Long Term Sequelae of Multisystem Langerhans' Cell Histiocytosis

Vasanta Rao Nanduri

MB BS

MRCPCH

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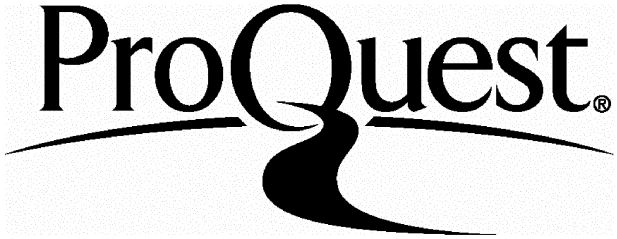
Departments of Haematology/ Oncology and Endocrinology
Institute of Child Health
Great Ormond Street Hospital for Children NHS Trust



Abstract

Langerhans' cell histiocytosis (LCH), a chronic granulomatous disorder, can involve one or more organs/ tissues including bone, skin, lungs, liver, spleen, bone marrow, pituitary gland and brain. Long term sequelae involving these organs have been reported, but their true prevalence is unknown.

In order to assess long term outcome in survivors of multisystem LCH, we performed a cross-sectional study of 40 patients, all of whom were more than 5 years from treatment. Most of the patients had had involvement of bone and /or skin, with other organs being affected less often. They had received a wide range of treatments, including surgery, steroids, radiotherapy and chemotherapy.

The study involved clinical examination, MRI scan of brain, endocrine function tests, neuropsychometry, respiratory function tests and audiometry. Most patients had one or more long term sequelae. Half of the patients had endocrine abnormalities, ranging from isolated diabetes insipidus to panhypopituitarism. Brain involvement, including cerebellar involvement, was the most worrying problem, occurring in 10 patients, with severe abnormalities in seven.

New findings include the presence of significant learning deficit in 20% of patients, psychological and behavioural abnormalities in 11 patients (27.5%), and an acquired abnormality of the skull base, basilar invagination, in 8 patients (20%).

A specific morbidity score was devised and provided an objective measure of outcome. Using this scale only 10 patients (25%) had no sequelae. Eleven (27.5%) had mild impairment which required no specific treatment, 9 (22.5%) had moderate disability, including diabetes insipidus, growth hormone insufficiency and moderate hearing loss, while 10 (25%) had severe disabilities such as panhypopituitarism, learning difficulty, motor deficit and psychological abnormalities resulting in significant handicap and inability to lead an independent adult life. We assessed the Health-Related Quality of Life and found that this correlated with the Morbidity score. Both these measures can easily be applied to any patient with LCH and can be incorporated into long term follow up studies.

In conclusion, long term sequelae are more common in survivors of multisystem LCH than previously recognised and cause significant long term morbidity. An important implication of the work presented in this thesis is that carefully planned regular long-term follow up is essential for all patients 'cured' of LCH to ensure that sequelae are recognised early and the appropriate interventions made to improve the patients' "quality of life".

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Chapter 1. Background

Introduction

The term 'Histiocytosis X' was coined by Lichtenstein in order to unify a rare group of granulomatous disorders previously known by several different names, including lipoid granulomatosis, Hand-Schüller-Christian disease, Abt-Letterer-Siwe disease and eosinophilic granuloma (Lichtenstein 1953). At the inaugural meeting of the Histiocyte Society in 1985, it was recommended that the term Langerhans' cell histiocytosis, first proposed by the Minnesota group (Risdall et al. 1983), be used to replace all previous designations. This suggestion followed general recognition that the 'sine qua non' of diagnosis is the Langerhans'-like cell (the "LCH cell" or "pathological Langerhans' cell") (Chu & Jaffe 1994).

Section 1.1. Historical perspective

It is possible that the oldest description of LCH was in the Hyppocratus corpus dated about 450 to 400 BC (Donadieu & Pritchard 1999). The text mentions a disorder of bone causing inflammation and pain with separation of the skin from the head. Although these features may fit other inflammatory conditions such as chronic osteomyelitis or tuberculosis, it is possible that this is the original description of LCH.

It has been suggested that the Yorkist Prince Edward V, might have had 'histiocytosis X' (Hargreaves & MacLeod 1994). In 1483, the 12-year old prince moved to the Tower of London, awaiting his coronation. Tradition has it that he and his younger brother Richard died there and that their bodies were buried in a wooden chest, within the Tower precinct. Two children's skeletons were discovered in 1674, and were moved to Westminster Abbey in 1678. In 1933, Lawrence Tanner, Keeper of the Muniments and William Wright, Professor of Anatomy examined the remains of the skeletons in an attempt to establish whether or not the skeletons were those of the 'Princes in the Tower'. They felt, as did others after them, that these were the bones of children of the reported ages of the Princes. In the mandible of the elder child, below the lower left molar teeth, there was a well-demarcated, scooped-out oval lesion. The abnormality had previously been thought to be due to one of a variety of possible conditions, including sepsis following caries or gum disease, osteitis or osteomyelitis. Hargreaves and

MacLeod compared the radiograph of the mandible, with that of a 3-year old boy known to have 'histiocytosis X' and found that they had a similar, typical pattern of bone loss, with the appearance of teeth 'floating in air'. Since it is not possible to re-examine the skeleton and there are no pathognomonic tests for LCH of the bone of this antiquity, the exact diagnosis will probably remain a mystery.

Other instances of probable LCH have been described for over a century. Dr Fraser suggested that the first case in the literature was reported by Dr. Thomas Smith in 1865 (Fraser 1935). Smith described a four and a half year old boy who presented with a soft, fluctuant swelling, thought to be an abscess, over the occipital bone. As the swelling was pulsatile and there was a deficiency of the underlying skull, he felt it would be unsafe to incise it. A few months later, the child died after a bout of whooping cough and Dr. Smith performed an autopsy. He found that the swelling was made up of yellowish inspissated material resembling a dried up abscess and that there were multiple bony defects of the skull (Smith 1865) (**Fig. 1.1**). Dr. Alfred Hand Jr., a resident physician in the Children's Hospital in Philadelphia, in his paper 'Polyuria and tuberculosis', described a 3-year old boy with polyuria, exophthalmos, an enlarged liver and spleen and a skin eruption who died. At autopsy, there were several destructive lesions in the child's cranial vault and infiltration of the liver, spleen and kidneys. Hand originally thought that the diagnosis was tuberculosis (Hand 1893) but, 28 years later, having seen many cases of tuberculosis in the intervening years, thought his original diagnosis had probably been wrong (Hand 1921).

In 1906, Kay reported a 7 year old boy with a rash, chronic ear discharge, loss of teeth, enlargement of the lymph nodes and a soft region on his head, who later developed exophthalmos and polyuria (Kay 1906). He proposed that the causative lesion was likely to be in the floor of the fourth ventricle. Later, Dr. Artur Schüller, a professor at the Zentral-Röntgeninsitut in Vienna, described 2 cases of an acquired skeletal disease, associated with abnormalities of the hypophysis (Schuller 1915). The first of these 2 patients was a 16-year-old boy, who presented with protrusion of the left eye, bony changes in the skull, obesity and underdeveloped genitalia (dystrophia adiposogenitalis). The second was a 4-year-old girl with exophthalmos, bony defects of the skull, polyuria and excessive thirst. He concluded his paper with the statement – "we can make a presumptive diagnosis of anomaly of the skeleton as a result of disease of the hypophysis". In 1920, Dr Henry Christian described a 3-year old girl who developed swollen and tender gums, with loosening of the teeth (Christian 1920). At the age of 3½, her right eye, and later both eyes,

became prominent. She began to drink more water and pass urine frequently. She also complained of a headache and hearing loss. On examination, she had numerous irregularities of the skull, with two large areas of softening, one in the fronto-parietal and the other in the parieto-temporal region. She also had marked exophthalmos and her gums were retracted and ulcerating with several loose teeth. Roentgenographic study revealed osteolytic defects, with the appearance of 'moth-eaten flannel' in the skull bones, with milder changes in the pelvis. Christian compared this child to the two cases described by Schüller and felt that they suffered from a similar disease process. In view of the disturbance of function of the pituitary gland in all three cases, he postulated that the bony defects were a result of 'dyspituitarism'.

Soon after this, Erich Letterer, a pathology resident at the University of Würzburg, described a 6-month old infant with hepatosplenomegaly, anaemia and a purpuric rash (Letterer 1924), who died within four days of presentation. At autopsy an infiltrate of large pale reticulo-endothelial cells was found in the liver, spleen, bone marrow, skin and lymph nodes. Several other authors reported similar cases and Dr Sture Siwe, describing another such child, grouped the previous cases with his own into a single entity (Siwe 1933). He believed that the disease was due to 'peculiar granulomatous lesions of indeterminate nature'. In a review of the literature, the resemblance between the cases described by Letterer and Siwe was recognised and the name "Letterer-Siwe's disease" suggested (Abt & Denenholz 1936). The condition was later also known as Abt-Letterer-Siwe disease.

In 1940, Jaffe and Lichtenstein described a solitary bony lesion, which consisted of tumour-like aggregates of large phagocytic cells, interspersed with eosinophils and called it 'eosinophilic granuloma of bone' (Jaffe & Lichtenstein 1940). They then became aware (Jaffe & Lichtenstein 1944), that some patients had multiple bone lesions, each resembling the solitary eosinophilic granuloma. Taking into consideration a report (Green & Farber 1942) that the underlying pathological bone lesion was histopathologically similar to the lesion of Schüller-Christian and Letterer-Siwe disease, they suggested that eosinophilic granuloma of bone, Schüller-Christian disease and Letterer-Siwe disease were different clinical presentations of the same disorder. The term 'eosinophilic granuloma' referred to the 'mild' form - one or more bony lesions; "Hand-Schüller-Christian disease" denoted the intermediate, chronic form with the triad of lytic defects in membranous bones, exophthalmos and diabetes insipidus; "Letterer-Siwe

disease", which most often occurred in infants and young children, represented the most severe form with fever, hepatosplenomegaly, rash, bone marrow involvement and, often, fulminant progression with a fatal outcome.

Concerned about the confusion caused by the different names for the condition, Lichtenstein proposed that the disease entities "eosinophilic granuloma", "Schüller-Christian disease" and "Letterer-Siwe disease" might be encompassed by the single name - Histiocytosis X (Lichtenstein 1953). This term emphasised Lichtenstein's view that the histiocyte was the primary abnormal cell in this disease whilst the 'X' indicated that the cause was unknown. The term 'Langerhans' cell histiocytosis' (LCH) was first coined by the Minnesota group (Risdall, Dehner, Duray, Kobrinsky, Robison, & Nesbit, Jr. 1983) to acknowledge that the pathognomonic lesional cell was a Langerhans'-like cell - the 'LCH cell' and four years later it was recommended (McLelland, Pritchard, & Chu 1987;Writing group of the Histiocyte Society et al. 1987) that this term should replace the old nomenclature. The term 'LCH' therefore spans the entire spectrum of the disease ranging from the single bony lesion, through the chronic disease form including the Hand-Schüller-Christian triad, to the fulminant, widespread illness of infants.

The first workshop on Childhood Histiocytoses was convened in Philadelphia by Dr D'Angio in May 1985 with 15 participants. It was the origin of the International Histiocyte Society with Dr Christian Nezelof as the first President. A support group The Histiocytosis Association of America, " an International Partnership of Parents, Patients, Physicians and Friends in search of a cure" was formed soon after. In 1987, The Nikolas Symposium in Greece, an annual "think tank" was founded by the Kontoyannis family and gives those interested in the histiocytoses the opportunity to meet once a year and exchange knowledge and ideas.

Figure1.1. Multiple deficiencies of the skull (Smith 1865)
This picture shows multiple deficiencies in the skull of a child who was possibly the first patient with histiocytosis to be described in the literature.

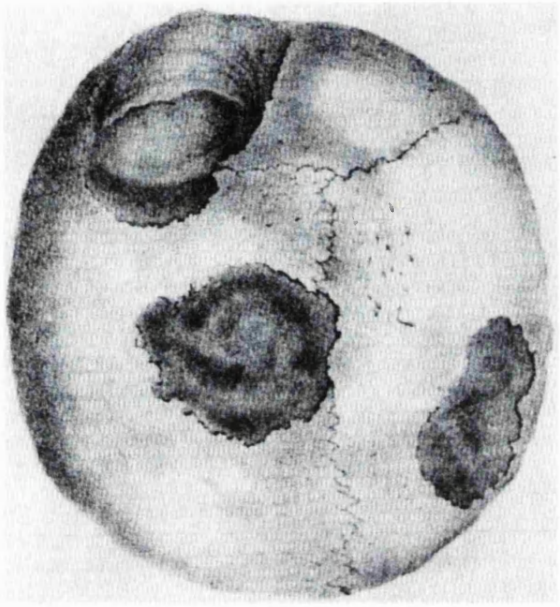


Figure 1.2. Paul Langerhans (1847 to 1888)

Langerhans is best known for the discovery of the Islets of Langerhans in the pancreas. He also described the characteristic dendritic cells in the skin, later known as Langerhans cells.

Section 1.2. The Langerhans' cell and the LCH cell

Paul Langerhans, who was born in 1847, studied medicine at the Universities of Jena and Berlin (**Fig.1.2**). While a student at the Institute of Pathology in Berlin under Professor Virchow, he made two important discoveries. The first was the presence of islands of cells in the pancreas described in his doctoral thesis in 1869 – subsequently shown to be the source of insulin and later named the 'islets of Langerhans'. He also identified a dendritic cell at the dermal-epidermal junction of the skin (Langerhans 1868). As these cells stained with gold ("aureophilia") and had short surface processes, he first felt that they were end points of nerves, but later retracted this view (Langerhans 1882).

It is now known that Langerhans' cells (LCs) are a form of dendritic cell that arise from bone marrow haemopoetic stem cells and are derivatives of the mononuclear-macrophage system. It has been shown that cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF), tumour necrosis factor-α (TNF-α) and TGF–β (Geissmann et al. 1998) can induce maturation of bone marrow precursor cells to produce LCs. The cells then traffic in the blood from the bone marrow to the skin. In the epidermis, they transform to their characteristic dendritic morphology, the finger-like processes increasing the surface area available for antigen recognition. Having made contact with a foreign antigen, LCs migrate via the afferent lymphatics to the regional lymph node where they present the antigen to 'T' lymphocytes, inducing an immune response. LCs are therefore found in the regional lymph nodes and thymus, as well as in the epidermis of the skin. They also line the bronchial tree, where they detect inhaled antigens.

Jaffe and Lichtenstein first recognised that the lesional cell was a form of histiocyte (Jaffe & Lichtenstein 1940). In 1961 Birbeck, Breathnach and Everall described characteristic intracytoplasmic, lamellar bodies – later known as Birbeck granules or Langerhans cell granules - on electron microscopy of the skin in patients with vitiligo (Birbeck, Breathnach, & Everall 1961). In 1965, Basset described an ultrastructural, pentalaminar racquet-shaped body in the cytoplasm of cells from a lesion of pulmonary Histiocytosis X (Basset & Turiaf 1965), later known as the 'X body' or 'X granule'. It is also known by the eponym 'BBB (Birbeck, Breathnach, Basset) granule' and is now considered to be a crucial morphological marker of both normal and abnormal Langerhans' cells. In 1973, the Langerhans-like cell was recognised as being the pathological cell in Histiocytosis X (Nezelof, Basset, & Rousseau 1973).

The Langerhans' cell histiocytosis cell (LCH cell)

In LCH, the 'LCH cells', accumulate and proliferate in one or more organs. This causes not only organ enlargement with/without dysfunction, but also results in tissue damage and fibrosis, possibly via cytokine production, either by the lesional cells themselves or by associated inflammatory cells. LCH cells and LCs have an almost identical surface phenotype. However, there are differences of uncertain functional significance. The expression of markers such as peanut agglutinin (PNA), placental alkaline phosphatase (PLAP) and the interferon γ receptor (IFNγR) is useful in differentiating normal LCs from LCH cells (Chu & Jaffe 1994). PNA staining of LCH cells is characteristic, with dense paranuclear and cell surface staining. Normal LCs show either no staining, or diffuse cytoplasmic staining with PNA. PLAP staining is seen in LCH cells, but LCs only show positivity for a brief period following activation. The interferon γ receptor has not been identified on normal LCs but is seen on LCH cells. LCH cells produce a variety of cytokines and chemokines resulting in a "cytokine storm" (Egeler et al. 1999) (Geissmann & Thomas 1999), including interleukins (IL1, IL8), TNF-α (Willman & McClain 1998), leukemia inhibitory factor (LIF) and GM-CSF (Kannourakis & Abbas 1994). LCH cells from bone lesions have been shown to produce increased amounts of IL-1 and prostaglandin E_2 (Arenzana-Seisdedos et al. 1986). These cytokines may be responsible for stimulation of osteoclastic activity, resulting in lytic bone lesions.

1.2.1. Clonality of LCH cells

Until a few years ago, LCH was felt to be a reactive rather than a neoplastic disorder. One of the most important characteristics of neoplasia is "clonality" or "monoclonality" – that is, origin from a single genetically abnormal cell. Molecular assays for assessment of clonality are based on the random process of X-chromosome inactivation in females ('Lyonisation'). In 1994, Willman et al published their study demonstrating that LCH is a clonal disease of 'LCH cells' (Willman et al. 1994). They used a DNA probe to an X-linked polymorphic gene (HUMAR- human androgen receptor) to assess clonality in lesional tissue and lymphocytes from 10 female patients with LCH. The HUMARA assay identified 'clonality' of the lesional cells in 9 of the 10 patients, the percentage of clonal cells approximating that of the CD1a positive cells. In the 10th patient clonality could not be determined due to extreme constitutional lyonisation. Lymphoid clonality was excluded in all patients. This confirmed, with a negative internal control

(lymphocytes) that the clonal cells in LCH are the dendritic CD1a positive cells. Extending Willman's study, Yu *et al* used flow cytometry to purify CD1a+ve cells from lesional tissue from 3 female patients with multisystem disease. They showed that the CD1a+ve cells were essentially 'clonal', while a control population of CD1a –ve cells from the same lesion were polyclonal (Yu, Buluwela, & Chu 1994). To date 4 groups have independently worked on the molecular analysis of clonality in LCH using the HUMARA assay and have shown that the lesional tissues in 16/16 females contained 'clonal' CD1a+ve cells (Willman & McClain 1998). Clonality of lesional histiocytes has also been confirmed in lung tissue from 5 women who had isolated pulmonary histiocytosis (Willman & McClain 1998).

Significance of clonality

The demonstration of clonality of the 'LCH cells' suggests that LCH is a "neoplasm" of the histiocytes, rather than a reactive disorder. It is now recognised that most cancers arise from poorly controlled proliferation of a single cell that has acquired one or more somatic mutations. The identification of clonality of a specific cell population indicates that LCH is a neoplastic disorder. However, unlike specific types of 'cancer', the disease process in LCH often varies widely. Therefore, the finding that a disorder is clonal does not necessarily predict its biological behaviour, clinical severity or outcome.

1.2.2. Cytogenetic Abnormalities in LCH

Cancers derived from the bone marrow have specific and characteristic chromosomal abnormalities. If LCH is a 'clonal' disorder, then specific chromosomal abnormalities should be demonstrable in the LCH cells. Betts *et al* have demonstrated different cytogenetic abnormalities in lesional tissue from 5 patients. In one patient there was an abnormal clone with a t(7;12)(q11.2;p13) translocation detected in a small percentage of cells. This case and 3 others also contained non-clonal chromosomal abnormalities and an increase in chromosomal breakage. The fifth case had a constitutional inversion of chromosome 13q (Betts et al. 1998). Other groups have not yet confirmed these findings, and further work is necessary before conclusions about the 'critical genes', involved in LCH pathogenesis, can be reached.

Section 1.3. Epidemiological aspects

1.3.1. Epidemiology

LCH is a relatively rare disease with a reported annual incidence of 5.4 per million (Carstensen & Ornvold 1993), but it is likely that this is an underestimate of the true incidence as some, and perhaps many, cases are probably never recognised. There is a male predominance with a male to female ratio of 2:1. However, this difference is much less obvious in patients with multisystem disease than in those with isolated skeletal involvement. The reason for these gender differences is unknown. Although it can present at any age, from the neonatal period through to adulthood, the peak age of presentation is from 1 to 3 years. Multisystem disease usually presents under the age of 2 years, while unifocal bone disease is commonest in older children and young adults, suggesting that the host 'milieu' may be disease-modifying.

Exploratory epidemiological studies have found that factors associated with an increased risk of LCH included maternal urinary tract infection during the index pregnancy, feeding problems during infancy, blood transfusions during infancy (Hamre et al. 1997) and neonatal infections, solvent abuse and a lower incidence of childhood immunisation (Bhatia et al. 1997). However, further studies are required before firm conclusions can be drawn.

1.3.2. Genetic factors

LCH had been considered a sporadic disorder, with no genetic component. However, over the years there have been reports of familial clustering of cases with LCH, in particular in monozygotic twins (Bierman 1966;Caldarini 1966;Enjolras et al. 1992;Freundlich et al. 1972;Juberg, Kloepfer, & Oberman 1970;Kanold et al. 1994;Katz et al. 1991;Kuwabara & Takahashi 1990). Members of the Histiocyte Society conducted a survey in order to establish the number of cases of familial LCH and to define their characteristics. (Arico et al. 1999). They identified nine families in whom more than one member was affected by LCH. There were 5 families with twin pairs, 2 with sibling pairs and 2 sets of first cousins. Three twin pairs not concordant for LCH were also studied. The presumed monozygotic twins had simultaneous and early disease onset (mean age 5.4 months) with similar clinical features, while onset was at 21 months in the dizygotic twins. The three healthy twins in the discordant pairs remained asymptomatic. Consanguinity of the parents was noted in 3 of the 4 families with affected siblings or cousins. They felt

that their data supported a role for possible genetic factors in LCH. They suggest that careful, extensive family history and chromosome studies should be part of the work-up of newly diagnosed patients and that where possible, constitutional and/or lesional DNA should be obtained for future study.

A rare pedigree has been identified in whom there is association of histiocytosis with joint contractures and sensorineural deafness (Moynihan et al. 1998). The condition is inherited as an autosomal recessive trait with linkage studies mapping to the region of chromosome 11q25. It is hoped that identification of the gene responsible for this condition will further add to the understanding of the aetiology of LCH.

