Children requiring a liver transplant for acute sclerosing cholangitis at diagnosis may survive without reactivation in the graft, and those who respond to chemotherapy do not necessarily go on to develop chronic liver disease and end-stage biliary cirrhosis.[50]

CONCLUSIONS

More than half a century on from recognition of the common pathology underlying the "Histiocytosis X syndromes," we are tantalisingly close to discovering the mechanisms responsible for this anomalous histiocytic behaviour. Once the errant processes are understood, targeted pharmacological and immunological interventions will hopefully follow. In the mean time, progress can only be made by continuing evaluation of known drugs in alternative schedules in the context of international, randomised clinical trials.

Competing interests: None.

Patient consent: Obtained from the parents.

Provenance and peer review: Commissioned; externally peer reviewed.

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