# Adults with LCH – orphans with an orphan disease

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*Clin Med* 2006;6:404–8

This conference was held at the Royal College of Physicians on 10–11 November 2005 and was organised in association with the Royal College of Paediatrics and Child Health and supported by the Leukaemia Research Fund.

## Introduction

In the 1950s, Dr Sidney Farber (a clinician) and Dr Louis Lichtenstein (a pathologist) were the first to appreciate that three clinical entities – eosinophilic granuloma, Hand–Schüller–Christian disease and Letterer–Siwe disease – were variants of a single pathological process. Lichtenstein noted close histological similarity between them and coined the all-embracing term 'Histiocytosis X'. The term 'Langerhans cell histiocytosis' (LCH) was adopted by the Histiocyte Society in 1989, after it had been shown that Langerhans-like cells are essential to confirm the diagnosis.

The majority of early clinical and pathological observations were made from childhood cases, yet LCH is also commonly diagnosed during adult life.[1] Progress in treatment for children with LCH has rapidly moved forward with multi-national randomised trials and increasing awareness of LCH-related problems in later life.[2] Coordinated care for affected adults, however, has lagged behind causing adults with LCH to be described as 'orphans with an orphan disease'.

The conference's aim was to highlight and address current deficiencies in the hope and expectation that:

- LCH in adults will be 'de-orphanised'
- more adult investigators will become interested in studying this scientifically intriguing and clinically challenging condition.

## The natural history and nature of LCH

The natural history of LCH is variable and may follow a similar pattern in children and adults. When only one organ system (usually bone or skin in children, or skin, bone or lung in adults) is involved, the disease often regresses spontaneously or with little treatment. On the other hand, multi-system disease almost always progresses, its course fluctuating in severity and affecting various organs over several years. This form of the disease often causes scarring that can seriously impair function and quality of life.[1] These sequelae cause considerable handicap in up to 50% of children with LCH. The proportion of sequelae seen in adult LCH are not yet properly documented, but the pattern of complications seems to be similar. In 10–20% of child cases, usually infants, LCH is fatal due to irreversible lung and liver damage or the consequences of severe pancytopenia, which often accompanies severe multi-system disease. Adult LCH can also be fatal but prognostic factors are not yet clear. Clonality was identified in lesional LCH cells but its significance is still hotly debated. Some feel that this finding proves that LCH is either a form of cancer or a pre-cancerous condition whilst others prefer to believe that monoclonality is a secondary manifestation of a reactive condition. Evidence is emerging that LCH may be a pre-malignant condition similar to monosomy 7, whilst lung-only LCH is more likely to be reactive in origin.

## Langerhans' cells and LCH cells: the pathology of LCH

Normal Langerhans cells are bone marrow derived dendritic cells that are found only in the squamous epithelium of the skin, upper aerodigestive and female genital tracts where they play a crucial role in antigen processing. Upon activation they migrate to secondary lymphoid tissues where they mature into functional antigen-presenting cells (APCs). 'LCH cells' are also activated but have a poorly characterised 'maturation block' preventing differentiation into fully functional APCs.

A complex 'cytokine storm' caused by the interaction between the various cell types in the LCH lesion leads to tissue damage. Local factors presumably determine the type of damage that occurs in tissues targeted by LCH.[2] These secondary causes of organ damage are not usually reversible. Although organ transplantation is feasible in some cases of end-stage liver or lung disease, prevention or reversal of these processes is clearly the more desirable option.

## Pathology including immunophenotype

LCH cells are non-phagocytic histiocytes with abundant pale cytoplasm and elongated nuclei with central grooving. They are characterised by the presence of cytoplasmic Birbeck granules – rod-shaped or

tennis-racket shaped organelles derived from infolded surface membrane. LCH cells express CD1a, S100 protein and CD207 (langerin, a protein associated with Birbeck granule formation). LCH lesions comprise a mixture of inflammatory cells and LCH cells.