1.3.3. LCH and malignancy

There does appear to be an association between LCH and malignancy, with an increased coincidence of the two conditions in the same individual (Arico et al. 1993;Camargo et al. 1993;Egeler et al. 1994;Ferrari et al. 1997). In 1991 members of the Histiocyte Society formed the LCH-Malignancy Study Group, whose aim was to define the occurrence of malignancy and LCH in the same individual, and to investigate the patterns of association. The initial results were published in 1994 (Egeler, Neglia, Arico, Favara, Heitger, & Nesbit 1994), and by 1997, 56 patients were registered on the study (Egeler et al. 1998), as follows:

***LCH and acute leukaemia*:** Twenty- nine patients had LCH in association with acute leukaemia. In 12 cases the diagnosis was acute lymphoblastic leukaemia (ALL), and in 7 of these patients the leukaemia preceded the diagnosis of LCH by 6 to 12 months. The other 5 patients developed ALL from 3.5 to 7 years after the diagnosis of LCH. LCH was associated with acute non-lymphoblastic leukaemia (ANLL) in the other 17 patients. Sixteen of the 17 patients developed ANLL after LCH, with an interval of more than 2 years (median 5.5 yrs) between the diagnosis of LCH and of ANLL. In all 16 cases the LCH had been treated with chemotherapy, radiotherapy or both. Cytogenetic abnormalities were found in the leukaemic cells in 10 of 11 patients studied.

LCH and solid tumours: LCH was associated with a solid tumour in 25 patients. Four patients had lymphomas, 4 had retinoblastoma, 4 basal cell carcinoma and the other 13 had a variety of other malignancies. The diagnosis of LCH preceded the tumour in 16 patients, and in 10 of them the malignancy arose within the radiation field used for treatment of the LCH.

The occurrence of LCH following ALL suggests that the chemotherapy-induced immunosuppression may play a role in the development of at least some cases of LCH. As most patients with ALL rapidly attain remission on starting treatment it is felt to be less likely that the LCH develops as a "reaction" to the leukaemia. The occurrence of ANLL and solid tumours following LCH suggests that the therapy for the LCH may have a role in oncogenesis. It is well recognised that epipodophyllotoxins may induce the development of secondary leukaemia (Hawkins et al. 1992). Etoposide (VP16), an epipodophyllotoxin widely used in the treatment of LCH, has been reported to cause secondary ANLL, especially when used in high cumulative doses of above 4000 mg/m^2 and in high intensity schedules (Haupt et al. 1997). This concern was taken into account when planning the International treatment trials (LCH I and LCH II) where the cumulative dose of Etoposide did not exceed 3,600 mg/m^2. However, even lower doses of Etoposide are not without risk and there may well be no entirely 'safe' dose. The development of solid tumours in the radiation field used for LCH treatment indicates that radiotherapy is the oncogenic stimulus in these patients. In others, chemotherapy may play a role.

In summary, there appear to be two patterns of association between LCH and malignancy. ALL usually precedes LCH, whilst ANLL and solid tumours develop after LCH, probably as a consequence of the treatments used.

Section 1.4. Classification of Histiocytic disorders

In 1987, in an attempt to resolve the existing confusion in the nomenclature, members of The Writing Group of the Histiocyte Society proposed a Classification of Histiocytosis syndromes in Children (Writing group of the Histiocyte Society, Chu, D'Angio, Favara, Ladisch, Nesbit, & Pritchard 1987). They classified the histiocytoses into:

Class I: Langerhans' cell histiocytosis

Langerhans' cell histiocytosis (LCH) includes all the conditions previously known as Histiocytosis X. This group includes the conditions lipoid granulomatosis, Hand-Schüller-Christian disease, Abt-Letterer-Siwe disease and eosinophilic granuloma. Identification of the 'LCH' cell is crucial to the diagnosis.

Class II: Histiocytosis of mononuclear phagocytes other than Langerhans' cells

This includes conditions where there are collections of non- Langerhans' histiocytes. The two most common conditions in this group are familial haemophagocytic lymphohistiocytosis (HLH) and the infection-related acquired haemophagocytic syndrome (IAHS).

Class III: Malignant Histiocytic disorders

These disorders are distinctly malignant processes of the histiocytic lineage and include acute monocytic leukaemia, malignant histiocytosis, and so-called 'histiocytic lymphomas'.

Recently, Favara and colleagues in the Histiocyte Society, published a revision of this classification (Favara et al. 1997)

Contemporary Classification of Histiocytic Disorders

Disorders of varied biological behavior

Dendritic cell-related

- Langerhans' cell histiocytosis
- Secondary dendritic cell processes
- Juvenile xanthogranuloma and related disorders
- Solitary histiocytomas of various dendritic cell phenotypes

Macrophage-related

- Hemophagocytic syndromes
  - Primary hemophagocytic lymphohistiocytosis
  - (Familial and sporadic; commonly elicited by viral infections)
  - Secondary hemophagocytic syndromes
    - Infection-associated
    - Malignancy-associated
    - Other
- Rosai-Dorfman disease
  - (Sinus histiocytosis with massive lymphadenopathy)
- Solitary histiocytoma with macrophage phenotype

Malignant Disorders

- Monocyte-related
  - Leukemias (FAB and revised FAB classifications)
    - Monocytic leukemia, M5A and B
    - Acute myelomonocytic leukemia, M4
    - Chronic myelomonocytic leukemia
  - Extramedullary monocytic tumor or sarcoma
  - (monocytic component of granulocytic sarcoma)
- Dendritic cell-related histiocytic sarcoma (localized or disseminated)
  - specify phenotype; follicular dendritic cell, interdigitating dendritic cell
- Macrophage–related histiocytic sarcoma (localized or disseminated)

Section 1.5. Clinical Features and Investigations

The normal Langerhans' cell is seen only in the skin, the major airways, the thymus and the lymph nodes. However, the granulomatous lesions of LCH can affect several organs/ organ systems with a wide clinical spectrum. The main systems affected are bone, skin, lymph nodes, oral mucosa, bone marrow, liver, spleen, gut and brain including the hypothalamo-pituitary region.

Older children often present with 'single system' LCH with isolated bone involvement. Infants tend to have multisystem disease with involvement of vital organs, including liver, spleen, bone marrow and lungs with progression to 'organ failure'. They tend to have a more aggressive disease with a higher mortality. There is also a large group of patients with an intermediate form of disease with multisystem involvement, which follows a more chronic course and a greater likelihood of developing long-term sequelae. However, the histopathological appearance in the different forms of the disease is identical and, despite this wide variation in clinical presentation, strongly supports the notion that LCH is a single disease entity.

The prognosis for patients with LCH depends on the systems involved and the rate of progression. In the 1970's a 'staging' system was devised to assess prognosis depending on the degree of 'organ dysfunction' of the liver, lungs and bone marrow (Lahey 1975a). In a retrospective analysis it was found that of patients who had evidence of 'organ dysfunction' only a third survived. However, of a group of 50 patients who did not have 'organ dysfunction' 66% responded to therapy and only 2 patients died, neither death being directly attributable to LCH (Lahey 1975b). Although it was originally felt that young age (under 2 years at diagnosis) was an adverse prognostic factor, it has now been shown that infants without 'organ dysfunction' have a prognosis similar to older patients.

The lesions of LCH tend to heal with scarring and fibrosis leading to damage of the involved organs. This damage leads to the development of long term sequelae. As there is often considerable overlap between the "active " phase of the disease and the development of these permanent consequences they are discussed in the section below which describes the clinical features of the condition. In some cases, presumably because the 'active' phase of the LCH was subclinical or undiagnosed, sequelae are present at the time of diagnosis.

1.5.1. Bone

Skeletal involvement is very common in LCH and occurs in the majority of patients (Bollini et al. 1991;Donadieu & French LCH Study group. 1996;Raney, Jr. & D'Angio 1989;Willis et al. 1996). The flat bones of the skull (**Fig.1.3**), pelvis, vertebrae and ribs, and the long bones, especially the femur and humerus (**Fig.1.4**) are most frequently involved. Bony disease usually presents with swelling, which may be painful. The small bones of the hands and feet are rarely involved. Extension of skull vault lesions into the adjacent tissue of the scalp causes superficial soft tissue swellings and / or dural displacement. Orbital disease causes proptosis and involvement of the petrous temporal bone can cause mastoid infiltration and hearing loss. Granulomas may affect the jaw with ulceration of the overlying gum and loosening of teeth. Spinal disease may present with pain, reduced mobility or collapse of one or more vertebrae (vertebra plana). Pelvic and limb involvement usually presents with pain, occasionally with restriction of movement.

Plain X-rays of flat bones demonstrate the characteristic 'punched-out' lytic lesions with accompanying soft tissue swelling. The lesions may have a sclerotic margin indicating healing. Lesions in long bones are often accompanied by exuberant periosteal reaction and may resemble malignant bone tumours such as Ewing's sarcoma or osteogenic sarcoma. The history and presence of lesions in other sites, on clinical examination and radiological skeletal survey, may help in distinguishing LCH from these conditions. Radionucleide bone scanning has been recommended as being useful in detecting active lesions (Dogan et al. 1996;Wagenknecht et al. 1990) but is felt by others to be less specific (Crone Munzebrock & Brassow 1983;Siddiqui et al. 1981) and, in practise, may only be complementary to the role of plain radiography.

Sequelae of bony involvement: Facial abnormality and residual proptosis are often seen. Some patients have permanent defects of the bony skull. Orthopaedic disability is less common. Patients with involvement of the spine may have vertebral reconstitution with minimal disability (Ippolito, Farsetti, & Tudisco 1984;Nesbit, Kieffer, & D'Angio 1969;Raab et al. 1998). The younger the child, the greater the growth and reconstitution of the vertebral body (Robert, Dubosset, & Miladi 1987).

Figure 1.3.Plain X Ray of the skull showing multiple lytic lesions
Skull X ray showing the characteristic multiple lytic lesions of LCH

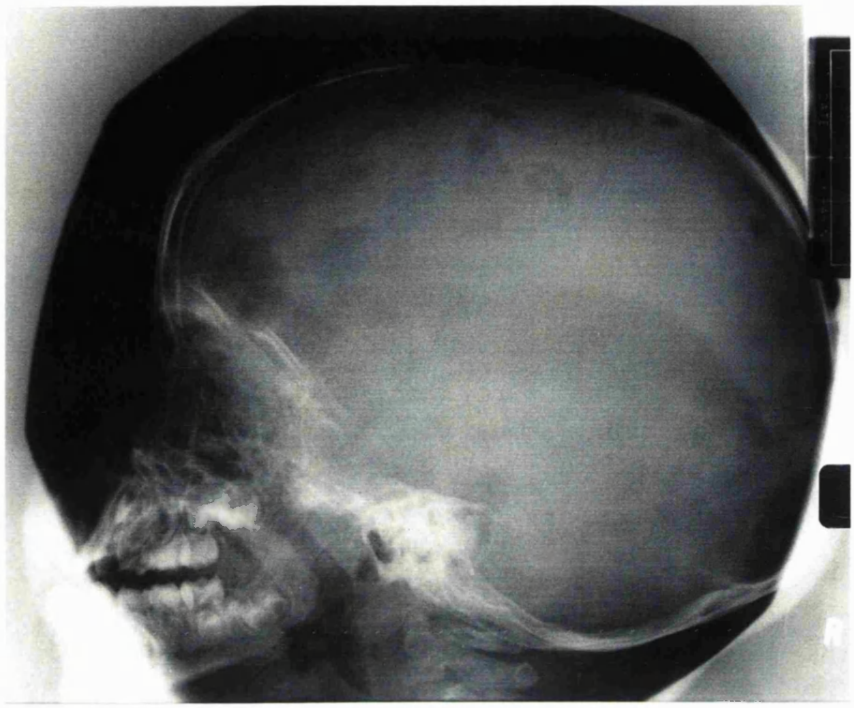
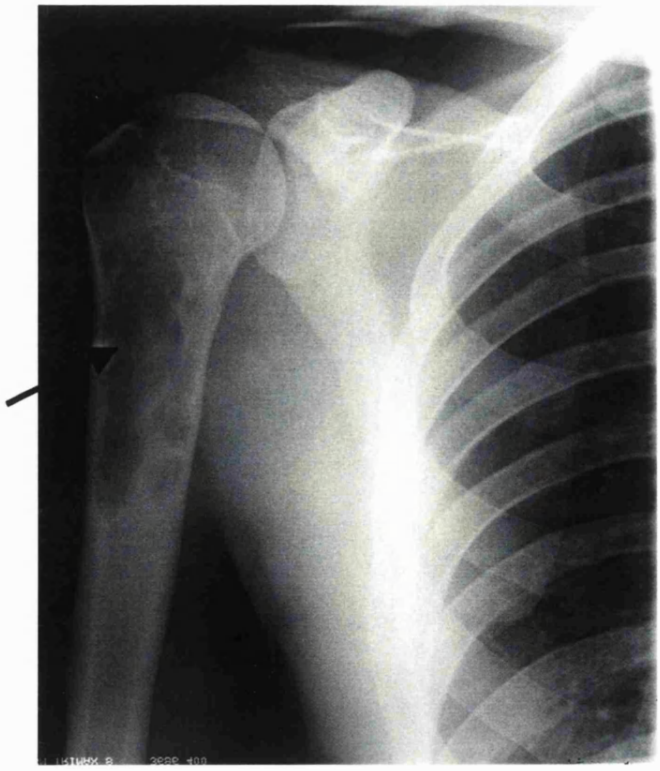


Figure 1.4. Plain X ray showing a lytic lesion of the humerus



1.5.2. Skin

Skin involvement is seen in up to half the patients (Munn & Chu 1998). The usual presentation is with a rash on the scalp and in the intertriginous areas. Scalp involvement is widespread and erythematous with scaly, flaking lesions resembling seborrheic dermatitis or intractable 'cradle cap' (**Fig. 1.5**), with which LCH is often confused. A post-auricular rash may be seen. The flexures of the axillae, groins, perianal region and neck creases are often affected by a maculopapular and erythematous rash, which may ulcerate leaving raw or fissured areas (**Fig.1.6**) which predispose to secondary infection. The skin of the trunk may show a widespread maculopapular rash but occasionally isolated brown pigmented papules may be the only finding. The external genitalia, especially the vulval region, may be involved with ulceration. In approximately 10% of the patients, skin is the only tissue involved and spontaneous regression may occur. Some LCH patients who present with apparently isolated skin involvement may go on to develop signs of other organ involvement (Minkov, Grois, & Gadner 1999). Infants occasionally have the form known as "Hashimoto-Pritzker disease", which is a benign self-healing condition, involving only the skin, characterised by a superficial varicelliform rash which may affect any part of the body, including the palms and soles (Hashimoto & Pritzker 1973). There is an association of LCH with juvenile xanthogranuloma (JXG)- with both lesions occurring in the same patient and individual lesions showing features of both disorders (Munn & Chu 1998).

Sequelae of skin involvement: Areas of previous involvement may show scarring and/or deposits of lipid-filled material with the appearance of juvenile xanthogranuloma (Hoeger et al. 2001).

1.5.3. Lymph nodes and thymus

Enlargement of the lymph nodes may be part of widespread multisystem disease, or can be localised to regions draining areas of affected bone or skin. The cervical lymph nodes are most commonly affected, but other groups may also be involved. Occasionally a lymph node discharges through the overlying skin to form a chronic indolent sinus, which is often resistant to treatment (Sacks et al. 1986). Healing can be slow with scarring of the skin and subcutaneous tissue, which may be disfiguring. Thymic enlargement may be recognised as a mediastinal mass on chest X-ray and is usually asymptomatic. Although seen as part of multisystem disease, the thymus may occasionally be the only organ involved.

Figure 1.5. LCH presenting as "cradle cap"

Widespread seborrheic rash on the scalp of an infant, who presented with intractable "cradle cap".

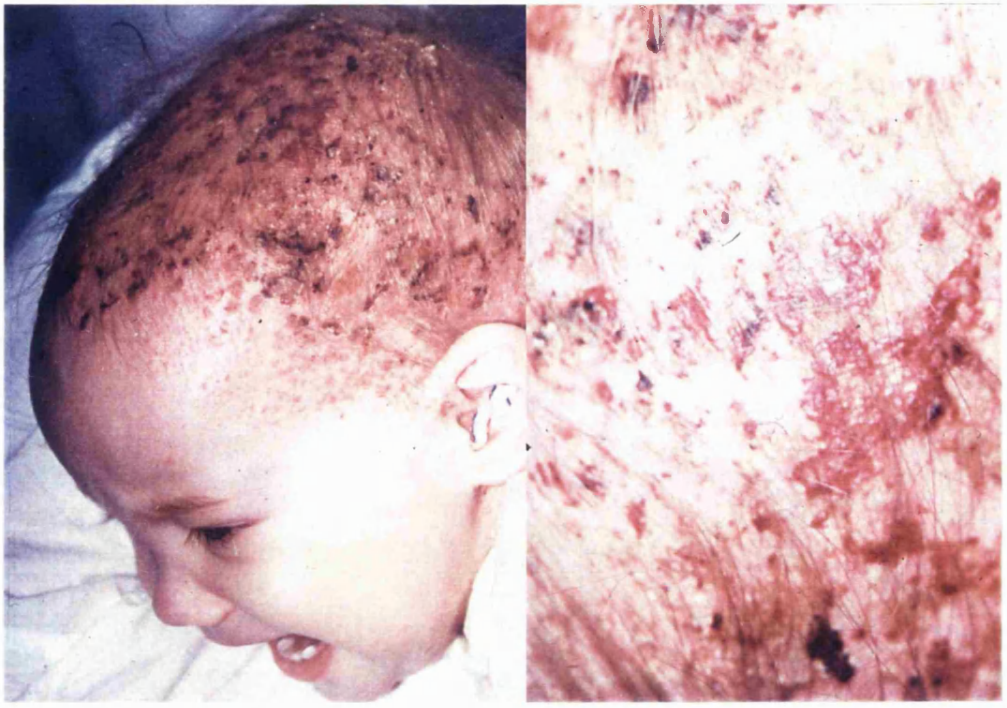
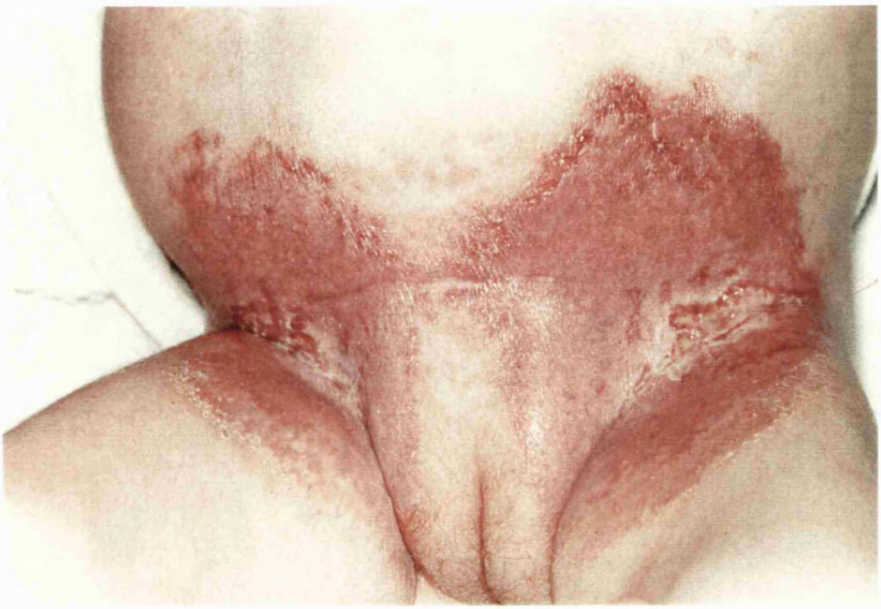


Figure 1.6. LCH rash affecting the groin and perineal region

Erythematous, ulcerating rash affecting the groin and perineal region mimicking "nappy rash".



1.5.4. Ears

Aural discharge may be a manifestation of either otitis externa, as part of skin disease, or mastoid involvement with the formation of polyps. The reported incidence of ear involvement ranges from 15% to 61% (McCaffrey & McDonald 1979;Smith & Evans 1984;Tos 1966). Inner ear involvement tends to be rare, as the bony labyrinth is relatively resistant to destruction by granulomatous tissue, but if it occurs, can lead to permanent hearing loss and should therefore be sought carefully and treated early (Nanduri et al. 1999a). Hearing deficits secondary to mastoid or inner ear involvement can be permanent and may require the use of hearing aids. Children with documented ear involvement, especially those with mastoid disease, should be carefully assessed with serial audiometry and imaging. Thin slice, high resolution CT scans of the petrous bone provide detailed images of the mastoid, middle ear cavity and inner ear (**Fig.1.7**), while MRI scans demonstrate the soft tissue component (**Fig.1.8**).

1.5.5. Bone Marrow

Patients with LCH may present with pancytopenia, but this does not always represent bone marrow involvement. In some the anaemia is a non- specific consequence of a chronic illness – "anaemia of chronic disorders" - with a low iron and transferrin concentration, but normal iron binding capacity. Bone marrow 'dysfunction' is arbitrarily defined by a haemoglobin concentration of <100 g/l (without iron deficiency), white cell count of $<4.0 \times 10^9$ /l, neutrophil count of $<1.5 \times 10^9$ /l, or a platelet count of $<100\times 10^9$ /l (Lahey 1975a). Patients with multisystem disease and/or pancytopenia should have a bone marrow aspirate and trephine performed. Bone marrow infiltration with LCH cells is often associated with widespread disease, and a poor outcome (Raney, Jr. & D'Angio 1989;Rivera-Luna et al. 1996). Macrophage activation may result in secondary haemophagocytosis and is an established cause of pancytopenia in LCH.

1.5.6. Spleen

The reported incidence of splenomegaly is 5% (Donadieu & French LCH Study group. 1996), but enlargement is usually only moderate. In the very young there may be massive splenomegaly and secondary pancytopenia, due to 'hypersplenism' and haemophagocytosis.

Figure 1.7. Destruction of the petrous temporal bones

Transverse CT scan of the petrous temporal bones showing bilateral destruction

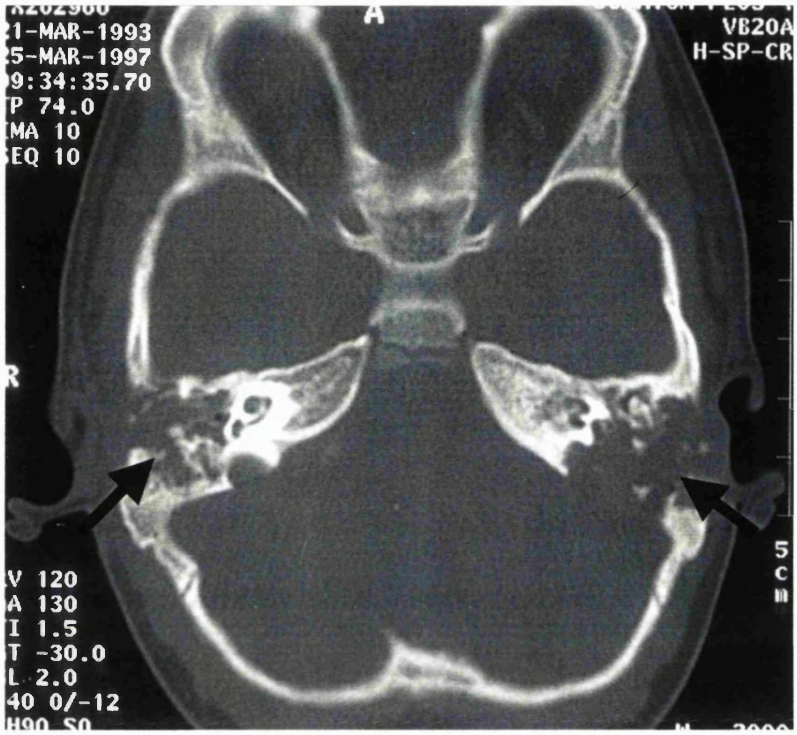
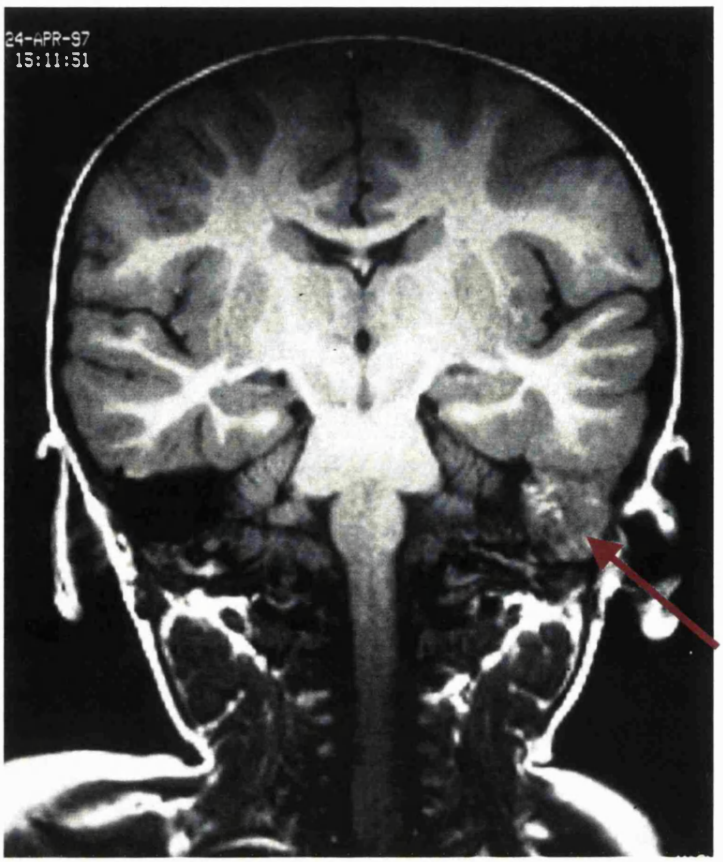


Figure 1.8. Abnormal soft tissue in the left mastoid region

Coronal T-1 weighted MRI showing abnormal soft tissue in the left mastoid region



1.5.7. Liver

Hepatomegaly has been reported in 10% - 14% of patients with LCH, but 'dysfunction' is detectable in < 5% (Donadieu & French LCH Study group. 1996). Liver dysfunction is defined by the presence of cholestasis (serum bilirubin > 5 times normal), hypoalbuminaemia (albumin < 25 g/l) in the absence of a protein losing enteropathy, or a 50% increase in prothrombin time relative to normal (Lahey 1975a). Infiltration of the periportal regions is characteristic and may lead to destruction of the bile ducts.

Chronic liver disease: Healing of the periportal infiltrate of LCH is associated with fibrosis and scarring which can result in biliary obstruction. The clinical picture and histopathological findings are those of sclerosing cholangitis with cirrhosis and progressive liver failure (Thompson et al. 1984). The only curative treatment for such patients is liver transplantation, which has been carried out successfully in several centres (Concepcion et al. 1991;Debray et al. 1994;Melendez et al. 1996;Rand & Whitington 1992). There is however evidence that children who undergo orthotopic liver transplantation following LCH are at risk of developing post-transplant lymphoproliferative disease (Melendez, Dhawan, Mieli-Vergani, Rela, Heaton, Pritchard, & Mowat 1996;Newell et al. 1997). Manipulation of immunosuppresive therapy may result in amelioration of the condition, although some patients may go on to require chemotherapy. It has recently been reported that LCH may recur in the transplanted liver in patients who have active LCH at other sites (Hadzic et al. 2000).

1.5.8. Lungs

Lung involvement in LCH, though rare, can have longstanding effects (Basset et al. 1978;Ha et al. 1992;Lewis 1971). Lung involvement in children manifests in two main forms (Carlson et al. 1976). It is most often seen as part of multisystem disease, and may be detected in up to 50% of patients (Ha, Helms, Fletcher, Broadbent, & Pritchard 1992). Although it may present with tachypnoea, intercostal and subcostal retraction and cough, it is often an incidental finding on chest X-ray or respiratory function testing. Rarely the presenting feature may be a spontaneous pneumothorax due to the rupture of a bullous lesion. In the initial 'active' stage the lesions show the characteristic histological pattern of LCH. In later stages there may be increasing scarring and fibrosis. Children very occasionally have primary pulmonary histiocytosis with lung disease only, resembling that seen in adults

where often no other organ is involved (Carlson, Hattery, O'Connell, & Fontana 1976;Ha, Helms, Fletcher, Broadbent, & Pritchard 1992;Nondahl et al. 1986). It is often seen in smokers (Hance et al. 1989) and presents with gradual onset of respiratory distress which is often relentlessly progressing to chronic respiratory failure. X-rays show diffuse, fine, interstitial shadowing, with occasional bullous formation or pneumothorax (**Fig. 1.9**). Cystic changes result from destruction of the affected bronchioles and from traction of scar tissue, leading eventually to a 'honeycomb' appearance (Basset, Corrin, Spencer, Lacronique, Roth, Soler, Battesti, Georges, & Chretien 1978). CT scan demonstrates micronodules with cystic change. Respiratory function tests show 'small stiff lungs' with a restrictive pattern of abnormality - low vital capacity and reduced ratio of FEV1 to FVC.
Confirmation of the diagnosis requires the finding of 'LCH cells' in bronchial washings or on lung biopsy (Auerswald, Barth, & Magnussen 1991;Chollet et al. 1984).

Sequelae of lung involvement: Although involvement of the lungs is often seen as part of widespread disease in infants and young children, long term sequelae due to lung fibrosis are relatively uncommon in survivors of this form of multisystem involvement. This might be because the infant lung has a greater ability to repair and regenerate. Some older patients may however develop progressive pulmonary fibrosis resulting in chronic restrictive lung disease (**Fig.1.10**). There is often considerable overlap between the 'active' phase and the 'late' sequelae. The incidence and severity of lung damage is greater in smokers than in non-smokers (Basset, Corrin, Spencer, Lacronique, Roth, Soler, Battesti, Georges, & Chretien 1978;Hance, Basset, Saumon, Danel, Valeyre, Battesti, Chretien, & Georges 1989). End-stage lung disease may require lung transplantation (Grossman et al. 1990;Habib et al. 1998) but there is a risk of recurrence of LCH in the transplanted organ (Habib, Congleton, Carr, Partridge, Corrin, Geddes, Banner, Yacoub, & Burke 1998).

Figure 1.9. Interstitial shadowing

Chest X ray demonstrating diffuse interstitial shadowing in the acute phase of LCH

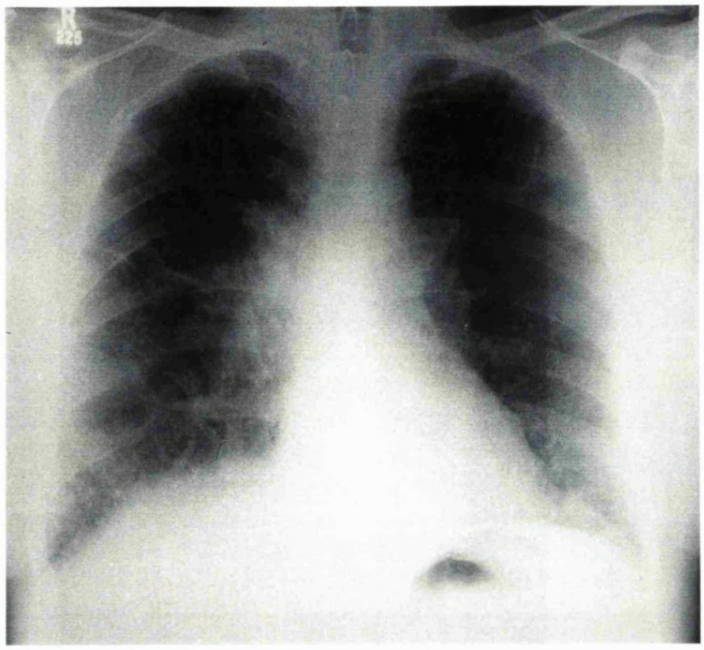
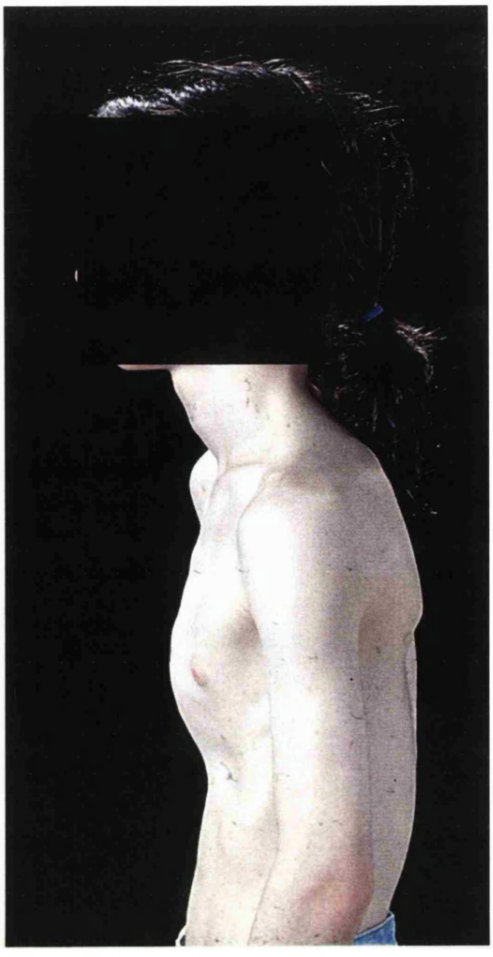


Figure 1.10. Severe restrictive lung disease

Deformity of the chest due to severe restrictive lung disease with antero-posterior flattening of the rib cage.



1.5.9. Gastrointestinal tract and pancreas

The incidence of gastrointestinal involvement by LCH is uncertain, as the gut is not often biopsied. Any region of the GI tract, from the mouth to the anal margin, may be affected. Ulceration of the gingival or palatal mucosa are common, with erosion of the gum margins. Premature eruption of the deciduous teeth in infants, is a curious presenting feature, which is as yet unexplained. Patients may present with chronic diarrhoea, failure to thrive, protein-losing enteropathy or malabsorption (Keeling & Harries 1973). Until recently, colon involvement was thought to be unusual, but is probably underdiagnosed, as the colon is not routinely examined for evidence of disease (Nanduri et al. 1999b). Contrast radiology is not very sensitive or specific at identifying the lesions and diagnosis is best made by direct visualisation, using upper and lower GI endoscopy with biopsy of suspicious areas. There has been a report of involvement of the pancreas, identified on autopsy, in a child who died of widespread disease (Yu et al. 1993).

1.5.10. Hypothalamo-pituitary involvement

Hormone deficiencies are a well-recognised feature of LCH and Hand's original paper described a patient with polyuria (Hand 1893). Schüller recognised the abnormality of the hypophysis (Schuller 1915) and others postulated that the cause of histiocytosis might be 'dyspituitarism' (Christian 1920;Hand 1921). The reason for the propensity of LCH to 'target' the hypothalamo-posterior pituitary axis in this way is unclear. Diabetes insipidus (DI) is seen in up to 50% of LCH patients (Grois et al. 1995),(Broadbent & Pritchard 1997;Donadieu & French LCH Study group. 1996;Dunger et al. 1989;Sims 1977;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996) but anterior pituitary involvement is less common. Autopsy studies reveal that the LCH process infiltrates the hypothalamo-pituitary region, even in cases with no clinical evidence of DI. Kepes and Kepes in 1969 reported 4 cases of histiocytosis affecting the central nervous system (Kepes & Kepes 1969). Three of the 4 patients had diabetes insipidus, and it was felt that the 4th patient might well have had DI, but was possibly too ill to express increased thirst. All 4 patients died as a result of their disease and on necropsy were found to have granulomatous infiltration of the hypothalamus and posterior pituitary. These hypothalamic granulomas have been known over the years by several different eponyms including Ayala's disease (Ayala 1934) and 'Gagel's granuloma' (Gagel 1941). There have been several reports of the histological appearance of these lesions and detailed descriptions can be found in the chapter on Histiocytosis X in

the Handbook of Clinical Neurology (Kepes 1979). An autopsy study in 20 patients with LCH (not all of whom had clinical abnormality of the pituitary) showed direct infiltration of the parapituitary region in 17, pituitary stalk in 5, and the posterior pituitary in 9 patients (Vawter, Greenberger, & Crocker 1986). The supra optic nucleus was present in 14 patients, but was atrophied in 4. Three of the patients had the equivalent of stalk transection. Seven of the 20 patients had DI, while 2 had probable DI. It does therefore appear that a large number of patients with LCH have infiltration of the hypothalamo-pituitary region with granulation tissue, although not all develop clinically evident DI or GHI.

1.5.10.1. Diabetes insipidus

The presenting symptoms are excessive thirst and an increased urine output. As the onset is often in early childhood, these symptoms may be mistaken for habitual excessive water drinking – a behavioural manifestation in the toddler.

At diagnosis of LCH, symptoms of DI are present in less than a third of all the patients in whom this complication eventually develops. The remainder develop symptoms later on (Sims 1977). At the time of diagnosis of LCH, 4% of patients in the DAL-HX 83 study had DI, with a cumulative risk of 11% after a median observation time of 5 years 3 months (Grois, Flucher Wolfram, Heitger, Mostbeck, Hofmann, & Gadner 1995). In another study of 52 children (Dunger, Broadbent, Yeoman, Seckl, Lightman, Grant, & Pritchard 1989a), only 2 had DI at presentation, but the cumulative risk of developing DI during the first 4 years after diagnosis of LCH was 42%.

Investigation of diabetes insipidus: Although the diagnosis of DI is often made on clinical grounds and a low osmolality on 'early morning' urine, confirmation requires a water-deprivation test. The standard test is performed over 12 to 16 hours (Hughes 1986). Plasma and urine sodium and osmolality are measured at 0, 8 and 12-16 hours. In the normal subject the plasma osmolality remains below 295 mosmol/kg and the urine osmolality increases three-fold to at least 750 mosmol/kg. DI is diagnosed if there is a failure to concentrate urine and the plasma osmolality exceeds 300 mosmol/kg. Desmopressin (1-desamino-8-D arginine vasopressin or DDAVP) is then administered and a response is diagnostic of pituitary ADH deficiency. Failure to respond to DDAVP indicates a renal cause (nephrogenic diabetes insipidus).

As the standard water-deprivation test lasted >12 hrs, it was often impractical and difficult to perform, especially in the younger child. Dunger et al. developed a

modified procedure - a shorter period of water-deprivation with measurement of urinary osmolality and arginine vasopressin (AVP) levels (Dunger et al. 1988). This test was first performed in 16 normal children aged between 2 and 12.5 years. Following 7-hour water deprivation, urinary osmolality ranged from 827 to 1136 mosmol / kg of water and urinary AVP concentrations from 114 to 320 pmol / litre. The normal ranges having been established, the study was then performed in a cohort of children with LCH (Dunger, Broadbent, Yeoman, Seckl, Lightman, Grant, & Pritchard 1989). Patients with frank DI had maximal urinary AVP concentrations between 1.7 and 12 pmol/l, with corresponding, maximal urinary osmolality levels between 97 and 218 mosmol/kg. The test was also performed every 6 months in 21 children who had LCH diagnosed < 4 years previously, who had no symptoms of DI. Three of these children developed DI during the course of the study. Of the 21 patients with no symptoms of DI, 16 had urinary AVP concentrations and osmolality measurements within the normal range, but 5 (24%) had concentrations between 42 and 57 pmol/l indicating a partial defect of posterior pituitary function. Concentrations of urinary AVP were therefore particularly useful in detecting patients with partial DI, who might not have been diagnosed on clinical grounds or by a standard water-deprivation test yet need careful follow up.

For several years, attempts have been made to halt progression of pituitary disease using external beam radiotherapy or chemotherapy with some anecdotal reports of improvement of posterior pituitary function following treatment for LCH (Greenberger et al. 1979). There is however, no good evidence that treatment alters the natural history of DI in LCH and complete DI is almost certainly, irreversible (Broadbent & Pritchard 1997;Rosenzweig, Arceci, & Tarbell 1997). There is the added concern that radiotherapy, especially in large doses, may result in anterior pituitary dysfunction. Therefore, pituitary radiotherapy is now rarely used. There is inferential evidence that the early institution of combination chemotherapy may prevent the development of DI (Ceci et al. 1993;Grois, Flucher Wolfram, Heitger, Mostbeck, Hofmann, & Gadner 1995), but this has not been substantiated by other groups of researchers. It has been postulated that the use of etoposide early in the active phase of the disease may reduce the chance of developing DI. However, there was no significant difference in the incidence of DI in patients treated on the 2 arms of the LCH 1 trial i.e. with vinblastine or etoposide. This suggests that etoposide might not be more effective than vinblastine at preventing pituitary damage. It is difficult to compare the incidence of DI in patients treated on different protocols, in different centres, as criteria used for

the diagnosis vary widely. There is still a body of opinion that holds that there may be a case for early, aggressive treatment in the prevention of diabetes insipidus. To establish whether or not this was true, a prospective, randomised study, with standardised guidelines for treatment and evaluation of patients would be needed.

1.5.10.2. Anterior Pituitary dysfunction

Growth retardation is a well-recognised sequela of LCH and is reported to occur in up to one third of patients (Avioli, Lasersohn, & Lopresti 1963). Possible causes for growth failure in children with LCH include chronic illness, treatment with steroids or radiotherapy and anterior pituitary dysfunction. Growth hormone (GH) deficiency occurs in less than 10% of patients with LCH (Ceci, Terlizzi, Colella, Loiacono, Balducci, Surico, Castello, Testi, Bernardi, Indolfi, Macchia, Madon, Mancini, & Rosati 1993;Dean, Bishop, & Winter 1986;Donadieu & French LCH Study group. 1996;Sims 1977). The granulomatous tissue of LCH tends to infiltrate the infundibulum and the hypothalamic region rather than the anterior pituitary gland itself, so it is likely that the endocrinopathy is either due to hypothalamic involvement by LCH, with deficiencies of hypothalamic releasing factors (Braunstein & Kohler 1972), or secondary to irradiation treatment (Dean, Bishop, & Winter 1986;Jorgsholm 1958).

GH deficiency has been clearly documented in patients with LCH. In 1972, Braunstein and Kohler evaluated anterior and posterior pituitary function in 13 children with "Hand-Schüller-Christian disease", 8 of whom had growth retardation. They found that in 7 of the 8 patients with short stature, and in 3 others who had developed the disease after reaching their final adult height, there was evidence of GH deficiency. They identified GH deficiency only in those patients who had DI, and postulated that a single hypothalamic lesion could explain both abnormalities (Braunstein & Kohler 1972). Latorre and colleagues studied pituitary function in 13 children with 'histiocytosis X', 8 of whom had heights below the 3rd centile and 3 on the 10th centile. Seven patients had low levels of GH in response to stimulation of whom 6 also had DI. Another 3 patients had DI without evidence of GH deficiency. They suggested that the association of anterior and posterior pituitary dysfunction was not invariable and that each might occur independently. They also found that of 6 patients who had received cranial irradiation, only 2 had evidence of GH insufficiency and concluded that irradiation of the skull did not necessarily cause GH deficiency (Latorre et al. 1974). On the other hand, Dean et. al. found that although 4 out of their 12 patients had evidence of impaired GH secretion, true

growth failure occurred in only one child who had received 3000 rads (cGy) to the hypothalamo-pituitary region. They concluded that 'classical' GH deficiency is not a common complication of histiocytosis and only seemed to occur if relatively high dose (3000cGy) hypothalamo-pituitary radiotherapy had been administered (Dean, Bishop, & Winter 1986).

The diagnosis of GH deficiency is a controversial issue (Rosenfeld et al. 1995;Rosenfeld 1997). It is commonly based upon the GH response to a provocation test (Hindmarsh & Swift 1995). Although these tests are considered to be the 'gold standard' for diagnosing GH deficiency, they do not reflect true physiological GH secretion. The cut off limit of adequate response depends on the assay used to measure plasma GH, the results of which can be variable (Celniker et al. 1989;Dattani et al. 1992). When considering results of GH stimulation tests, it is therefore important that the type of test performed and the assay used to measure GH are taken into account, as these factors can affect the interpretation (Nanduri et al. 1996).

Gonadotrophin deficiency is less common than GH deficiency and presents with delayed or arrested puberty. Adrenocorticotrophic hormone (ACTH) and thyrotropin (TSH) deficiency are very rare and usually develop in patients with a large hypothalamo-pituitary mass.

Hypothalamic damage: Hypothalamic involvement by LCH has been described in the past, but the emphasis has been on the endocrine manifestations of hypothalamo-pituitary involvement (Tabarin et al. 1991). It is less well recognised that hypothalamic damage in these children can result in the "hypothalamic syndrome" with abnormal eating patterns, temperature instability and behavioural abnormalities and these problems have not been reported in the literature as extensively as the hormone deficiencies.

Growth: Growth failure is a well-recognised problem in LCH (Avioli, Lasersohn, & Lopresti 1963;Braunstein & Kohler 1972;Latorre, Kenney, Lahey, & Drash 1974;van den Hoek et al. 1995). It can be caused by one or more factors including chronic illness, vertebral collapse following infiltration by LCH tissue, prolonged steroid therapy and growth hormone deficiency.

Replacement Therapy: Endocrinopathies of the posterior and anterior pituitary require replacement of the appropriate hormone. Desmopressin (1-desamino-8-D arginine vasopressin or DDAVP) is effective therapy for DI and various formulations including a solution and spray for intranasal use and oral tablets are now available. The liquid preparation orignially required refrigeration, making it difficult for children to keep their medication with them and have access to it when required. There were also problems due to inactivation of the drug when not stored at the appropriate temperature resulting in the medication being ineffective. The development of a new formulation has removed the necessity for refrigeration and has made it much more convenient. The tablet formulation is often preferred by older children and adolescents who find it easier to carry and less obvious when taken by mouth than using the spray.

The treatment of GH deficiency is now well established in children with LCH. Patients with GH insufficiency may require growth hormone injections during childhood and adolescence and those with severe GH deficiency may need to continue their treatment into adult life. Studies (Braunstein et al. 1975;Howell, Wilton, & Shalet 1998) have shown that GH replacement therapy, in appropriate doses, results in a significant improvement in growth rate, similar to that seen in children with GH deficiency due to other causes. There were no significant side effects from the treatment and no increase in the recurrence rate of LCH.