## Epidemiology and family studies

There have been no population-based studies of LCH in adults and most publications involve just a few cases, mainly from single specialty clinics. The incidence in children ranges from 2.2–5.4 per million per year aged 0–15 years with the highest incidence in children under two years. Males are affected more often than females. Reports suggest that there are at least as many adults as children with LCH.[3] The peak age at presentation in adults is between 20–35 years (range 18–90 years) with multi-system disease reported in 30–70% of cases. Some of the clinical features differ between adults and children (Fig 1). Case control studies exploring risk factors for LCH in children have identified different associations, for example with thyroid disease in their families. Smoking is the only known risk factor for LCH in adults; the majority of patients with pulmonary LCH are smokers.[4] A slight excess of breast cancer in adult females with LCH was noted in one study. LCH is usually not considered to be a familial disease. However around 1% of children with LCH have another case in their family and a high concordance rate has been found in monozygotic twins with multi-system LCH compared to dizygotic twins.[6] In siblings with LCH, age at onset is variable and patterns of disease may be different.

## Clinical presentation

LCH in adults presents in many different ways; the sites most commonly affected are skin, lungs and bone. Lung disease is especially prominent in adults, so will be described first and in detail.

## Lung disease

Lung involvement in adults occurs mainly in tobacco or marijuana smokers aged less than 40 years; it is often the only manifestation of LCH.[7] Cough and/or exertional dyspnoea are present in 75% of these patients, with systemic symptoms (fever, weight loss) in around 33%. Pneumothorax occurs in 25% and often recurs. Airflow obstruction is the most frequent ventilatory defect, with lung restriction in advanced fibrotic disease. Pulmonary LCH is characterised by destructive granulomas containing large numbers of LCH cells grouped around distal bronchioles.

High resolution computed tomography (HRCT) is very

## Conference programme

**Aims of meeting: Writing group and publication**
Dr Jon Pritchard, Royal Hospital for Sick Children, Edinburgh
Dr Vasanta Nanduri, Watford Hospital and Hospital for Sick Children, London *(co-organisers)*

**WHAT WE KNOW ABOUT THE PATHOBIOLOGY OF LCH (supported by Leukaemia Research Fund)**

**Normal Langerhans cells – differentiation and function**
Dr Pieter Leenen, Erasmus MC, Rotterdam, The Netherlands

**'LCH cells' and LCH** Professor Maarten Egeler, University Medical Centre, Leiden, The Netherlands

**The pathology of LCH and cell plasticity** Dr Andrew Norton, St Bartholomew's Hospital

**Epidemiology** Mrs Jane Salotti, University of Newcastle

**Genetic and family studies in LCH** Professor Maurizio Arico, Children's Hospital, Palermo, Italy

**CHILDREN AND ADULTS WITH LCH – COMPARE AND CONTRAST**

**Treatment contrasts: two viewpoints**

**Adults and children: the same....?** Professor Robert Arceci, John Hopkins University, Baltimore, USA

**or different....?** Dr Tony Chu, Hammersmith Hospital, London

**FOCUSSING ON ADULTS**

**Pathology of lung disease** Professor Andrew Nicholson, Royal Brompton Hospital, London

**The lungs: Clinical presentation and medical management**
Professor Athol Wells, Royal Brompton and Harefield NHS Trust

**The role of lung transplantation** Professor Paul Corris, University of Newcastle upon Tyne

**The bones** Mr Daniel Porter, Royal Infirmary and Royal Hospital for Sick Children, Edinburgh

**The skin and the brain** Dr Tony Chu

**The hypothalamo-pituitary axis in adult patients with LCH**
Dr Gregory Kaltsas, Laiko University Hospital, Athens, Greece