Gonadotrophin deficiency is managed by replacement of the appropriate sex steroid. Less is known about fertility and pregnancy in these patients on replacement and further long term follow up studies are necessary. Patients with ACTH deficiency need to be on life-long steroid replacement therapy and are at risk of 'adrenal crisis' during illness or in other stressful circumstances. TSH deficiency is managed by replacement with oral thyroxin.

Imaging: Computed tomography (CT) was initially used to delineate the anatomy of the hypothalamo-pituitary axis in patients with LCH. Magnetic Resonance Imaging (MRI) is now acknowledged to be a superior technique. It not only avoids the use of ionizing radiation, but is also more sensitive at detecting small lesions, which may be missed on CT. Another advantage is that scans can be performed in the sagittal plane, which is ideal for examining pituitary morphology (Broadbent et al. 1993). Enhancement with Gadolinium-DTPA has improved the sensitivity of MRI and increased the detection of both structural and functional abnormalities of the hypothalamo-pituitary axis in LCH (Rosenfield, Abrahams, & Komp 1990).

T-1 weighted MR images, in most normal individuals, show high signal in the postero-inferior portion of the pituitary fossa. This posterior pituitary hyperintensity is thought to represent the presence of Arginine Vasopressin (AVP) in the cells of the posterior pituitary and is absent in patients with DI (Brooks et al. 1989;Colombo et al. 1987;Gudinchet et al. 1989). However, 10% of the normal population lack the posterior pituitary 'bright spot' (Colombo, Berry, Kucharczyk, Kucharczyk, de Groot, Larson, Norman, & Newton 1987).

Patients with anterior pituitary hormone deficiencies may have a thickened stalk or a hypothalamic mass. The pituitary gland may either be enlarged or very small, with an 'empty sella' appearance. Maghnie *et al* in 1992, found that the pituitary stalk was thicker in 7 of 14 children with LCH in comparison with a control group of 28 normal children. They also confirmed that all patients with DI lacked the posterior pituitary bright spot (Maghnie et al. 1992a;Maghnie et al. 1992b).
The same group have shown that dynamic, fast-frame MR imaging in LCH patients with DI reveals delayed enhancement of the posterior pituitary lobe suggesting there may be a 'pituitary vasculopathy'. Patients with DI who have delayed enhancement are more likely to develop an evolving endocrinopathy with anterior pituitary dysfunction than those who have normal pituitary enhancement times (Maghnie et al. 1994).

1.5.11. Central nervous system (CNS)

There has recently been a great deal of interest in the involvement of the brain by LCH. Initial descriptions focused on the hypothalamo-pituitary manifestations, but in an early comprehensive review of CNS involvement by "histiocytosis X" Kepes described the wide range of clinical presentations and histopathological findings in this condition, reflecting involvement of different parts of the brain (Kepes 1979). LCH may cause symptoms and signs during the 'active' phase as a result of infiltration of the brain and meninges. However, they more often develop several years after the disease has 'burnt out' ('long term sequelae').

As little was known about the incidence and pattern of brain involvement by LCH, members of the Histiocyte Society designed and conducted an 'LCH-CNS' study. They collected information on 38 patients, with signs and symptoms of CNS involvement, from 27 institutions world-wide (Grois et al. 1998). As with DI (Dunger, Broadbent, Yeoman, Seckl, Lightman, Grant, & Pritchard 1989), CNS involvement

tended to be more common in patients with multisystem disease and in those with lytic lesions in the skull. Although neurological symptoms occasionally preceded the diagnosis of LCH, they tended to come on several years after the original diagnosis had been made (median 4 to 5 years). The exact symptoms and signs depend on the site and type of the lesion.

Space-occupying lesions of the brain may arise adjacent to bony skull lesions, from the meninges or from the choroid plexus. Although very rare, when present, symptoms are usually due to raised intracranial pressure or to direct damage of the involved tissue. Patients may present with headaches, vomiting, papilloedema, seizures, or focal neurological deficit. The lesions may be single or multiple and can involve the cerebrum (Cerda Nicolas et al. 1980;Kepes 1979;Kepes & Kepes 1969;Khan et al. 1980;Rube, De La Pava, & Pickren 1967), spinal cord or the meninges (Kepes 1979;Kepes & Kepes 1969;Rube, De La Pava, & Pickren 1967). Surgical intervention may be required if a lesion is causing pressure symptoms. As these lesions are due to infiltration by 'active' LCH, chemotherapy and/ or radiation have been used.

Cerebellar disease in LCH is well-recognised (Cervera et al. 1997;Haslam & Clark 1971;Iraci et al. 1979), with the first report in the 1930's (Chiari 1933). There have since been several descriptions of the clinical and pathological findings (Braunstein, Whitaker, & Kohler 1973;Hayward, Packer, & Finlay 1990;Iraci, Chieco-Bianchi, Giordano, & Gerosa 1979;Kepes 1979;Kepes & Kepes 1969;Rube, De La Pava, & Pickren 1967). Its true incidence is unknown, but is reported to range from 1 - 12% with symptoms developing up to 20 years after the original diagnosis of LCH (Grois, Favara, Mostbeck, & Prayer 1998). The onset is often insidious, patients presenting with tremor, incoordination and ataxia. The natural history of this complication varies considerably ranging from spontaneous arrest of symptoms, through gradual worsening, to rapid progression leading to incapacitation and dependency in some patients. Although cerebellar damage is usually a 'late' manifestation of the disease, it has been reported to be the presenting feature in one patient, several years before the diagnosis of LCH was actually made {(Haslam & Clark 1971). Most patients with cerebellar symptoms have no evidence of 'active' disease elsewhere and it is difficult to understand why there is continued worsening of symptomatology and signs on imaging, when there is no 'active' LCH in the lesions. The converse may also be seen – changes on MRI with no clinical signs of cerebellar involvement. The implications of these findings are not yet understood.

The lesions show demyelination (Kepes 1979) or gliosis (Grois, Favara, Mostbeck, & Prayer 1998), rather than infiltration with LCH cells. Kepes in his treatise, described what he called 'the most remarkable form of the disease', which involved diffuse or multifocal demyelination of white matter, now recognized as the histopathological appearance seen in the cerebellum in patients with ataxia and incoordination.

The cause and pathogenesis of cerebellar involvement in LCH are uncertain but there is a view that the damage may be cytokine mediated. It has been suggested that there could be similarities between the pathology of CNS involvement in LCH and that seen in HIV-related dementia (Histiocyte Society workshop on CNS disease in LCH 1997). Patients with HIV demonstrate an excessive activation of glutamate receptors by neurotoxins or cytokines, apparently secreted by stimulated macrophages or microglia, associated with neuronal injury and cell death (Lipton & Gendelman 1995;Lipton & Rosenberg 1994). An autoimmune mechanism of brain damage has also been postulated after the discovery of autoantibodies to vasopressin-secreting cells in patients with LCH and DI (Scherbaum et al. 1986). However, as these results have not been confirmed by other workers, and the damage does not respond to treatment with steroids which are often useful in other 'auto-immune ' conditions, it is still a matter of speculation.

Imaging: Cerebellar involvement is usually seen as bilateral, symmetrical signal change on MRI scan. Infiltrative lesions of the cerebrum, spinal cord and meninges often enhance with gadolinium, but lesions of the cerebellum, pons and basal ganglia tend not to enhance. The LCH-CNS study originally group proposed a rather complex classification of the morphology of lesions on MRI scanning into 6 main types (Grois, Favara, Mostbeck, & Prayer 1998) -Type I white matter changes, Type II gray matter changes, Type III meningeal abnormalities, Type IV abnormalities of the hypothalamo-pituitary region, Type V – atrophy and Type 6 treatment – related changes. This classification is now felt to be too complicated for everyday use, and does not necessarily directly correlate with the clinical findings. A new classification has now been proposed – axial (involving brain-cerebrum, cerebellum, brain stem) and extra-axial (involving structures that lie outside the CNS - the hypothalamo-pituitary region and meninges) (Grois et.al personal communication). This classification will now be adopted by the CNS study group to categorise patients and it is hoped that it will be used by all groups to enable a 'single language' to be used internationally.

Several types of treatment including corticosteroids, cyclosporin A, interferon and intravenous immunoglobulin, have been tried in patients with progressive cerebellar involvement, but there is no convincing evidence that any of these work. In the CNS-LCH study no specific agent was found to be truly effective. A trial of retinoic acid has been tried, by the French LCH study group, in patients with neurological impairment (Donadieu et al- unpublished data). A recent finding of an increase in pineal cysts in patients with CNS disease (Grois et al, unpublished data) has led to speculation about the role of the pineal gland, and its secretory product melatonin, in the pathogenesis of CNS disease. It had been suggested that melatonin may be useful in the treatment of patients with progressive neurological deterioration.

Neuropsychological sequelae: Survivors of childhood cancer, in particular leukaemia, have neuropsychological sequelae (Mulhern 1994). Cranial irradiation and intrathecal methotrexate used for CNS directed therapy have been shown to cause cognitive deficits in survivors of acute lymphoblastic leukaemia (ALL) (Copeland 1992). Learning deficits have now been identified in patients with LCH but, unlike those cured of ALL, the LCH patients have had no intrathecal methotrexate and most have not had any cranial irradiation. It therefore appears that the disease process itself is in some way responsible for the damage. Neuropsychological sequelae of LCH include learning deficit, delayed development, poor school performance and emotional disturbance. In an assessment of 4 patients with cerebellar involvement, 3 had associated intellectual impairment (Braunstein, Whitaker, & Kohler 1973). In a study by Ransom, 7 of 15 patients had an Intelligence Quotient (IQ) below average (Ransom et al. 1978). The Southwest Oncology Group found that of 60 survivors of 'histiocytosis X', 5 had an intellectual deficit (Komp et al. 1980). The most recent report (Whitsett et al) is a detailed neuropsychological assessment of 2 children who had neurological involvement. Both patients showed marked deficits in global intellectual functioning (measured by WISC-III) with IQs below the 20th percentile. They also had deficits in short term memory, and behavioural abnormality. All these are retrospective reports of patients with clinical CNS involvement and no study, as yet, has looked at the neuropsychological outcome in patients who do not have neurological symptoms or signs. This is one of the questions addressed by this study.

Section 1.6. Diagnosis of LCH

1.6.1. Histopathology

The histopathology of LCH is usually similar in the lesions, regardless of the distribution and severity of disease, but may occasionally be influenced by the site of the lesion and its age.

Morphology

The granulomatous lesions of LCH consist of collections of inflammatory cells, including lymphocytes, neutrophils, eosinophils and the characteristic 'LCH cells'. On staining with Haematoxylin and Eosin (H&E) 'LCH cells' are mononuclear and measure about 12μm in diameter. Each has homogeneous pink cytoplasm and a single lobulated nucleus, often with a groove, giving it a "coffee-bean" appearance. Multinucleate giant cells, which lack the characteristic markers of LCH cells, may also be seen within the lesions. A significant proportion of 'LCH cells' stain with proliferation markers such as Ki-S1 and Ki-67, indicating that they are dividing in the involved tissue rather than simply migrating to the site (Hage et al. 1993). Early on in the disease the lesions are proliferative and large numbers of histiocytes are present, but later in the course of the illness, the lesions become less cellular, with more necrosis and fibrosis. Organs such as the lung and liver show marked fibrosis, often progressing to lung fibrosis and cirrhosis, respectively.

Immunohistochemistry

Positive cytoplasmic staining for S-100 protein is seen in approximately 60% of LCH cells. Peanut lectin/peanut agglutinin (PNA) is a membrane marker but may stain as a paranuclear 'dot' and is a sensitive marker of skin involvement. 'LCH cells' also stain positively with ATPase and α-D-mannosidase and are strongly positive to anti-CD1a antibodies (**Fig.1.11**).

Electron Microscopy

Birbeck granules are pathognomonic of both normal (LC) and pathological Langerhans' cells ('LCH cells'). The characteristic Birbeck granule is a pentalaminar rod and/or racquet-shaped structure, felt to represent an infolding of the cell membrane in an attempt to increase the cell's surface area to enhance antigen presentation (**Fig. 1.12**).

Figure 1.11. Positive immunostaining of LCH cells with CD1a antibody
LCH cells show characteristic membrane staining with CD1a antibody.

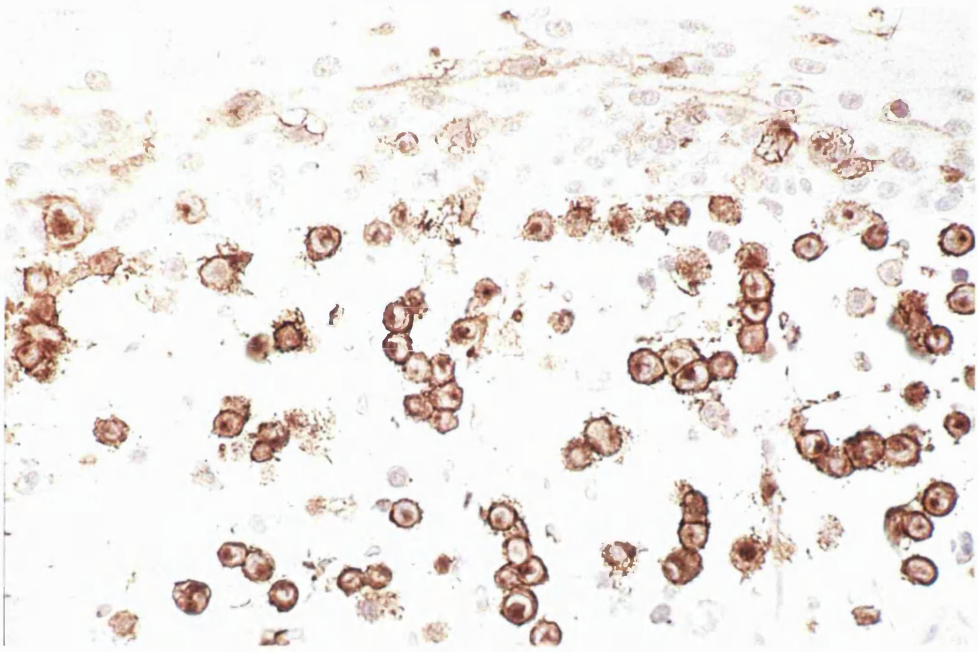
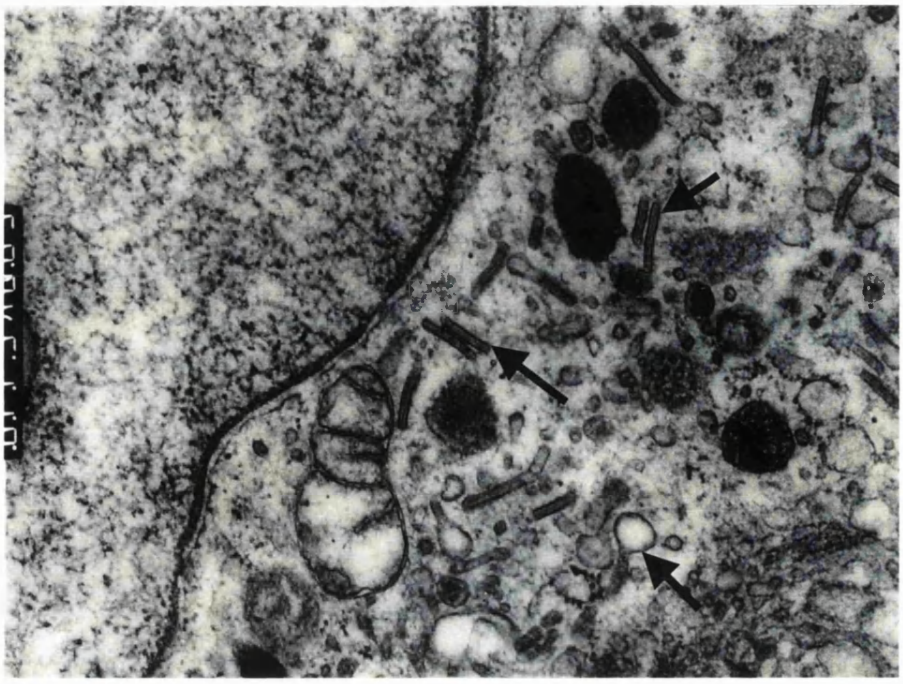


Figure 1.12. Birbeck granules
Electron microscopy of Langerhans cells showing the characteristic laminar Birbeck granules.



1.6.2. Diagnostic Criteria

In 1987, the Writing Group of the Histiocyte Society defined objective criteria for the histopathological diagnosis of LCH (Writing group of the Histiocyte Society, Chu, D'Angio, Favara, Ladisch, Nesbit, & Pritchard 1987). A **'presumptive diagnosis'** was made when the findings on light microscopy using conventional stains (Haematoxylin &Eosin) were felt to be 'consistent' with those described in the literature. A **'diagnosis'** could be made when, in addition to these findings, the biopsy material showed two or more of the following: positive stain for ATPase, S-100 protein, alpha- mannosidase, or characteristic binding of peanut lectin (PNA). In addition to the light microscopy findings, a **'definitive diagnosis'** required the identification of Birbeck granules by electron microscopy or positive staining with CD1a antibody.

The discovery (Krenacs, Yidzavicz, & Boumsell 1993) of the monoclonal antibody 010, which detects CD1a in formalin-fixed and paraffin-embedded tissues, made the diagnosis of LCH easier. It became possible to make a diagnosis without using frozen tissue. Since there was no longer any need to use the less specific markers S-100, alpha- mannosidase or PNA, it was felt that only two levels of confidence in the diagnosis of LCH were now required (Favara, Feller, Pauli, Jaffe, Weiss, Arico, Bucsky, Egeler, Elinder, Gadner, Gresik, Henter, Imashuku, Janka-Schaub, Jaffe, Ladisch, Nezelof, & Pritchard 1997). Therefore **'definitive diagnosis'** now requires either demonstration of Langerhans' (Birbeck) granules on electron microscopy (the 'gold standard') or CD1a antigen on the lesional cells, using either conventional antibody on frozen sections or the 010 antibody on paraffin sections. A **'presumptive diagnosis'** is made on the basis of conventional histology (H&E staining) alone.

1.6.3. Diagnostic Evaluation

The Histiocyte Society's approach to the clinical and laboratory evaluation of children with LCH stresses the need for a uniform assessment for all patients (Clinical Writing Group of the Histiocyte Society et al. 1989). The Group suggests mandatory baseline clinical, laboratory and radiographic assessment of all patients, with further tests to be performed in specific cases. The use of these guidelines results in uniform criteria for diagnosis and investigation that assist in the development of international collaborative studies for treatment and follow up of patients with LCH.

Section 1.7. Treatment

Over the decades many different types of therapy have been used, influenced by the contemporary theory of pathogenesis of LCH. Hand used opium and quinine in an attempt to control the fever and systemic upset (Hand 1893) and Christian successfully used pituitary extract to ameliorate polyuria and polydipsia (Christian 1920). Fraser reported that radium packs over affected bone and deep radiotherapy assisted healing (Fraser 1935). He discussed other options for management, including a cholesterol free diet, with a high percentage of green vegetables and pituitary extract for patients with diabetes insipidus, but felt that deep radiotherapy was the most useful. Jaffe and Lichtenstein felt that the surgical treatment of choice for their patients with eosinophilic granuloma was wide excision, or curettage. Although they often used post-operative roentgen therapy, they suggested that it might not be essential for recovery (Jaffe & Lichtenstein 1940). Others also recommended curettage followed by radiotherapy (Green & Farber 1942).

Before and during the 1950's the disease was felt to be infective in origin and was often treated with antibiotics (Aronson & Lind 1951;Bierman, Lanman, & Dod 1952). The next decade brought forth the theory that histiocytosis was a malignant condition. Following the recognition that chemotherapy was effective in the treatment of leukaemia, between 1960-1970, several groups published their results of treatment of histiocytosis with single or combination chemotherapy (Al-Rashid 1970;Beier, Thatcher, & Lahey 1963;Hertz & Hambrick 1968;Lahey 1970;Segni, Mastrangelo, & Tortorolo 1968). The drugs used included vinblastine, vincristine, daunamycin, chlorambucil, cyclophosphamide, 6-mercaptopurine, methotrexate and etoposide. Corticosteroids were also found to be effective, both for isolated skin involvement and for multisystem disease (Avioli, Lasersohn, & Lopresti 1963;Cox 1955;Goldberg & Diamond 1965;Hertz & Hambrick 1968), and are still in common use. Combinations of chemotherapy and corticosteroids were tested with success. Lahey compared 3 treatment regimens (vinblastine alone versus vinblastine and prednisone versus 6-mercaptopurine and prednisone) and found that they were equally effective, with no statistical difference between the response rates in the 3 groups (Lahey 1975b). In the 1980's a change in thinking lead to the concept that LCH was an immunological condition and treatment with both crude and synthetic thymic hormones was reported (Davies et al. 1983;Osband, Lipton, & Lavin 1981).

The formation of the Histiocyte Society in 1985 made it possible to systematically collect data on a large group of patients and to ensure that they were evaluated in the same way. Later, randomised trials of treatment were initiated by the Society, leading to the establishment of standardised protocols in centres across the world. Current therapeutic regimens are usually based on the extent of disease. Patients with single system involvement often have little or no treatment, while those with multisystem involvement usually require systemic therapy with one or more agents.

1.7.1. Single System involvement

Isolated, single bone lesions can often be treated conservatively. Painless lesions can be managed by a "wait and watch" policy. Curettage of the lesion is often therapeutic, as it seems to accelerate healing. The injection of intralesional steroid is also useful (Egeler et al. 1992). Local radiotherapy is no longer generally recommended in view of sequelae, such as its effect on growth of bone and soft tissue, anterior pituitary dysfunction following pituitary radiotherapy and the development of secondary tumours in the field of radiation. However, it may be indicated as an emergency treatment in patients with compromise to vital structures, such as the eye or spinal cord. Patients with polyostotic involvement may need therapy with oral corticosteroids. An alternative is the non-steroidal anti-inflammatory agent indomethacin, which has been shown to have not only an analgesic effect, but also possibly accelerates bone healing (Munn et al. 1999). More recently concerns have been raised that polyostotic disease may have a worse outcome than involvement of single bones and it has been suggested that these patients receive more rigorous treatment (LCH III protocol). Skin involvement may be treated with topical corticosteroids, or in more severe cases by the topical application of nitrogen mustard, which has been shown to be both effective (Sheehan et al. 1991) and, in the medium term at least, safe (Hoeger et al 1999).

1.7.2. Multisystem disease

The most appropriate treatment strategy for patients with involvement of several systems, but no 'organ dysfunction', has not yet been established. In the 1980's there were two main schools of thought – those who believed in polychemotherapy and those who considered that 'conservative treatment' was as effective and less toxic. (McLelland et al. 1990). Over the years great effort has been put into the

development of collaborative treatment trials which have taken into consideration the various options.

Standard management, these days, consists of the use of combination chemotherapy. The first large prospective trials of treatment, DAL-HX83/90 were organised by the German- Austrian group and stratified patients according to "risk groups" (Gadner et al. 1994a) (Minkov et al. 2000). Treatment in the DAL-HX83 consisted of an induction with etoposide, vinblastine and prednisoslone followed by a years consolidation with 6-mercaptopurine, vinblastine, steroid in all patients with additional etoposide and methotrexate in those patients in the higher risk groups. In the first Histiocyte Society study - the LCH I trial- (Ladisch et al. 1994), patients were randomly assigned to receive a 24 week course of either etoposide 150 mg/m^2 for 3 days every 3 weeks, or vinblastine 6 mg/m^2 weekly. Patients in both arms also received an initial bolus of methyl prednisolone 30mg/kg daily for 3 days. The aim of the study was to compare the response rate, rate of reactivation and morbidity in the 2 arms. The most important finding was that evaluation at 6 weeks was the best predictor of response, with failure to respond at 6 weeks predicting a poor outcome. There was no statistical difference between the responders and non-responders in terms of age, number or type of organs involved or the presence of organ dysfunction. Those patients who did not show a response at 6 weeks on one arm of the treatment trial were switched to the other arm. One third (34%) of these patients had a favourable outcome, but the others did not. There was no significant difference in the two treatment arms in respect to initial response, number of reactivations, sequelae or mortality (Gadner et al. 2001).

The LCH-I study results were compared retrospectively, by case-control methodology to the DAL-HX 83/90 studies. Kaplan-Meier analysis showed that survival, event-free survival and reactivation-free survival were higher in patients treated on the DAL-HX trials. It was not clear if this apparent benefit was due to the inclusion in the DAL studies of a) continuous prednisolone b) the combination of etoposide and vinblastine or c) continuation therapy with 6-mercaptopurine for a year. To clarify some of these questions a new treatment trial was needed.

In an attempt to identify patients with multisystem involvement who did not require polychemotherapy, data from the LCH I and DAL trials were compared. Retrospective analysis of the characteristics of patients who responded to therapy revealed that a sub group (20%) of patients with multisystem involvement had a 90% probability of response and a 100% probability of survival. This group consisted of children, over the age of 2 years, who did not have involvement of the

lungs, liver, spleen or bone marrow. As a consequence, they were classified as being at "low risk" (of recurrence and mortality). All patients with multisystem disease with involvement of at least one of the following organs – bone marrow, liver, spleen or lungs – were categorised as "Risk Group" patients i.e. those at high risk of morbidity and possibly mortality.

The LCH II study opened on 1st May1996 and closed in 2001. In this clinical trial, patients in the "Risk Group" category were randomized to initial treatment with oral prednisolone and vinblastine with or without the addition of etoposide. Treatment arm A consisted of an initial 6-week period of treatment with continuous prednisolone and weekly vinblastine, followed by continuation therapy for 18 weeks, with 3 weekly vinblastine and a 5 day pulse of prednisolone, in combination with daily 6-mercaptopurine. Treatment arm B contained additional etoposide administered at the same time as the vinblastine. As "low risk" patients have been shown to have a good outcome despite minimal therapy, they were excluded from the randomisation and received an initial 6 weeks of continuous prednisolone and weekly vinblastine, followed by a 6 month continuation with 3 weekly vinblastine plus pulsed oral steroid. As the LCH-II study showed no advantage with Etoposide, and this agent is known to predispose to malignancy, a decision was made to exclude this drug from the next trial. The current LCH-III trial opened in May 2001. It consists of an initial 6 week induction of remission using vinblastine and prednisolone followed by a period of maintenance lasting 6months or 1 year with further doses of vinblastine and steroid in combination with 6-mercaptopurine and methotrexate.

There is still controversy regarding the best treatment for patients with multisystem disease. Conservative management with steroids or single agent chemotherapy is well tolerated, has few side effects and there is virtually no requirement for hospital admissions because of treatment complications. In one non-randomized study, response to treatment and mortality were comparable in patients treated conservatively or with polychemotherapy (McLelland, Broadbent, Yeoman, Malone, & Pritchard 1990), but it has been suggested that patients treated on more aggressive protocols have fewer long term sequelae. This view is supported by data from the DAL-HX studies (Gadner et al. 1994b). Patients treated on the DAL protocol had a 15% chance of developing diabetes insipidus, compared to 42% on the LCH I treatment (monotherapy – vinblastine or etoposide). However, the patients in these various studies were treated over different time periods and at

different institutions making direct comparisons difficult. Criteria for patient selection also varied so there was an inherent selection bias. The prevalence of long term sequelae also varies between studies and depends on the methods used to detect them. For instance, criteria for definition and diagnosis of DI have not been standardised, so institutions that measured urinary AVP levels in addition to urine osmolality, detected patients with partial DI and therefore reported a higher incidence than others where DI was diagnosed clinically or by a standard water-deprivation test. Factors, including referral patterns, selection criteria and specific investigation need to be considered before the efficacy of a particular protocol can be assessed.

1.7.3. Other treatment options

Several other forms of treatment have been tried over the years, especially in patients with no response to 'standard' therapy. However, there is a difficulty in assessing the relative value of these therapies, often used on a "one-off" basis. There is certainly a publication bias, with negative findings often not being published. A forum such as the Histiocyte Society is useful in comparing results of treatment and discussing the way forward with new agents. In this setting, surveys of the use of new agents or methods are more likely to identify the true 'denominator', rather than published studies with their inherent reporting bias.

Cyclosporin: Cyclosporin A is an immunosuppresive and immuno-modulatory agent, which selectively inhibits the cellular immune response and cytokine-mediated cell activation. It blocks transcription and synthesis of lymphokines such as interleukin-2 (Lillehoj & Shevach 1985) and inhibits function of Langerhans cells in vitro (Furue & Katz 1988). Cyclosporin A has been reported to be effective in the treatment of children with LCH (Arico et al. 1995;Mahmoud, Wang, & Murphy 1991) and is relatively non-toxic and well tolerated. It was included in the first LCH-S (salvage) protocol for patients with progressive disease.

Bone marrow transplant: Following the discovery that cutaneous Langerhans cells arise from the bone marrow (Katz, Tamaki, & Sachs 1979), it was postulated that it may be possible to 'cure' the condition by bone marrow transplant (BMT). Morgan reviewed the outcome of 6 patients who had received myeloablative therapy for aggressive disease, followed by BMT, after failure to respond to 'standard' therapy (Morgan 1994). Four patients received an allogeneic graft from an HLA-matched sibling and in 3 of them successful engraftment of donor marrow

was seen. In the fourth patient LCH recurred. Of the two patients who received autologous marrow, one remained well and disease free. In the second patient, who died soon after transplant, LCH cells were identified on autopsy. Morgan concluded that BMT was a therapeutic option in patients with aggressive disease who had a poor prognosis on standard treatment. Marrow-ablative therapy followed by BMT was incorporated into the LCH-S study and was used in patients who had a matched donor available but, the results were disappointing.

2-Chlorodeoxyadenosine (2CdA) and 2' Deoxycoformycin (2dCF): 2 CdA is a purine analogue known to be toxic to monocytes and felt to be the most promising 'new' agent. It has been shown to have an excellent response in adults with hairy cell leukaemia and chronic lymphocytic leukaemia, and has a cytotoxic effect on monocytes and lymphocytes. It also has an immunosuppressive effect. It was therefore felt that 2CdA might have a useful role in the treatment of refractory LCH. There have been several reports of its use in patients with LCH with some responses and without major toxicity (Stine et al. 1997) and these reports have been summarised (Arceci, Brenner, & Pritchard 1998). 2 CdA has been used by the Histiocyte Society as salvage therapy for patients with refractory disease. Side effects include immunosuppression, prolonged lymphocyte depletion and neurotoxicity at high dose. The ideal dose and duration of treatment are not known. 2' Deoxycoformycin (2dCF) has also been used successfully as salvage therapy in the treatment of a few patients with resistant disease, with few toxic effects (Lombardi et al. 1997;McCowage, Frush, & Kurtzberg 1996).

Monoclonal antibody therapy: The monoclonal antibody NA1/34 has been shown to specifically target the CD1a+ve 'LCH cells' in vivo by binding to CD1a antigen on the cell surface (Kelly et al. 1994) and has been used successfully in imaging the disease (Kelly et al. 1993) (Chu et al personal communication). There is interest in the potential use of this antibody for "targeted" therapy in LCH (Kelly & Pritchard 1994) with or without a bound cytotoxic radiopharmaceutical compound such as I^{131}. Limiting factors at present include the propensity of the antibody, which is murine, to induce anaphylactic reactions and the limited supply of available antibody. *Humanising* the antibody may be the way forward.

Section 1.8. Long term sequelae

As treatment for children with Langerhans' cell histiocytosis has improved, so has long term survival. Patients with single system disease are often completely normal, but there are now a number of adolescents and young adults with sequelae of multisystem disease. Residual disabilities are seen in more than half the survivors of LCH (Komp 1981;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996). These problems are regarded as being the consequence of scarring of the various tissues/ organs affected by the disease. Treatment-related consequences are also seen, but unlike survivors of cancer, sequelae in children surviving LCH are predominantly 'disease-related'. 'Organ damage' can involve any of the systems initially affected by the disease and there can be overlap between 'active' disease and sequelae/permanent consequences in the same patient. The specific sequelae are described in the section on clinical features and in later chapters.

Table 1.1. Long term sequelae of LCH

LCH	Sequelae
Bone	Deformity, facial asymmetry
	Dental problems
Orbits	Residual proptosis, rarely visual loss
Ear	Deafness
Skin	Scarring, xanthomata
Brain	Cerebellar ataxia Learning difficulty Hydrocephalus, meningeal plaques
Hypothalamus and Pituitary	Diabetes insipidus GH and other anterior pituitary deficiencies Hypothalamic syndrome
Liver	Sclerosing cholangitis
Lung	Pulmonary fibrosis
Lymph nodes	Chronic discharging sinuses
General	Growth retardation
Consequences of therapy	Secondary malignancy Radiation sequelae

1.8.1. Long term follow up studies

There have been a number studies of long term follow up of children with LCH. Most studies have described the outcome of patients from a single institution. (Braier et al. 1999;Lahey 1975;Raney, Jr. & D'Angio 1989;Sims 1977;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996) or from multi-centre treatment trials from various countries (Ceci, Terlizzi, Colella, Loiacono, Balducci, Surico, Castello, Testi, Bernardi, Indolfi, Macchia, Madon, Mancini, & Rosati 1993;Donadieu & French LCH Study group. 1996;Gadner et al. 1994). Reports of long term sequelae are usually derived from case note reviews and/or questionnaire-based assessments (Donadieu & French LCH Study group. 1996;Gadner, Heitger, Grois, Gatterer-Menz, & Ladisch 1994;Sims 1977;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996). Very few reports are a result of examination and re-evaluation of patients at follow up (Sims 1977).

Sims et al describe the follow up of a cohort of 43 cases with both single system and multisystem LCH (histiocytosis X) seen at a single institution over a 29 year period (Sims 1977). Of the 43 patients, 29 (67%) survived and of them 28 were traced. Those who lived near the hospital (14 patients) were seen personally and the rest were sent questionnaires regarding outcome. Fifteen of the 29 (52%) had a detectable disability. Diabetes insipidus was the most common problem, occurring in 14 patients. Five adults had short stature, 3 of whom had had suboptimal growth hormone response to hypoglycemia. One patient had received GH therapy for a year, at the age of 19 years, with no improvement in growth. In 1 patient collapse of several vertebrae contributed to the ultimate short stature. Twelve patients underwent further investigations including blood counts and immune function, all of which were normal. Of 11 patients who had lung function tests performed, 1 had a reduced vital capacity and 3 had low forced expiratory volumes and peak flow rates. Reduced IQ was described in 3 subjects, but was felt to be possibly unrelated to the histiocytosis.

In a study published by the Southwest Oncology group, long term sequelae were systematically evaluated in a cohort of 60 children who had survived more than 5 years after the diagnosis of LCH (Komp, El Mahdi, Starling, Easley, Vietti, Berry, & George 1980). Half the survivors ahd sequelae the most common being DI, short stature, neurological and intellectual deficit and chronic lung disease.

A report from the Italian Cooperative study looked at a cohort of 90 patients with LCH (50 single system, 40 multisystem involvement) treated in the multicentre AIEOP_CNR_H.X '83 trial. They found that the overall incidence of disease related diasability was 47.7% the main problems being DI in 20%, orthopaedic abnormalities in 15%, growth defect in 5% and tooth loss and chronic hepatitis in 3% each. Only 1 patient developed cerebellar ataxia and 1 developed leukaemia probably secondary to etoposide treatment.

The largest study was conducted by the French Langerhans Cell histiocytosis study group, which collated data from 348 cases of LCH (50% isolated bone involvement, 39% soft tissue involvement, 11% organ dysfunction) diagnosed between 1983 and 1993 (Donadieu & French LCH Study group. 1996). Data were collected retrospectively using questionnaires filled out by clinicians in the individual treating hopsitals. In this series, 21.9% of patients had sequelae – DI in 17.5%, GHD and short stature in 4.7%, neurological abnormalities in 4%, and thyroid deficiency, orthopaedic disability and deafness in 2.5% each. Other sequelae were less frequent.

A study from the University of California (Willis et al. 1996) looked at 71 patients (43 single system, 28 multisystem) presenting over a 25 year period. Follow-up data were gathered using a mailed survey and telephone questionnaire sent to the families. This series reported the greatest prevalence of sequelae – 64%, with the most common being skeletal defects (42%), dental problems (30%), DI (25%), growth failure (20%), hearing loss (16%) and CNS dysfunction (14%). It is difficult to explain why patients in this series had such a high prevalence of sequelae, but it could be partly explained by acquistion of information from the families, rather than just collecting information from patient case notes.

Most studies have assessed all patients with LCH, and found that patients with single system involvement tend to have minimal (orthopaedic) or no sequelae. The patients with permanent consequences of the disease have usually had multisystem involvement (Ceci, Terlizzi, Colella, Loiacono, Balducci, Surico, Castello, Testi, Bernardi, Indolfi, Macchia, Madon, Mancini, & Rosati 1993;Henck et al. 1996;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996). Survivors of multisystem LCH are therefore the group of patients most in need of carefully planned assessment of sequelae of the disease, which is the basis of this study.

Table 1.2. Published studies of outcome in LCH

This table summarises the published studies of outcome in LCH.

Author, Date of Pubn	No. of patients	Survival	Prevalence of sequelae	Type of sequelae	Type of assessment at follow up
Sims 1997	43	67%	52%	Diabetes insipidus (DI), short stature	Questionnaire & examination Haematology/immunology investigation, lung function
Komp 1980	75	80%	50%	DI, short stature, neurological and intellectual deficit, chronic lung disease	Case note review, Clinical examination/ investigation
Ceci 1993	90	93%	48%	DI, orthopaedic disability, growth defect, loss of teeth, ataxia	Reported sequelae from participating institutions
Gadner 1994	106	91%	20%	DI, orthopaedic disability, growth defect, loss of teeth, lung / liver fibrosis	Reported sequelae from questionnaires sent out to participating institutions
French LCH study group 1996	348	92%	22%	DI, short stature, orthopaedic disability, neurological disorders, deafness, lung fibrosis	Reported sequelae from participating institutions
Willis 1996	71	88%	64%	Skeletal defects, dental loss, DI, growth failure, hearing loss, neurological deficit	Case note review, mail and telephone questionnaire

To summarise, there are insufficient data available about the incidence and prevalence of long term sequelae in survivors of LCH. Methods of diagnosis, treatment protocols and management of LCH and assessment of late effects have varied between individual institutions and countries. So it is difficult to compare data to arrive at firm conclusions regarding the most important "risk factors" for developing sequelae, defining the kind of treatment protocols which would minimise these problems and the best method of assessing long term outcome. Multidisciplinary, cross-sectional and prospective studies are required before conclusions can be drawn. The development of guidelines by the Histiocyte Society to assist in diagnosing and evaluating patients has helped to standardise methods internationally (Clinical Writing Group of the Histiocyte Society, Broadbent, Gadner, Komp, & Ladisch 1989). The development of guidelines for assessment of sequelae in survivors is the next objective.

Our study was developed to assess systematically sequelae in survivors of multisystem LCH. A better understanding of the chronology of development of sequelae would help in planning follow up after LCH and to decide on the ideal timing of investigation and intervention. This would have implications for future planning and allocating of resources for these patients. This study would provide a baseline, which in turn, could lead to clinical improvements in the future giving patients the best outcome with the least long term consequences.

Section 1.9. Aims and Objectives of this study

The aim of the study was to provide a better understanding of the sequelae of LCH and to provide a baseline upon which further studies could be based.

The main objectives were

a) to assess the prevalence and severity of sequelae in a cohort of patients with multisystem LCH, diagnosed and managed at one institution
b) to attempt to identify "risk factors", including treatment, involved in the development of these sequelae
c) to assess the impact of the disease and its sequelae on the patients' functional status and their ability to integrate into society and
d) to develop a "morbidity score" which would help in standardising assessment of late effects in patients from different institutions

Chapter 2. Patients and Methodology

This study was performed at Great Ormond Street Hospital for Children NHS Trust, a large paediatric teaching hospital, which has had a specific interest in the histiocytoses for over 20 years and has one of the largest single cohorts of patients in the world. As this is a tertiary centre, we do recognise that there is probably an inherent referral bias with the more severely affected patients being seen at this institution. However, several patients with single system disease were also seen.

Section 2.1. Patients

Criteria for inclusion

1. Patients with biopsy – proven Langerhans' cell histiocytosis
2. Multisystem disease i.e. involvement of two or more systems
3. More than five years from end of treatment i.e. 'long term survivors'.
4. Clinical consultations at Great Ormond Street Hospital for Children, NHS Trust.

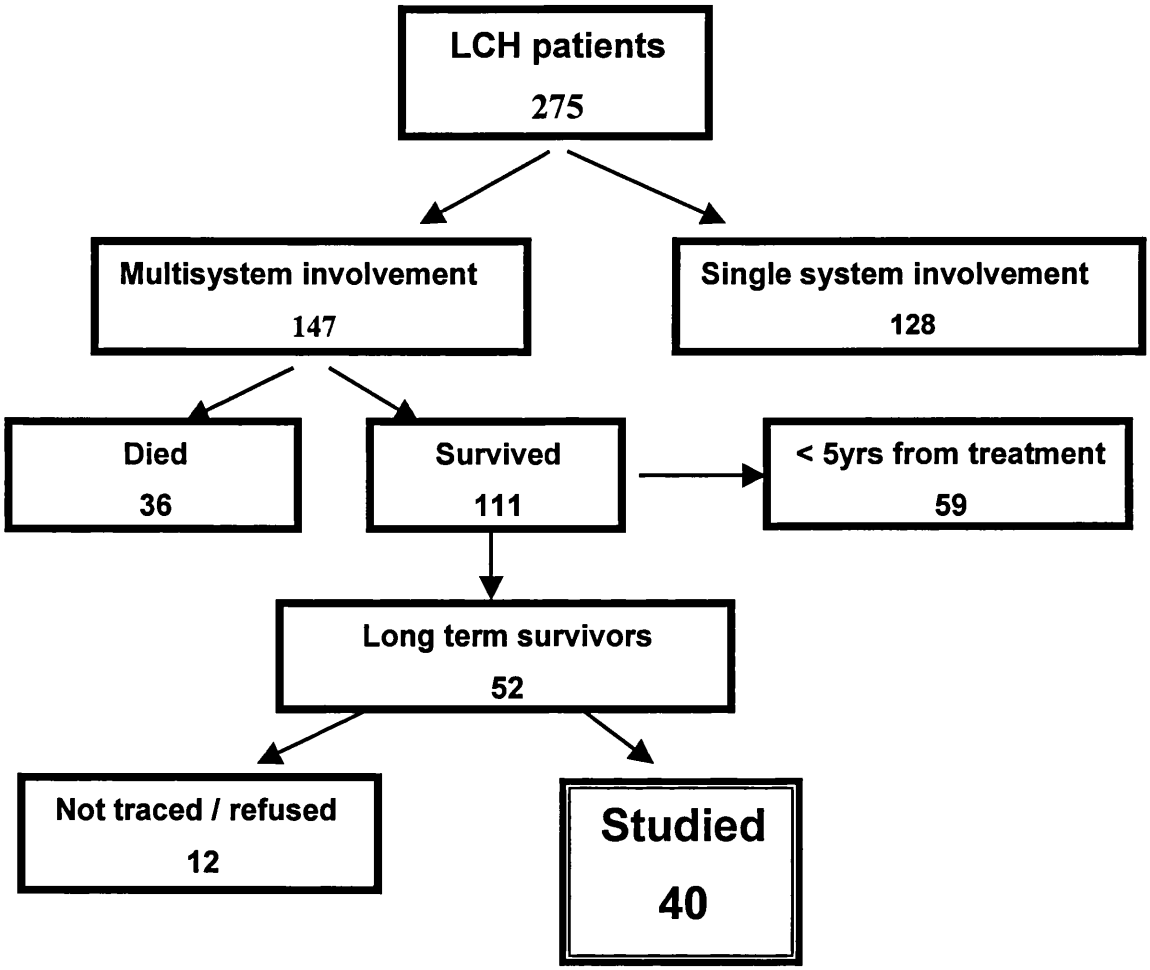
During the period 1966 to 1998, 275 patients with LCH were seen at the hospital. Of these children, 52 (18.9%) fitted the selection criteria for the study (**Fig. 2.1**)
The case notes were reviewed and details recorded of date of onset of illness, date of diagnosis, systems involved, treatments received and any known long term sequelae. Further details were obtained on interview of the subject and parents.

Description of the patient population

The study cohort consists of 40 patients with multisystem involvement who had LCH diagnosed on biopsy of one or more tissues. There were 21 boys and 19 girls and all were more than 5 years from the end of treatment. The age at diagnosis ranged from 6 weeks to 15.5 years (median 17.5 months, mean 29.2 months). The age at assessment ranged from 7 to 31.1 years (median 16.4 yrs, mean 16.7 yrs). The period of follow up after completion of therapy was 5 to 23 years (median 11.2 yrs, mean 11.9 yrs). Details of the patient's gender, age at diagnosis and the systems involved are given in **Table 2.1**. The systems involved in the 'active' phase of the illness are summarised in **Fig.2.2**. As would be expected, most patients had involvement of the bone and skin, and in nearly half the hypothalamo-pituitary axis was involved. As occult involvement of other systems is often present, this is a minimum estimate of the degree of involvement.

Figure 2.1. Patient Population

This algorithm shows the total number of patients treated at the Institution between 1966 to 1988, and the method of selection of long term (>5 years from end of treatment) survivors of multisystem LCH for this study cohort.



Treatment

As these patients were treated over a period of several years, a variety of agents were used, including oral steroids, chemotherapy, radiotherapy and immunotherapy. Most patients received more than one treatment modality. The details of individual treatments received, including dose and site of radiotherapy and cumulative doses of steroid are given in **Table 2.2**.