**The role of radiotherapy** Dr Fiona Cowie, Beatson Oncology Centre, Glasgow

**Two patients' views: What do we need from the professionals?** Mrs Sally Bahra, Leeds and Dr Claire Sargent, London

**Debate: What needs to be done?**
**Panel:** Professor Robert Arceci; Dr Fiona Cowie; Professor Sheila Weitzman, The Hospital for Sick Children, Toronto, Canada; Professor Athol Wells

**SETTING THE AGENDA FOR ADULTS**

**Diagnostic criteria** Dr Andrew Norton

**How should we investigate these patients?** Dr Vasanta Nanduri and Dr Sujal Desai, King's College Hospital, London

**How many subgroups are there? What treatments do we favour?** Professor Robert Arceci and Professor Athol Wells

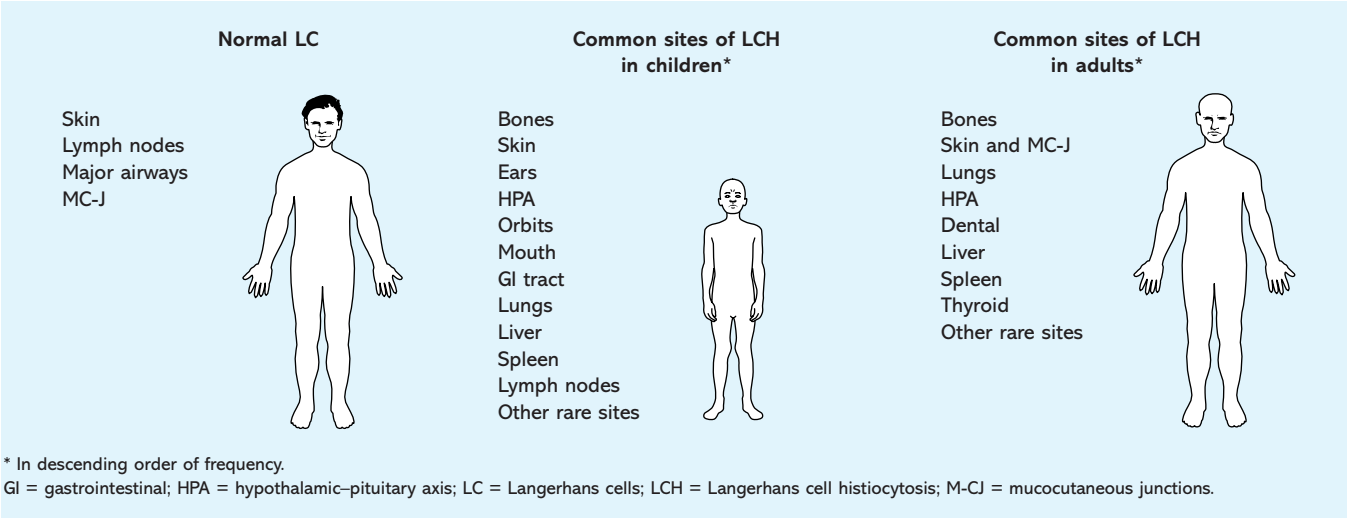


**Fig 1. Distribution of normal Langerhans cells (LC) and of 'LCH cells' in children and adults with Langerhans cell histiocytosis (LCH).**

useful for diagnosis, typically showing non-cavitating and cavitating nodules in early active disease and, as lung damage progresses, cystic lesions (Figs 2, 3). Bronchoalveolar lavage (BAL) is often non-diagnostic. In most cases a confident diagnosis can be made on the basis of the clinical presentation and characteristic lung HRCT findings. Some patients with atypical HRCT features require surgical lung biopsy to confirm the diagnosis of pulmonary LCH. The major differential diagnoses are emphysema (which can occasionally be surprisingly well circumscribed on HRCT, simulating the cystic changes of LCH) and lymphangioleiomyomatosis.

Prognosis is favourable in most patients though in a few the disease progresses to respiratory insufficiency, with prominent pulmonary vascular involvement. Smoking cessation is imperative; no other intervention consistently brings about regression of symptoms. LCH is a rare but well-recognised indication for lung transplantation.