Ethical Approval and Consent

Ethical approval for the study was obtained from the Great Ormond Street Hospital Ethics Committee. The aims and nature of the study were explained to all subjects and their families by the author, and reinforced by written information. Informed written consent was then obtained from the older children, adolescents and adult subjects and from one or both parents of the younger children and of those with learning difficulty.

Table 2.1. Patient details

This table shows the age at diagnosis of LCH and the systems involved in the active phase of the disease in individual patients. The numbering is based on the alphabetical order of the names of the patients. These data have been omitted to maintain confidentiality.

Pt No.	Gender	Age at diagnosis (months)	Systems involved in the 'active' phase
1	F	39	Bone, Skin, Ears, Lymph nodes, Pituitary
2	F	6	Skin, Lungs, Liver, Spleen, Lymph nodes
3	M	11	Bone, Skin, Ears, Mouth, Pituitary
4	F	124	Bone, Skin, Ears, Hypothalamus and Pituitary
5	F	17	Bone, Skin, Ears
6	M	5	Bone, Skin, Ears, Mouth, Bone marrow
7	M	92	Bone, Pituitary
8	F	35	Bone, Pituitary
9	F	35	Skin, Mouth, Lymph nodes
10	M	22	Bone, Skin, Ears
11	M	18	Bone, Skin, Ears, Mouth, Pituitary
12	M	42	Bone, Skin, Ears, Mouth
13	M	14	Bone, Skin
14	F	6	Bone, Skin, Lymph nodes
15	M	32	Bone, Skin, Ears, Lungs, Mouth, Lymph nodes
16	F	24	Bone, Lymph nodes
17	M	8	Bone, Skin, Ears, Lungs, Bone marrow, Lymph nodes
18	M	6	Bone, Skin, Lungs, Mouth, Pituitary
19	M	3	Bone, Skin, Ears, Liver, Spleen, Mouth, Brain
20	F	25	Bone, Skin, Ears, Lungs , Pituitary

Table 2.1. Patient details (contd)

Pt. No.	Gender	Age at diagnosis (months)	Systems involved in the 'active' phase
21	M	29	Bone, Skin, Ears, Mouth, Lungs, Bone marrow, Lymph nodes, Pituitary
22	F	7	Bone, Skin, Ears, Lungs, Bone marrow, Lymph nodes
23	F	13	Bone, Skin, Ears, Liver, Spleen, Lymph nodes, Pituitary
24	F	48	Bone, Pituitary
25	F	36	Bone, Skin, Ears, Mouth, Lymph nodes, Pituitary
26	M	1.75	Bone, Skin, Ears, Mouth, Lungs, Pituitary, Brain
27	M	15	Skin, Ears, Lungs, Pituitary
28	M	14	Skin, Ears, Mouth, Lymph nodes
29	M	15.6	Bone, Skin, Mouth, Lungs, Pituitary
30	M	8	Bone, Skin, Ears, Mouth
31	F	11	Bone, Skin, Ears, Mouth, Lungs, Lymph nodes, Pituitary
32	F	36	Bone, Skin, Ears, Bone marrow, Pituitary
33	F	36	Bone, Skin, Ears, Lungs, Bone marrow, Pituitary
34	M	33	Bone, Ears, Pituitary
35	M	6	Bone, Skin, Mouth, Lungs, Liver, Bone marrow, Lymph nodes
36	M	6	Bone, Skin, Ears, Lungs, Liver, Spleen, Mouth, Gut
37	F	23	Bone, Skin, Ears, Lungs, Liver, Spleen
38	F	22	Bone, Bone marrow
39	F	34	Bone, Ears
40	M	18	Bone, Skin, Ears, Pituitary

Figure 2.2. Systems involved in the 'active' phase

This bar graph shows the number of patients with involvement of each organ system during the 'active' phase of the disease.

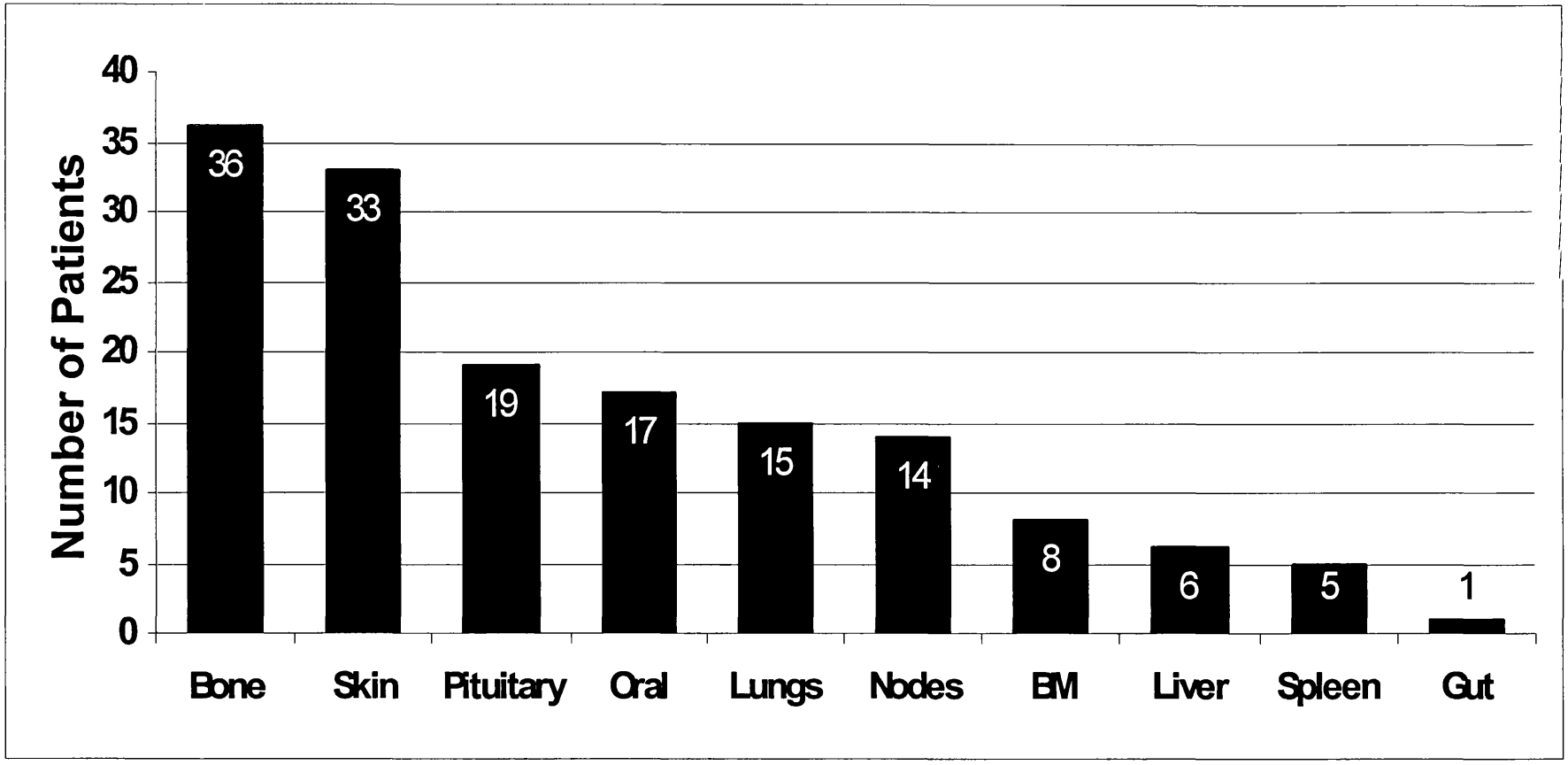


Table 2.2. Treatments received

This table summarises the treatments used during the active phase of the disease in each individual patient

Pt. No	Treatments (during 'active' phase of LCH)	Oral Steroid Cumulative dose/ duration	Radiotherapy Site/ dose in centigray (cGy)
1	none	-------	-------
2	Oral steroid	85 mg/kg / 5 months	-------
3	Surgery, oral steroid, intralesional steroid, Etoposide, topical Mustine	140 mg/kg / 12 months	-------
4	Surgery, intralesional steroid, radiotherapy	-------	1200cGy hypothalamus
5	Surgery, oral steroid	90 mg/kg / 2 months	-------
6	Surgery, oral steroid, intralesional steroid	105 mg/kg / 3 months	-------
7	Surgery, oral steroid, intralesional steroid, radiotherapy, Indomethacin	88 mg/kg / 3.5 months	1200 cGy, pituitary
8	Radiotherapy	-------	1000 cGy, pituitary
9	Surgery, oral steroid, intralesional steroid, Vinblastine	100 mg/kg / 3 months	-------
10	Surgery	-------	-------
11	Surgery, oral steroid, intralesional steroid, radiotherapy	>1000mg/kg / years	Forearm, skull
12	Surgery	-------	-------
13	Oral steroid, radiotherapy, Cyclophosphamide	180 mg/kg / 6 months	1000 cGy, ilium
14	Oral steroid	167 mg/kg / 6months	-------
15	Surgery, oral steroid, radiotherapy	> 1000 mg/kg / years	1200 cGy, neck
16	Surgery, oral steroid	38 mg/kg / 4.5 months	-------
17	Oral steroid, Etoposide	500 mg/kg / 15 months	-------
18	Oral steroid, radiotherapy	110 mg/kg / 4months	1200 cGy, pituitary
19	Oral steroid	57 mg/kg, 2.75m	-------
20	Surgery, oral steroid , radiotherapy	120 mg/kg, 7 mths	1200 cGy, orbit

Table 2.2. Treatments received contd.

Pt. No	Treatments (during 'active' phase of LCH)	Oral Steroid Cumulative dose/ duration	Radiotherapy Site/ dose in centigray (cGy)
21	Oral Steroid	305 mg/kg, 11.5 mths	-------
22	Oral Steroid, Vinblastine, Etoposide	150 mg/kg / 6.5 mths	-------
23	Surgery, Oral Steroid, Vinblastine, radiotherapy	430 mg/kg	1000 cGy, neck
24	Oral Steroid, Azathioprine	550mg/kg / 34 mths	-------
25	Oral Steroid, Vinblastine	377 mg/kg / 42 mths	-------
26	Surgery, Oral Steroid, Etoposide, topical Mustine	258 mg/kg / 10.5 mths	-------
27	Oral steroid, topical Mustine	146mg/kg, 6.5 mths	-------
28	Surgery	-------	-------
29	Surgery, Oral Steroid, radiotherapy	>1000mg/kg, years	3840 cGy lumbar spine, doses to jaw
30	Surgery, Oral Steroid, Vinblastine	260 mg/kg / 6.5 mths	-------
31	Surgery, Oral Steroid, Etoposide, Vincristine, topical Mustine	540 mg/kg, 24 mths	-------
32	Oral Steroid	286 mg/kg / 26 mths	-------
33	Oral Steroid	98.6 mg/kg / 3 mths	-------
34	IV steroid pulse	90 mg/kg of methyl prednisolone	-------
35	Oral steroid, Vinblastine, Vincristine, Etoposide, Methotrexate	500 mg/kg / 21 mths	-------
36	Surgery, oral steroid, topical Mustine	100 mg/kg / 3 mths	-------
37	Surgery, oral steroid, intralesional steroid, Vinblastine	300 mg/kg / 27 mths	-------
38	Surgery	-------	-------
39	Radiotherapy	-------	1000 cGy, ilium
40	Surgery, oral steroid , radiotherapy, Vincristine, Etoposide, intralesional steroid, Indomethacin	510 mg/kg / 28 mths	1200 cGy whole cranium + 300 cGy boost to occiput

Table 2.3. Patients excluded from the study

Twelve patients who fitted the selection criteria were excluded from the study for the following reasons: 2 patients have emigrated, 3 failed to attend their appointments and the rest could not be traced. Clinical details including gender, systems involved, treatments used and known sequelae are listed below. There was no statistical difference between these patients and those included in the study.

Gender	Systems involved	Treatments	Known Sequelae
F	Bone, skin, ear, mouth	Cyclophosphamide, steroid, azathioprine	No details available
F	Bone, skin, ear	Vinblastine and steroid	None
M	Bone, skin, bone marrow	Oral steroid	None, except partial collapse 1 vertebra
M	Bone, lymph nodes	Oral steroid	None, but has cerebral palsy
F	Bone, skin, mouth	Vinblastine, oral steroid, radiotherapy	None reported
M	Bone, skin, ears, liver, spleen, pituitary	Thymic hormone, vincristine, oral steroid	DI, GHI, deafness, residual proptosis
M	Lungs, pituitary	Surgery, vinblastine oral steroid (10mths)	Lung fibrosis, chest deformity, DI
M	Skin, pituitary	radiotherapy	DI
M	Bone, skin, lymph nodes	Oral and intralesional steroid	Not known
F	Bone, skin, ears, pituitary, brain	Vinblastine, oral steroid, methotrexate cyclophosphamide	DI, GHI, deaf in one ear, severe ataxia, learning difficulty, wheelchair bound
F	Bone, skin, liver, spleen, bone marrow, pituitary	Oral steroids, Etoposide, Vinblastine	DI, short stature
M	Bone, skin, lymph nodes, pituitary	Surgery, oral steroid (years), Vinblastine	DI, hypothalamic damage

Abbreviations:

DI = diabetes insipidus

GHI = growth hormone insufficiency

Section 2.2. Methods

This was a multidisciplinary, cross-sectional study, which involved the collection of clinical data. A full clinical history was obtained and physical examination conducted. The proforma used is shown in **Appendix. 2.** The multisystem investigations undertaken are outlined below. As the layout of this thesis is in separate chapters for each system involved, detailed relevant methods sections are located in each individual chapter.

2.2.1. Anthropometry

All patients were measured by trained auxologists, including the author. The parental heights were measured and the target height calculated. Pubertal assessments were performed by the author.

2.2.2. Neuropsychometry

Patients were assessed in the department of Neuropsychology. Tests included the measurement of intelligence, memory, language and attainment. The tests are described in detail in Chapter 4.

Intelligence Quotient (iQ) was assessed using the
Wechsler Intelligence Scale for Children – Third Edition UK (WISC-III^{UK}) <17yrs
Wechsler Adult Intelligence Scale- Revised (WAIS-R UK) in adults, and the
Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R)
The results were compared to the population norms

Memory Quotient (MQ) was assessed using the
Wechsler Memory Scale (WMS) and the
Children's Auditory Verbal Learning Test (CAVLT)
The results were expressed as percentiles

Educational attainment in reading, numerical skills and language was assessed using
Wechsler Objective Reading Dimensions (WORD)
Wechsler Objective Numerical Dimensions (WOND)
Wechsler Objective Language Dimensions (WOLD)
Receptive vocabulary was assessed using the
British Picture Vocabulary Scale (BPVS)

2.2.3. Investigations

The investigations performed in this study are outlined here. Details for each investigation are included in the relevant chapters.

2.2.3.1. Neuroimaging

MRI Scanning

Magnetic Resonance Imaging was performed on a 1.5 Tesla MR scanner. Axial T2-weighted images were obtained pre-contrast, while coronal T1-weighted images were obtained pre-contrast and coronal and sagittal images after enhancement with gadopentetate dimeglumine (gadolinium/ GdDTPA).

3-D CT Scan of the skull

CT scans of the skull and upper cervical spine were performed and 3-dimensional reconstructions made.

2.2.3.2. Respiratory Function Tests

All patients had measurement of Peak Flow Rate (PFR) and spirometry.

Chest X-ray

Chest X Ray was performed on those subjects who had abnormal lung function i.e. below 70% of predicted values.

2.2.3.3. Audiometry

Hearing was tested by pure-tone audiometry as recommended by the British Society of Audiology (British Society of Audiology 1981). Tympanometry was also performed according to the recommendations of the British Society of Audiology (British Society of Audiology 1992).

2.2.3.4. Endocrine Function

The results of pituitary function tests were retrospectively analysed.

Diabetes insipidus was diagnosed on a standard or modified "short" water-deprivation test. Anterior pituitary function was tested on stimulation tests, using either Insulin or Glucagon in combination with Thyrotropin Releasing Hormone (TRH) and Lutenizing Hormone releasing Hormone (LHRH).

2.2.4. Statistical methods

Assumptions of normality and homogeneity were established where appropriate.
To analyse growth data the paired *t* test and 2-sample *t* test were used to compare groups when data had a normal distribution. In other situations, non-parametric methods such were used. Analysis of cognitive function uses more detailed statistical methods that are described in the appropriate section. The other statistical methods used are described in the relevant chapters.

To summarise, this was a cross-sectional, multidisciplinary study, the aims of which were to assess the prevalence and severity of long term sequelae after multisystem LCH and to attempt to identify any " risk factors" for development of these sequelae. The study involved case note review, clinical history and examination, anthropometry, assessment of cognitive function and specific investigations including endocrine function tests, neuroimaging, audiology and respiratory function tests.

Forty (21 male, 19 female) long term survivors of multisystem LCH were studied. Twelve patients who fitted the criteria were excluded due to various reasons. These patients are similar to the study cohort in distribution of systems involved, treatments received and known sequelae. There therefore does not appear to be an inherent selection bias in our study cohort.

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The next 4 chapters discuss in detail the methods used, results obtained and discussion relating to endocrine deficiencies and growth, neurological abnormalities, changes on neuroimaging and skin, bone, lung and liver sequelae. Chapter 7 describes assessment of functional outcome and the findings of the study are summarised in the final chapter.

Chapter 3. Hypothalamo - Pituitary Abnormalities

Introduction

This chapter describes the hypothalamo-pituitary abnormalities identified in this cohort of patients. The endocrinopathies have been correlated with anatomical abnormalities of the hypothalamo-pituitary region seen on MRI scan. The growth pattern of the patients and height outcome, both with and without growth hormone deficiency, is described and discussed. Hypothalamic involvement may result in a "hypothalamic syndrome", which has been reported in other causes of damage, such as craniopharyngioma or following surgery or radiotherapy to this region. However, this syndrome has only recently been recognised in patients with LCH.

Hypothalamo-pituitary dysfunction is characteristic of LCH. Diabetes insipidus (DI) is the most common endocrinopathy (Grois, Favara, Mostbeck, & Prayer 1998), presenting with polyuria and increased thirst and in toddlers can often be mistaken for habitual drinking. It may develop before or within the first 5 years after diagnosis of LCH (Dunger, Broadbent, Yeoman, Seckl, Lightman, Grant, & Pritchard 1989). Involvement of the anterior pituitary is much less common than the posterior pituitary, with growth failure as the usual presenting feature. Growth hormone (GH) deficiency or insufficiency is reported to occur in < 10% of patients (Donadieu & French LCH Study group. 1996;Sims 1977), but other trophic hormone deficiencies are rare. Few studies have investigated the growth of patients with longstanding LCH (van den Hoek, Karstens, Egeler, & Hahlen 1995). Available data relate to patients who have established GH deficiency and have been treated with GH supplements (Braunstein, Raiti, Hansen, & Kohler 1975; Howell, Wilton, & Shalet 1998). They found that patients with LCH showed a growth response following GH therapy similar to children with idiopathic growth hormone deficiency with no significant side effects.

Section 3.1. Methods

3.1.1. Anthropometry

Measurements of height and weight were made by trained auxologists (Mrs S King, Mrs A Gaunt and the author). Available parents' heights were measured and in others their reported height was used. The target height for each patient was calculated from the parents' heights (Tanner, Goldstein, & Whitehouse 1970). Retrospective growth data on all patients were also collated. Growth velocity was calculated. Final height was considered to have been achieved when the epiphyses were fused and growth velocity was less than 2 cm per year. Pubertal status was assessed by the author, according to the method of Marshall and Tanner (Marshall & Tanner 1969;Marshall & Tanner 1970) and testicular volumes were measured using the Prader orchidometer. Bone age assessments were not routinely performed as the majority of the patients had completed their growth and reached final height. When performed, bone age was assessed by the author using the revised Tanner-Whitehouse method (Tanner et al. 1983).

3.1.2. Statistical analyses

Height standard deviation scores (SDS) were calculated at diagnosis of LCH, at diagnosis of GH insufficiency and at final assessment. The height and height SDS at each of these points were compared to the target height and its SDS. The paired *t* test and 2-sample *t* test were used to compare groups when data had a normal distribution. In other situations, non-parametric methods such as the Wilcoxon matched pairs signed rank sum test and the Mann-Whitney test were used. A two-tailed *P*-value of <0.05 was considered statistically significant.

3.1.3. Endocrine Function Tests

Endocrine results were analysed retrospectively from investigations done at the time of clinical signs and symptoms, often several years before the long term follow up study. Those patients who developed symptoms/ signs during the study period were assessed prospectively.

Investigation of diabetes insipidus

Children with polyuria and polydipsia had been subjected to either a standard water-deprivation test with measurement of plasma and urine osmolality or a modified "short" (7 hour) water-deprivation test (WDT) with measurement of plasma

and urine osmolality and urinary AVP levels (Dunger et al. 1988). Patients who did not have symptoms of DI and who had not been investigated earlier had measurement of an early morning urine osmolality at follow up assessment. DI was diagnosed, on a standard water-deprivation test, if the plasma osmolality was greater than 295 mosmol/kg with inappropriately dilute urine. On a 'short' water-deprivation test DI was diagnosed by a failure to concentrate urine (urinary osmolality <300 mosmol/kg) in the presence of raised plasma osmolality (>300 mosmol/kg) and with urinary AVP levels <10 pmol/L after water-deprivation. Partial DI was diagnosed when urine osmolality ranged between 300 and 800 mosmol/kg, with urinary AVP levels between 10 and 100 pmol/L.

Investigation of anterior pituitary function

Children with short stature (height < -3SD below mean) or poor growth velocity (< 4 cm/year in the prepubertal child) and those with a hypothalamo-pituitary mass on imaging, had anterior pituitary function tests performed. Growth hormone secretion was stimulated using either insulin-induced hypoglycaemia (short-acting insulin 0.05 to 0.1 U/kg) or glucagon stimulation (0.1mg/kg). In 10 of the 12 patients this test was combined with administration of Thyrotropin Releasing Hormone (TRH) (7mcg/kg to a maximum of 200 mcg) and Lutenising Hormone Releasing Hormone (LHRH) (25 mcg/m^2). (Hughes 1986). Patients who were GH insufficient and had completed growth had a reassessment of anterior pituitary function.

Definition of Anterior pituitary deficiencies

Over the observation period, the cut-off values for diagnosis of GH insufficiency have varied and we have accepted the diagnosis made using the appropriate values for the test of GH secretion and assay used at that time. More recently, a diagnosis of GH insufficiency was made when the peak GH remained below 15-20 mu/L during a stimulation test of GH secretion. Gonadotrophin deficiency was diagnosed in the pubertal child by failure of rise in gonadotrophin levels after stimulation with lutenizing hormone releasing hormone (LHRH). Adrenocorticotrophic hormone (ACTH) deficiency was diagnosed if, after an insulin tolerance test, the plasma cortisol did not rise 2 to 3 fold above basal levels or to >500 nmol/L. An exaggerated, delayed thyroid stimulating hormone (TSH) response to thyrotropin releasing hormone (TRH) stimulation indicated hypothalamic hypothyroidism.

Section 3.2. Results

The results of endocrine evaluation were collected retrospectively and analysed. Endocrine abnormalities were seen in 20 of the 40 patients (50%), all but one of whom had diabetes insipidus. GH insufficiency was present in 13 patients (32%), 6 of whom had other anterior pituitary hormone deficiencies in addition. The endocrine abnormalities in individual patients are listed in **Table 3.1** and depicted graphically in **Fig. 3.1**.

3.2.1. Diabetes insipidus

Nineteen of the forty patients (48%) developed DI within 5 years of diagnosis of LCH. The presenting symptoms were polyuria and increased thirst. The results from the water-deprivation tests were collected retrospectively. Thirteen patients had a 'short' water- deprivation test. Ten of the 13 patients had DI with low urinary AVP levels and 3 patients had partial DI with intermediate AVP levels. These results have been previously published from this institution (Dunger et al. 1989b) Six others had a standard WDT but no measurements of urinary AVP. Details of the time to diagnosis of DI and results of the WDT are given in **Table 3.2.** In 2 patients, symptoms of polyuria and polydipsia preceded the diagnosis of LCH, but the diagnosis of DI was not confirmed on water-deprivation until the diagnosis of LCH had been made. None of the remaining 21 patients have developed DI over a median follow up period of nearly 16 years. These data are represented in **Fig. 3.2.**

Table 3.1. Endocrine abnormalities

PT NO	ENDOCRINOPATHY
1	DI
3	DI
4	Panhypopituitarism –DI, GHI, Gn, TSH, ACTH deficiency, obesity, "hypothalamic syndrome"
7	DI
8	DI
11	GHI
18	DI
20	GHI
21	DI, GHI, Gn deficiency
23	DI, GHI
24	DI
25	DI, GHI, Gn deficiency
26	Partial DI, GHI, early puberty, "hypothalamic syndrome"
27	Partial DI, GHI, delayed puberty, "hypothalamic syndrome"
29	Panhypopituitarism –DI, GHI, Gn, TSH, ACTH deficiency, "hypothalamic syndrome"
31	Partial DI, GHI
32	Panhypopituitarism –DI, GHI, Gn, TSH, ACTH deficiency, "hypothalamic syndrome"
33	DI, GHI, TSH deficiency
35	DI
40	DI, GHI

This table shows the endocrine abnormalities in individual patients

Abbreviations:

DI = diabetes insipidus

GHI = Growth hormone insufficiency

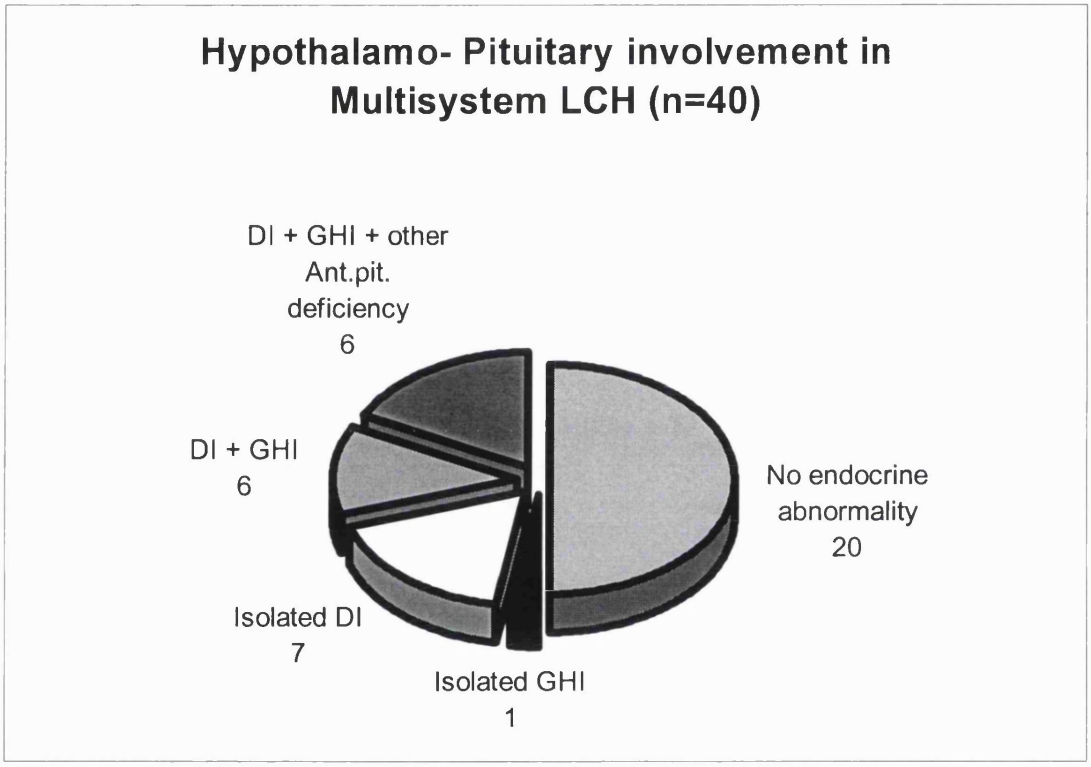
Gn = Gonadotrophins

TSH= Thyroid stimulating hormone

ACTH = Adrenocortical stimulating hormone

Figure 3.1. Prevalence of hypothalamo-pituitary involvement

This chart shows the number of patients who had hypothalamo-pituitary endocrinopathy.



20 patients (50%) had one or more hormone deficiencies.

Diabetes insipidus (DI) was present in a total of 19 patients (48%).

Growth hormone insufficiency (GHI) was present in 13 patients (32%).

7 patients (17.5%) had isolated diabetes insipidus

6 patients (15%) had diabetes insipidus and growth hormone insufficiency

6 patients (15%) had DI and multiple anterior pituitary hormone deficiencies

- 3 had panhypopituitarism
- 1 had growth hormone insufficiency and gonadotrophin deficiency
- 2 had GHI, Gonadotrophin deficiency and secondary hypothyroidism

1 (2.5%) had isolated growth hormone insufficiency

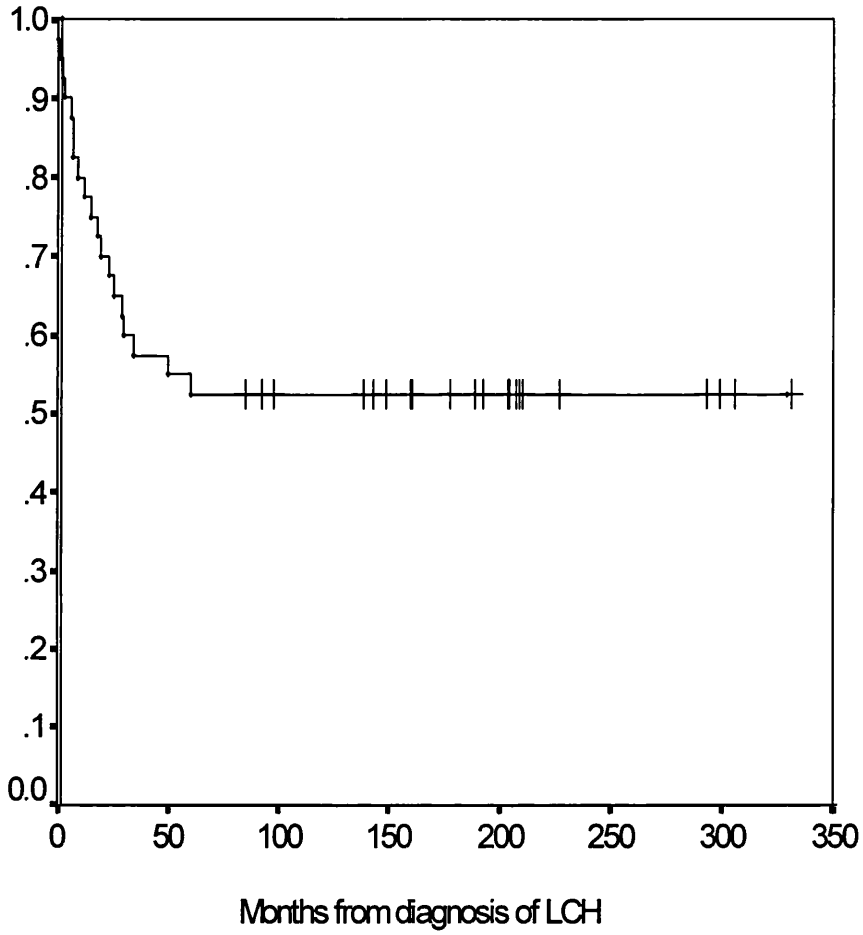
Table 3.2. Water-deprivation test in patients with diabetes insipidus

Pt. No.	Time between diagnosis of Di and diagnosis of LCH	Urine Osmolality (mosmoi/kg)	Urine AVP (pmoi/L)
1.	7 months	87	0.8
3.	12 months	198	5.9
4.	2 months	154	0.9
7.	50 months	127	<5.0
8.	15 months	96	1.2
18.	30 months	360	5.6
20.	3 months	45	<0.2
21.	7 months	122	0.1
23.	25 months	169	Not available*
24.	0 months	468	Not available*
25.	1 months	149	Not available*
26.	60 months	740	21.7 (partial DI)
27.	34 months	630	34.6 (partial DI)
29.	29 months	68	Not available*
31.	19 months	318	28 (partial DI)
32.	9 months	97	3.1
33.	6 months	242	3.4
34.	18 months	95	Not available*
40.	23 months	137	4

This table gives the time from diagnosis of LCH to the diagnosis of diabetes insipidus and the results of either a standard water – deprivation test or a 'short', modified 7-hr water-deprivation test. All patients presented with polyuria and polydipsia. DI was diagnosed if the urinary osmolality was <300 mosmol/kg and urinary AVP <10 pmol/L. Partial DI was diagnosed if urinary osmolality was between 300 and 800 mosmol/kg with urinary AVP concentrations between 10 and 100 pmol/L (Dunger et.al. 1988, 1989)

*Results of urinary AVP were unavailable in 5 patients.
3 patients had had the test performed at another institution
2 had the tests before measurements of AVP were introduced

Figure 3.2. Risk of developing diabetes insipidus in LCH



This Kaplan-Meier graph shows the cumulative risk of developing diabetes insipidus in this cohort. Nineteen patients (48%) developed DI, all within 5 years (60 months) of diagnosis of LCH. None of the remaining 21 patients have developed DI over a median follow up period of nearly 16 years (range 83 to 329 months)

There was no obvious relationship between the development of DI and treatment received for the 'active' disease. Seven patients received irradiation to the head, and in 4 of these the radiotherapy was used in an attempt to ameliorate the symptoms of DI. There was no reversal of DI following radiotherapy in these patients and no reduction in DDAVP requirement. Serial testing revealed a transient improvement in AVP secretion following treatment with etoposide in only one patient (Pt no.26). The patient had partial DI initially, with urinary AVP levels below 50 pmol/L following a 7-hr fast. Following 6 courses of oral etoposide, the test was repeated and the AVP level rose to 149.5 pmol/L (within the normal range). Six months later, the AVP concentration after water-deprivation had dropped again to 21.7 pmol/L (i.e. partial DI) on testing, but even now, 9 years later, he has no polyuria or polydipsia and has not required DDAVP replacement.

In 17 patients, DI is well controlled by DDAVP replacement, using either Desmopressin nasal spray (13 patients) or tablets (4 patients). No patient has had serious side effects of DDAVP therapy such as water overload, or convulsions due to sodium and water imbalance. One patient (Pt. No. 29) was initially commenced on intranasal DDAVP. Later, he found that control of DI became increasingly difficult so his physician advised a change to chlorthalidone tablets, which give him reasonably good symptom control.

3.2.2. Anterior Pituitary Dysfunction

Thirteen patients have evidence of anterior pituitary abnormalities. Seven have GH insufficiency, and 6 have other anterior pituitary hormone deficiencies in addition. Twelve of the 13 also have diabetes insipidus. The presenting features, time from diagnosis of LCH to diagnosis of anterior pituitary dysfunction and results of pituitary function testing are given in **Table 3.3**. The results from these investigations have been collated retrospectively. Six patients (Pt. Nos. 20, 21, 23, 25, 40) have had repeat endocrine function performed after attainment of final height. The results of retesting are given in **Table 3.4**.

In order to assess the influence of radiation on the development of GHI we examined the temporal relationship between the administration of cranial irradiation and the diagnosis of GHI. Seven patients in the entire cohort received radiation to the head (4 to the hypothalamo-pituitary region, 1 to the orbit, 2 to the skull). Two other patients received radiotherapy to the cervical lymph nodes but the fields did

not encompass the hypothalamo-pituitary area. Only 5 of the 7 patients who received cranial radiation have anterior pituitary hormone deficiencies, and in all but one instance, GHI preceded the radiotherapy. The dose and site of radiation, the indication for radiotherapy and the time between radiotherapy and development of GHI in these 5 patients is also included in **Table 3.3**.

Ten of the thirteen patients with GHI were given GH replacement therapy. Three patients did not receive GH treatment. The growth pattern of two of them (Pts. No. 23, 24), following the diagnosis of GH insufficiency, was felt to be normal and therefore no replacement was instituted. The third patient (Pt no 4) had hypothalamic damage with hyperphagia resulting in gross obesity. She continued to grow despite having no detectable GH on testing. (Further details of this patient are given in the section on hypothalamic involvement). Recombinant growth hormone injections were administered daily 6 or 7 nights a week in a dose of 15 to 20 units/m^2/ week. The median duration of therapy was 7.2 years (1.5 to 10 years), with 3 patients still on GH therapy. One boy (pt no.27) has not yet completed growth. One other patient (pt no. 29) was diagnosed as having GH deficiency in late adolescence. He was started on GH therapy as an adult (as he had symptoms of excessive weight gain and tiredness, thought to be due to GH deficiency) and remains on treatment. The third patient has also recently been restarted on GH as an adult due to symptoms of excessive tiredness and lack of motivation.
Patients who were treated during childhood demonstrated catch-up growth, but did not reach their expected target height. The growth data are discussed in more detail in the next section.

3.2.3. Growth

The growth data for individual patients are presented in the Appendix. Results for groups of patients are expressed in this chapter as mean values, with the ranges in brackets, unless otherwise stated. To assess the effect of both GH insufficiency and LCH on growth, the patients were divided into 2 groups based on GH status. Patients with GH insufficiency (GHI) were called Group 1(n = 13). Patients without GH insufficiency (non-GHI) were classified as Group 2 (n =27). Each group was further subdivided into
a: patients who have completed growth/attained final stature (1a n=12, 2a n = 13)
b: patients who have not yet attained final stature (1b n=1, 2b n = 14)

Group 1. Patients with GH insufficiency

The growth data for the 13 patients with GHI, all but one (pt 27) of whom have completed their growth, are shown in **Tables 3.5 and 3.6**. The mean age at diagnosis of LCH was 4.35 years, median age was 2.9 yrs (0.1 to 16.9 years). The height SDS at diagnosis of LCH was –0.87 (-2.7 to 2.2). The age at diagnosis of GHI was 9.7 years (4.7 to 18 years). The height SDS at diagnosis of GHI was –2.2 (-4.5 to – 0.1). Following treatment with GH, all patients showed catch-up growth with increased height velocity and an improvement in height SDS.

Short and long term response to GH therapy: The mean growth velocity SDS increased from –2.1 (-5.5 to 1.2) to 3.9 (-3 to 8.6) after 1 year of therapy [$p<0.001$]. The mean final height SDS was –0.85 (-2.4 to 1.4) which was significantly greater than pre-treatment height SDS [$p = 0.012$]. However, final stature remained significantly below the mid-parental target height; 163.3 cm (148.9 to 181.1) vs 169.2 cm (159 to 183.7) [$p <0.05$]. Target height SDS was –0.14 (-1.2 to 0.89). The height SDS for patients in Group 1a at diagnosis of LCH, at diagnosis of GHI and at final height are compared to the target height SDS in Fig. 3.3. The comparison of final height to target height for individual patients in Group 1a is shown in **Fig. 3.5**.

Group 2a. Patients without GH insufficiency who have completed growth

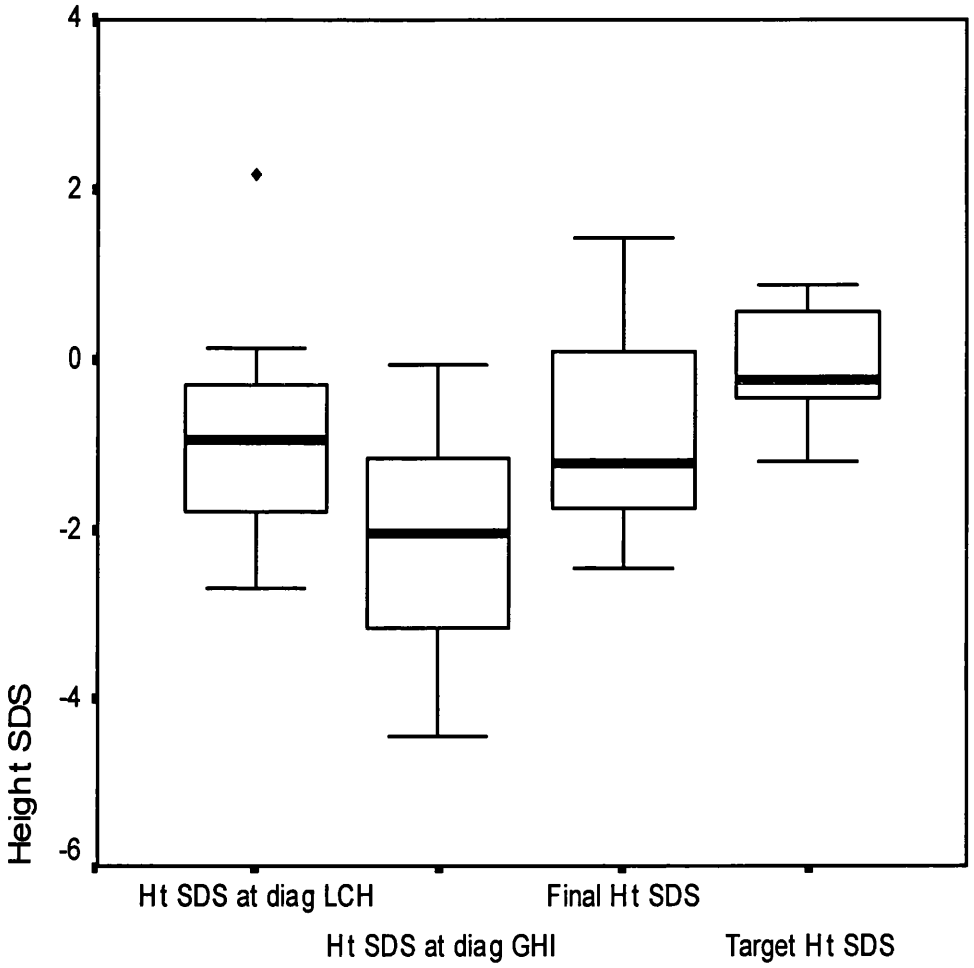
Thirteen patients who do not have GHI have reached their final height. Their growth data is shown in **Table 3.7**. The mean age at diagnosis of LCH was 3.31 years, median age 1.6 yrs (0.6 to 11.2 years). Height SDS at diagnosis of LCH was –1.2 (-3.3 to 0.57). Mean final height SDS was -0.68 (-3.5 to 1.4). Final stature remained below mid-parental target height; 165.2 cm (140.6 to 183.3) vs 168.3cm (155.5 to 183.5). Target height SDS was –0.28 (-1.38 to 1.46).

The comparison of height SDS at diagnosis of LCH and at final height with target height SDS is shown in **Fig. 3.4**. The comparison of final height versus target height for individual patients is shown in **Fig. 3.6**. There was no significant difference in final height between the GH insufficient and non- GH insufficient patients - 163.3 cm (148.9 to 181.1) vs 165.2 cm (140.6 to 183.3).

Group 2b. Patients without GH insufficiency who have not completed growth

Fourteen patients who are GH sufficient have not yet reached final height. Their growth data are shown in **Table 3.8**. Mean age at diagnosis of LCH for this group was 1.6 yrs, median age 1.3 years (0.4 to 3.8 years). Mean height SDS at diagnosis of LCH was –0.61 (-2.08 to 1.13). Height SDS at the last visit was –0.33 (-2.0 to 1.59). Target height SDS was –0.31 (-1.29 to 1.68). **(Fig. 3.7)**

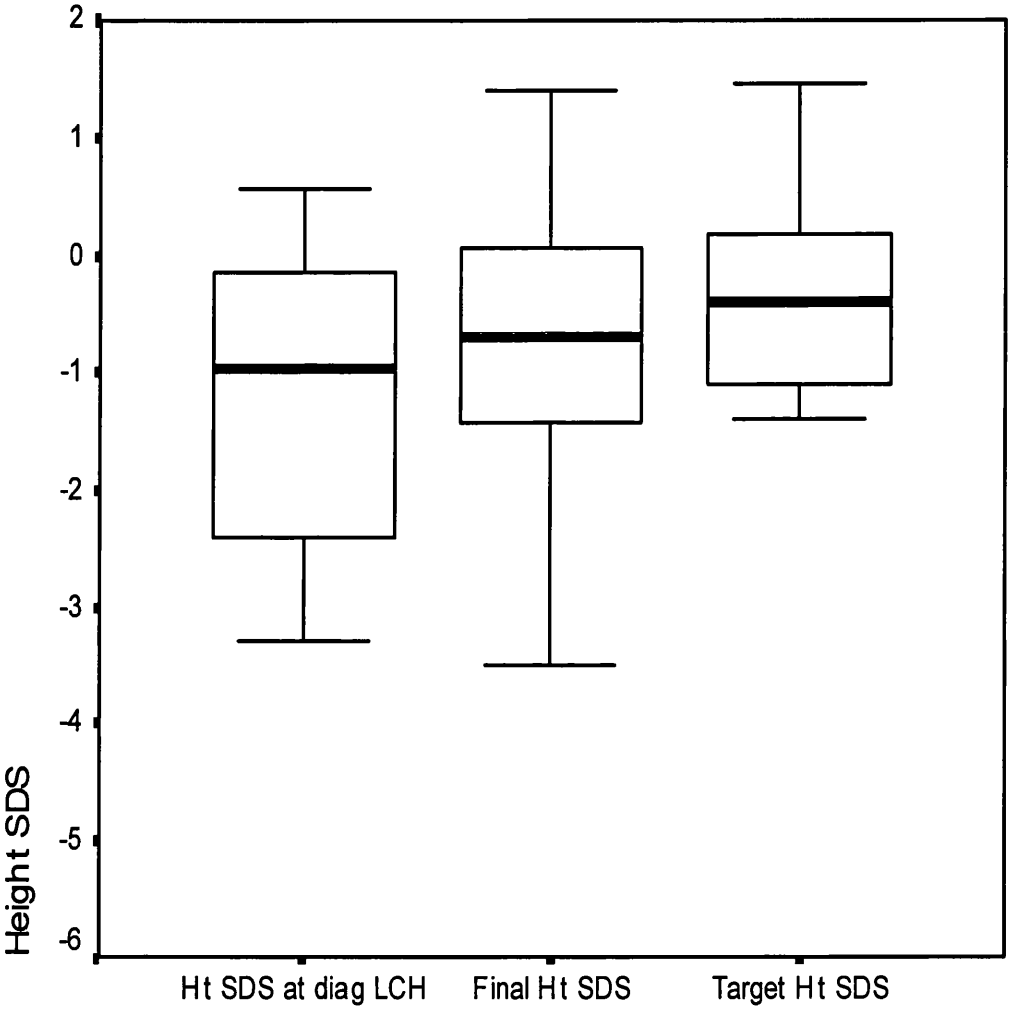
Figure 3.3. Growth of patients with GH insufficiency (Group 1a)



This graph depicts the growth of patients (n=12) with growth hormone insufficiency (GHI) who have reached their final height. The box plot compares the height standard deviation score (SDS) at diagnosis of LCH, at diagnosis of GHI, and at final height in these patients with their target height SDS based on parental heights. The graph shows the median, the interquartile range, and outlier for height SDS. The mean final height SDS was significantly greater than pre-treatment height SDS [$p = 0.012$] but, final stature remained significantly below the mid-parental target [$p < 0.05$].