## Other disease sites

As LCH in adults can present in many different ways and in a variety of sites, diagnosis can be extremely difficult as almost any combination of organ involvement can be encountered. Cutaneous disease is common and can be particularly troublesome in intertriginous areas such as the vulva,[8] perineum or axillae (Fig 4). LCH skin disease can mimic the presentation of other skin conditions, although nail involvement is rare. Solitary or multiple lytic lesions in bone are classical findings in LCH and severe bone pain may be present without any CT or MRI scan abnormality. LCH should also be considered where there is oral disease, particularly with gum involvement or bone loss in the maxilla or mandible leading to 'floating teeth', lymphadenopathy or unusual symptoms and signs involving the hypothalamic–pituitary axis (classically diabetes insipidus), or the central nervous system, liver or thyroid.

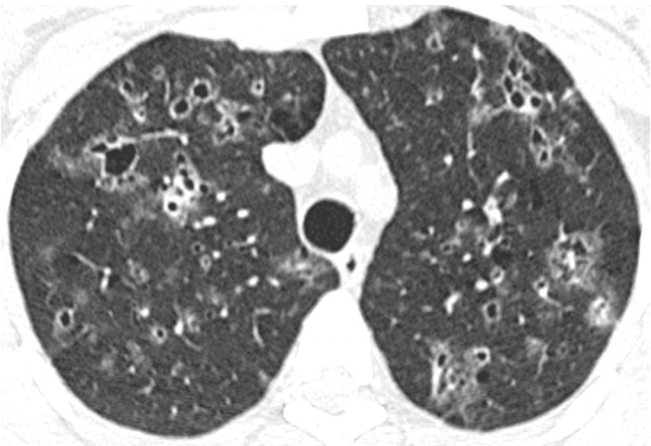

**Fig 2. Typical CT appearance of active pulmonary Langerhans cell histiocytosis in a smoker.** There are profuse well-formed nodules, many of which have cavitated.

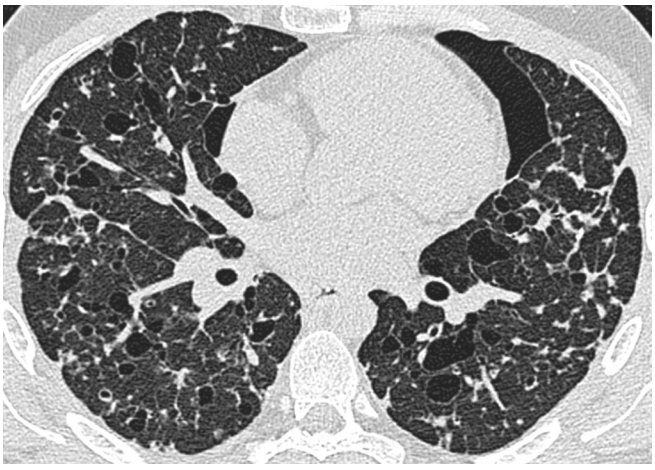

**Fig 3. CT appearance of advanced Langerhans cell histiocytosis in a former heavy smoker.** There are multiple well-formed cysts, varying in size and shape.

## Treatment for children and adults – the same or different?

Children with single system disease and those with only skin and bone involvement are classified as having a 'low risk' of treatment failure and are treated with short courses of vinblastine and corticosteroids; patients with more extensive multi-system disease are at higher risk of relapse and are treated more intensively.

A chronic picture of relapsing and remitting disease is common in adults, who may require longer-term treatment to maintain remission. A major problem is that adults do not seem to respond as well to treatment for LCH. Most children tolerate and respond well to corticosteroids and vinblastine, but adults seem to experience more toxicity, especially peripheral neuropathy and abdominal pain from vinblastine. The Histiocyte Society's treatment protocol for adults (LCH-A-1) opened in April 2004, using a combination of vinblastine and prednisolone induction followed by six month maintenance treatment with mercaptopurine and methotrexate. Risk factors for relapse in adults, unknown at present, should emerge from this and future trials.

Other drugs including cladribine (the most promising),[9,10] azathioprine and methotrexate have been used in a few centres. The cladribine/cytosine arabinoside (araC) combination has been strikingly effective in very sick children whose LCH has been resistant to standard therapy but has not yet been used in adults. Etoposide, once popular and effective in children, is associated with secondary leukaemias, but has been successfully used in some adult centres. In most patients treated with etoposide, symptoms resolved but then recur in many cases. Addition of six mercaptopurine and methotrexate may prolong remissions but clinical trials are needed to confirm this point. Single bone lesions are often successfully treated with curettage, or intra-lesional steroid injection. Bisphosphonates are also used to slow further bone resorption. Radiotherapy is occasionally used to treat inaccessible or resistant LCH lesions, particularly localised areas of bone or soft tissue disease, but results are variable.

Adults with LCH may require treatment for depression reflecting the chronicity of the condition and also the severity of persistent bone pain, often requiring narcotic analgesics, which many patients with skeletal involvement endure.

In children long-term sequelae are more often disease-related than treatment-related and can affect almost any of the organ systems involved during the 'active stage' of LCH. Bone abnormalities, skin scarring, draining sinuses from affected lymph nodes, hypothalamo–pituitary abnormalities, restrictive lung disease, sclerosing cholangitis and neuropsychological problems may persist. Children growing up to be adults with chronic organ damage need to be considered when developing services for adults with LCH, even though they no longer have 'active' disease.

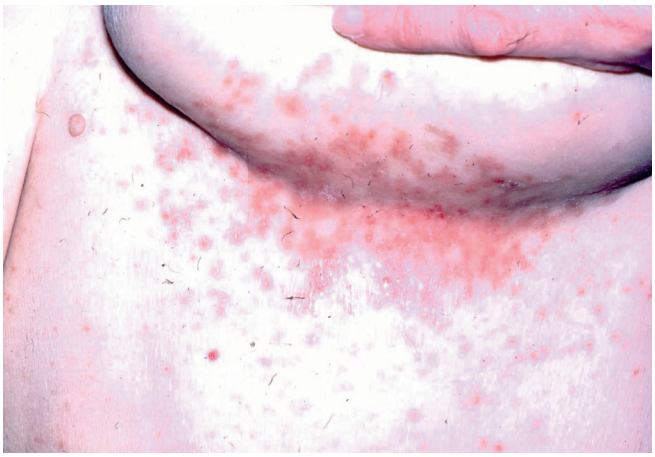

**Fig 4. Perianal skin involvement in a 65-year-old man.**

## What do the patients and their families need?

It is painfully clear that adult patients' needs are, at present, inadequately addressed. There is little awareness of LCH among the medical profession worldwide and hardly any UK general physicians have a specialist interest in the condition. LCH in adults may present to many different disciplines, and guidelines for investigation and management are only just being introduced. Diagnosis is therefore often delayed, care is poorly coordinated and inappropriate treatment may be given. All of these factors contribute to poor overall care and, perhaps, to the severity of some of the sequelae.

Who is in the best position to supervise adult patients' care? Children are usually managed by paediatric oncologists, but there is no such convention for adults. Clinical and medical oncologists are rarely comfortable when confronted by an adult with LCH, especially now that few patients are treated with radiotherapy. There is therefore an urgent need to develop accessible sub-specialty clinics, not only for patients diagnosed as adults but also for adolescents who require longterm follow-up as they outgrow paediatric services and move into adult life.

Other forms of 'networking', greatly accelerated by the internet and email, are now a reality and may provide the opportunity for adult sufferers to access the 'best opinions' for treatment. Telemedicine provides a splendid opportunity to develop an international network for advice. Another way to approach the problem would be to ensure that there is at least one specialist clinic within the UK for these patients. At the Conference there was a strongly expressed view that adults with LCH, except perhaps those with a solitary eosinophilic granuloma in bone – which is managed relatively easily – would be willing to travel to a specialist centre for an expert opinion. In the authors' experience, nearly all patients are reassured by visits like these, even if long journeys are involved. A greater emphasis should also be placed on the need for psychological support and on the education of patients and their families emphasising the need for more detailed explanatory literature.[11]

## Acknowledgements

The organisers (Jon Pritchard and Vasanta Nanduri) are indebted to: the Leukaemia Research Fund, Novo Nordisk,

Ferring Pharmaceuticals, Gilead Ltd and Allen & Hanburys for their generous sponsorship of this meeting; the speakers and delegates for their lively and excellent contributions, and Neil Jenkinson and Anne McSweeney for co-organising the workshop. All the authors thank Professor Dame Carol Black (PRCP) and Professor Sir Alan Craft (PRCPCH) for their encouragement in holding the workshop and for their end pieces to this article; Dr Tony Chu, Dr Fiona Cowie and Professor David Wray for providing illustrations and Rebecca Shearer for indefatigable and excellent secretarial support.

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## Comments from the Presidents of RCP and RCPCH

I was easily drawn to support this conference on Langerhans cell histiocytosis. Having spent nearly thirty years building a service and national network for patients with another uncommon disease – systemic sclerosis – I am familiar with their essential needs and the common problems they face.

What do they look for? They want well-informed highly motivated caring health professionals providing a service that meets their personal medical, psychological and social needs. They want continuity of care by known and trusted professionals who know them and their condition and the problems they must deal with. They are content with shared care, sometimes reinforced by email or telephone access. What clearly matters is having confidence in the quality of advice and the knowledge that an expert is in reach when the need arises.

It now better recognised that young people whose illness manifests in childhood, and their families, have special needs as they enter adolescence and adulthood. There has been neglect of service arrangements required to support the transition from paediatric to adult care. Fortunately there is a will to put this right, though there are considerable barriers to be overcome.

A major barrier is that of funding. Naturally many uncommon diseases require unusual and costly treatments, including the use of so-called orphan drugs. This presents a growing challenge, not least because although each individual disorder may be uncommon there are, in fact, many of them. According to the Wall Street Journal 'the cost of specialty pharmaceuticals – biotechnology drugs and other expensive medicines prescribed by medical specialists is growing twice as fast as [that of] traditional prescription drugs'. This mirrors advances in therapeutics that will continue. It also further highlights ways in which we determine the priorities given to different needs in the face of competing pressures upon limited resources.

Rare diseases do not command the priority given to common disorders. But we do not need reminding that the rarity of a disease is not the first concern of people who are afflicted or threatened by it.

PROFESSOR DAME CAROL BLACK
*Royal College of Physicians*

The Royal College of Physicians and the Royal College of Paediatrics and Child Health were pleased to be able to co-host this important conference. It brought together participants across two interfaces. Firstly, the patients themselves joined clinicians and scientists. Secondly, both children and adults, and those who care for them, were represented. It was clear that all parties benefited from the experience of others and undoubtedly new research collaboration will be developed and innovative ideas pursued.

One of the clear conclusions was the need to better understand the interface between children and adults. We now know that the first presentation of LCH occurs in adult life. A mechanism needs to be found to ensure that appropriate expertise is available in 'adult' services as it is inappropriate for older patients to be attending children's clinics. This, of course, is an issue which is not unique to patients with LCH. The art of 'transitional' care from paediatric to adult services was the subject of another recent joint College symposium.

The organisers of this conference are to be congratulated on their vision in providing a timely forum for a debate on the science and management of an orphan disease. This could be a useful model for other orphan diseases which span the age spectrum.

PROFESSOR SIR ALAN CRAFT
*Royal College of Paediatrics and Child Health*