Figure 3.4. Patients without GHI who have completed growth

(Group 2a)



This graph depicts the growth of patients (n=13) without growth hormone insufficiency who have reached their final height. The box plot compares the height standard deviation score (SDS) at diagnosis of LCH and at final height in these patients with their target height SDS based on parental heights. The graph shows the median and the interquartile range for height SDS. There was no statistically significant difference between final height and target height.

Figure 3.5. Final height versus target height in patients with GHI

This scatter plot compares the final height of each patient with GH insufficiency (on the Y axis) with their target height (on the X axis). The line of equivalence is drawn, and shows that 10 of 12 patients in this group lie below the line i.e. have not attained the expected height.

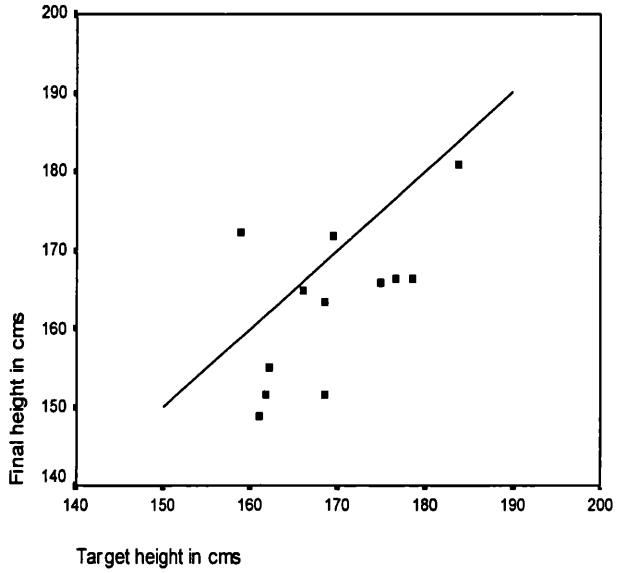


Figure 3.6. Final height versus target height in patients without GHI

This scatter plot compares the final height of each patient without GH insufficiency (on the Y axis) with their target height (on the X axis). Compared to Fig. 3.5 there is more even scatter around the line of equivalence showing that although 6 of 12 patients have not attained the expected height, their final height is closer to the target height than the patients with GHI.

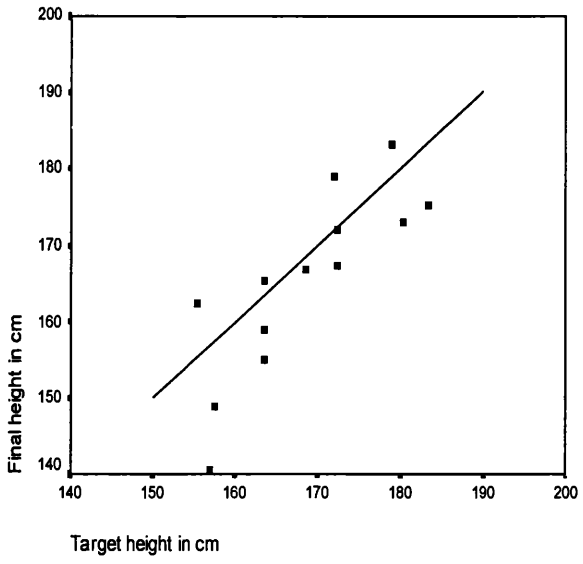
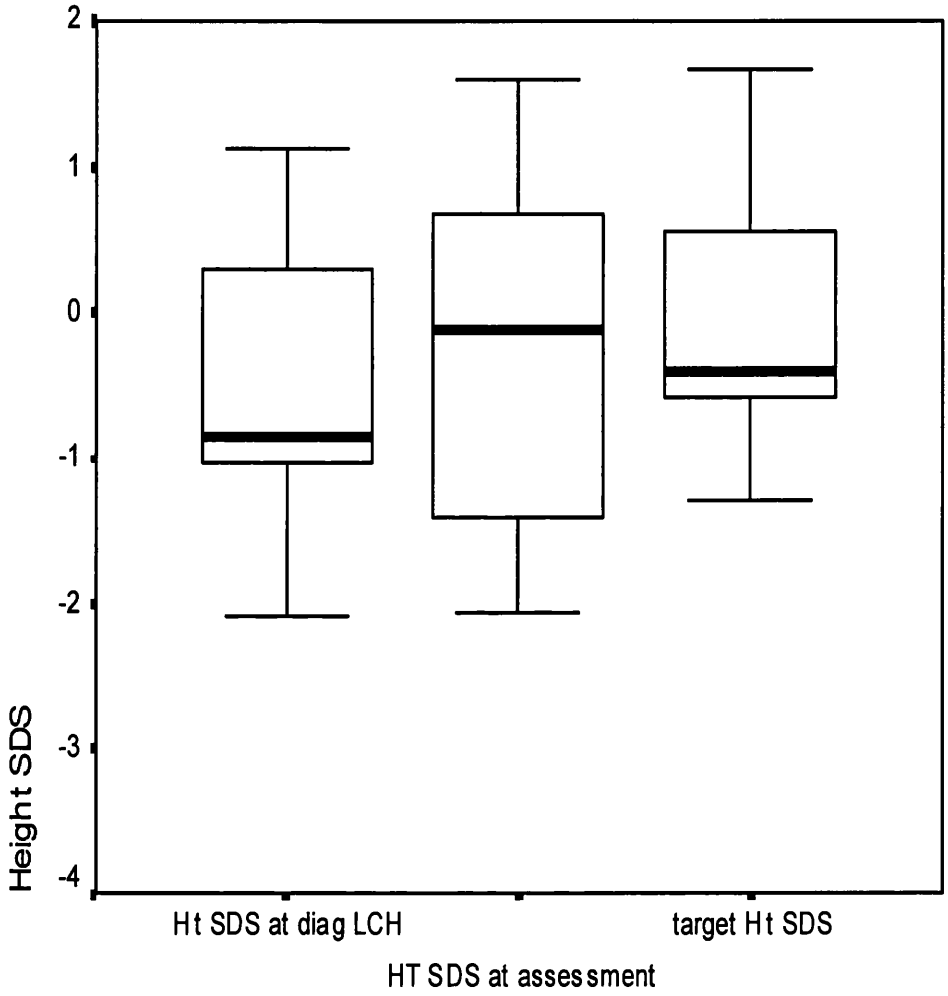


Figure 3.7. Patients without GHI who have not completed growth
(Group 2b)



This graph depicts the growth of patients (n=14) without growth hormone insufficiency who have not yet reached their final height. The box plot compares the height standard deviation score (SDS) at diagnosis of LCH and at last assessment in these patients with their target height SDS based on parental heights. The graph shows the median and the interquartile range for height SDS. There was no statistically significant difference between height at assessment and target height.

Other anterior pituitary deficiencies: Six patients have multiple anterior pituitary hormone deficiencies. Three (Pts. No 4, 29, 32) have panhypopituitarism and are on replacement therapy with thyroxine, hydrocortisone and the appropriate gonadal hormone. One patient (Pt. No. 21) has GHI and gonadotrophin deficiency, while two others (Pts. No 33, 40) also have secondary hypothyroidism. These results are included in **Table 3.3**.

Pubertal development: All patients with panhypopituitarism (n=3), or gonadotrophin deficiency in addition to GHI (n=2), required induction of puberty with the appropriate gonadal hormone and remain on replacement therapy. Patient no 29. developed LCH after the onset of normal puberty. He then demonstrated regression in pubertal development and required testosterone supplements. One boy with GH insufficiency (Pt No.27) had "constitutional delay" in the onset of puberty, which responded to a six-month course of testosterone supplements. Since stopping the testosterone injections he has continued to progress in puberty. Pt. No. 26, a male, had a relatively early onset of puberty (Tanner genitalia stage 3 at age 11 yrs). As this was associated with abnormal aggressive behaviour, requiring admission to a child psychiatry unit, he was treated with a gonadotrophin releasing hormone (GnRH) analogue (leuprorelin) for 20 months. The treatment resulted in regression of puberty and an improvement in behaviour. Following discontinuation of the GnRH analogue he continued to progress through puberty normally. All the other patients with GHI had normal pubertal development. Of the patients who do not have anterior pituitary dysfunction 8 were prepubertal at the time of assessment, 6 have had normal onset and progress of puberty, while 13 have completed pubertal development.

3.2.4. Hypothalamic involvement

Five patients (Nos. 4, 26, 27, 29, 32) had evidence of hypothalamic damage, manifesting as one or more of the following: behavioural change, abnormal eating patterns and temperature instability. In 3 of them (Pt Nos. 4, 26, 32) there was a hypothalamic mass on CT or MRI scan. As this aspect of hypothalamic involvement is not well described in the literature, and often goes unrecognised, I now describe the 5 patients in our cohort in some detail.

Patient No.4 presented at the age of 10 years with a history of excessive thirst and polyuria with regression of early pubertal development. Investigations confirmed diabetes insipidus and panhypopituitarism. She was found to have a hypothalamic

mass, measuring 15 mm, on CT scan (**Fig.3.8**) and was given emergency radiotherapy in an attempt to halt progression. Unfortunately, there was no improvement in endocrine function and she became severely hyperphagic. Despite several measures to restrict intake, including strict observation in hospital, she continued to overeat, with a resultant massive weight gain. Now, 11yrs later she still has hyperphagia and remains grossly obese. Although severely GH deficient, she nevertheless continued to grow without GH replacement therapy. Her height and weight charts are shown in **Fig. 3.9**.

The other 4 patients (Pts no. 26, 27, 29 and 32) with 'hypothalamic syndrome' had less difficulty with weight control, but suffered behavioural abnormalities including aggression, violent thought processes, temper tantrums, "rage attacks" and irrational behaviour, which were often intermittent, unprovoked and uncharacteristic for these children who were otherwise normally well behaved.

Patient No.26 was diagnosed as having LCH in the neonatal period. He later developed partial diabetes insipidus and growth hormone insufficiency and was found to have thickening of the region of the hypothalamus and infundibulum on a CT scan. At the age of 11yrs he was referred to the psychologists as there were concerns about his violent thought processes and a fascination with 'fire-setting' and required in-patient care for several months. During this period he was noted to have premature pubertal development and was commenced on treatment with a gonadotrophin-releasing hormone analogue (leuprorelin) to arrest puberty. There was an improvement in behaviour with lessening of aggression and he remained on the treatment for 20 months, but the improvement in behaviour was not sustained and 7 years later he continues to have considerable psychological problems, such as violent thoughts, cross-dressing and abnormal behavior.

Patient No.27 was diagnosed as having LCH at the age of 15 months. At the age of 24 months he developed polydipsia and polyuria. Soon after, he was noted to have a change in behaviour with intermittent periods of unprovoked aggression, biting and kicking family members and temper tantrums. His mother described him as having a "Jekyll and Hyde" personality. He also had spikes of fever, with temperatures up to 39^0C, which spontaneously subsided within hours. No underlying cause was found and this was felt to be a manifestation of deranged temperature control secondary to hypothalamic damage. He then developed abnormal eating patterns with intermittent "binge eating", during which he was

always hungry and ate huge quantities. Between these episodes he remained well and was described as a normal little boy. The symptoms improved on carbamazepine therapy, which he continues to take.

Patient No. 29 presented in late adolescence with hypothalamic disease manifesting as diabetes insipidus, panhypopituitarism, increased appetite and weight gain. He had arrest of puberty with regression in testicular volume and genital development. He was managed with full endocrine replacement therapy. He also experienced temperature instability, which persists to date.

Finally, **patient No. 32** also had DI and panhypopituitarism. She had marked behavioural abnormality including aggression and violence. These "rage attacks" were usually unprovoked and led to considerable friction with those around her. These problems have persisted making it difficult for her to adjust to independent living.

No patient had subjective loss of thirst sensation suggestive of involvement of the thirst centre but formal testing of the thirst centre has not been carried out.

Hypothalamo-pituitary appearances on MRI

The hypothalamo-pituitary region was abnormal on MRI in all the patients with endocrinopathy, at the time of the follow up study. The most common feature, seen in 14 patients, was thickening of the pituitary stalk, but 2 patients had a thin thread-like stalk. Pituitary gland size was abnormal (smaller or larger than normal) in 8 patients. A mass was seen in the hypothalamus at diagnosis of endocrinopathy in 3 patients (Pts No. 4, 26, 32). Further details of MRI appearances, with illustrations, are discussed in Chapter 5.

Figure 3.8. Hypothalamic mass lesion

Transverse CT scan of the hypothalamo-pituitary region showing an enhancing mass.

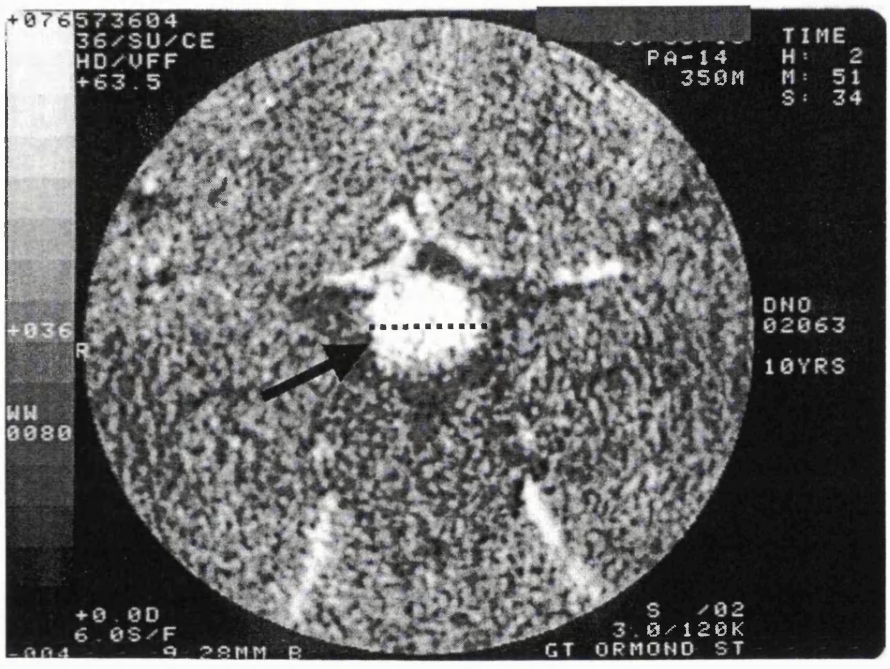
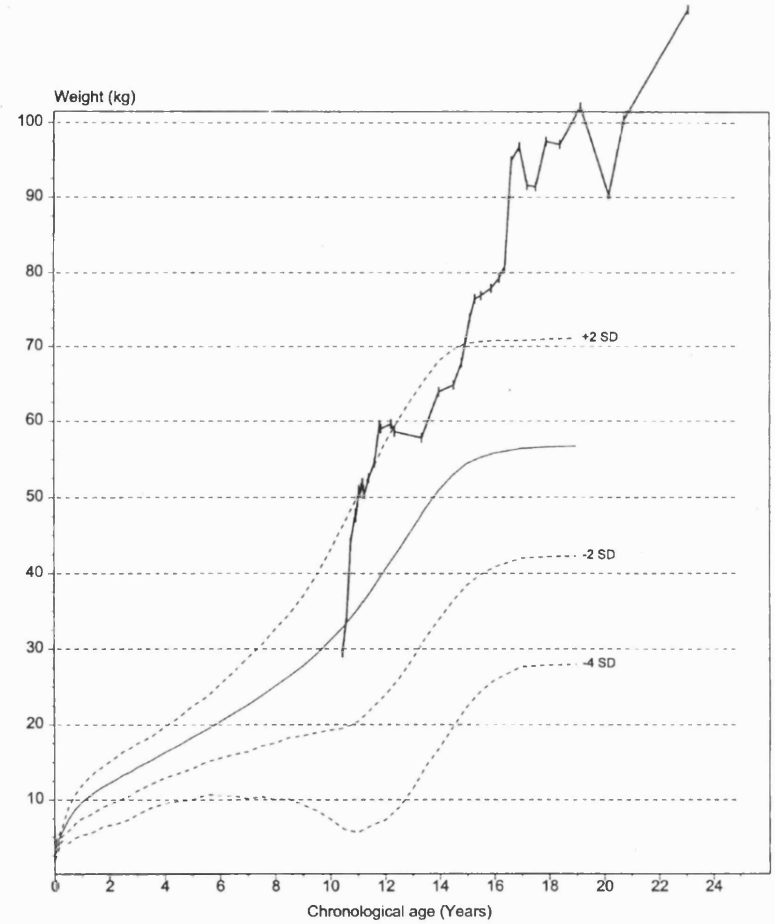
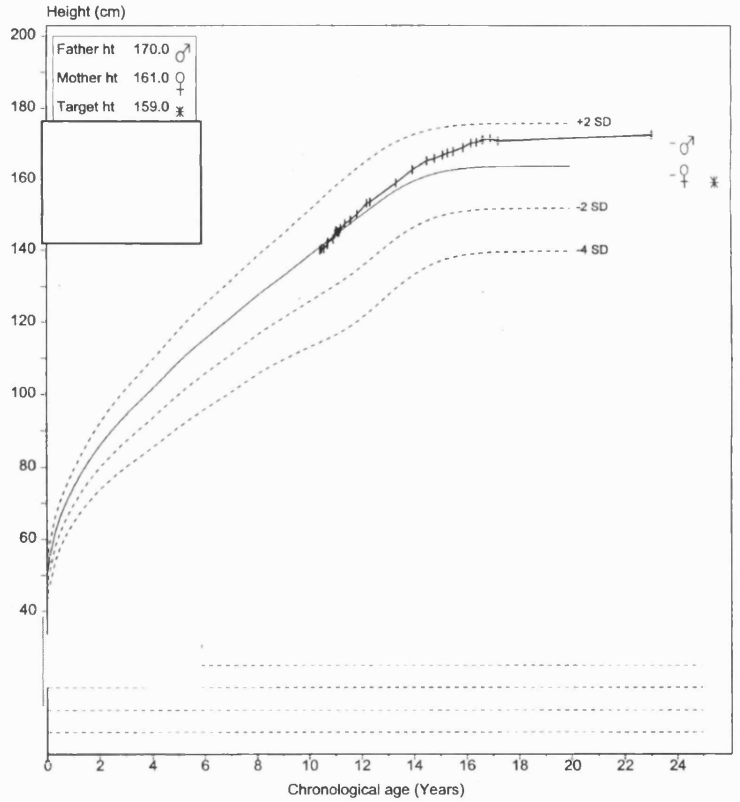


Figure 3.9. Weight and height charts for Patient No. 4

These charts show a rapid increase in weight from the age of 10 years, due to hyperphagia secondary to hypothalamic damage. Despite severe GH deficiency, there is an accompanying "normal" growth pattern, without the requirement for GH therapy.





Section 3.3. Discussion

This part of the overall study shows the value of careful assessment of patients for endocrine abnormalities and close monitoring of growth and puberty. Twenty patients in our cohort (50%) had hypothalamo-pituitary abnormalities, of whom 19 had diabetes insipidus and 13 (32%) had anterior pituitary hormone deficiencies. Growth was affected not only in patients with GHI, but also in some patients without endocrinopathy. This suggests that there are other mechanisms for the poor growth and short stature in survivors of LCH.

Diabetes Insipidus

Nineteen patients in our cohort (48%) had diabetes insipidus. The reported incidence of DI is between 15 and 50% (Broadbent & Pritchard 1997;Donadieu & French LCH Study group. 1996;Dunger, Broadbent, Yeoman, Seckl, Lightman, Grant, & Pritchard 1989;Grois, Flucher Wolfram, Heitger, Mostbeck, Hofmann, & Gadner 1995;Sims 1977;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996). This wide variation in incidence is a reflection of several factors including variation in the clinical caseload of different centres, differing criteria for establishing the diagnosis of DI and a reporting bias. A large number of patients in our study had measurement of urinary AVP level after water deprivation, which is more sensitive than the measurement of urine and plasma osmolality alone. By this technique we were able to identify patients who had partial DI. All but one of these children had symptoms of polyuria and polydipsia and the diagnosis of DI might have been missed on the standard water-deprivation test. The 7 – hour water-deprivation test is also easier to perform and less stressful for the child, and is therefore more likely to have been successfully completed than the standard water-deprivation test, improving the chances of identifying the patients with an abnormality. One patient with anterior pituitary dysfunction has no symptoms of increased thirst or polyuria and was never tested for DI. It is possible that he may have an abnormality of AVP secretion on testing, as it is unusual for GH deficiency to be present without DI.
There was no improvement in symptoms of DI in the few patients who received radiotherapy to the hypothalamo- pituitary mass lesion. This is in keeping with previous studies that have shown that established DI is irreversible and that radiotherapy has no role in the treatment of DI in LCH (Broadbent & Pritchard 1997;Rosenzweig, Arceci, & Tarbell 1997).

Anterior pituitary dysfunction

Thirteen patients (32%) in our series had anterior pituitary hormone deficiency, 4 of whom had panhypopituitarism. These figures are much higher than the previously reported incidence of GH insufficiency in less than 10% of patients (Dean, Bishop, & Winter 1986;Donadieu & French LCH Study group. 1996;Grois, Flucher Wolfram, Heitger, Mostbeck, Hofmann, & Gadner 1995;Kilpatrick et al. 1995;Sims 1977). It is possible that some of the difference may be accounted for by our studying patients with multisystem disease rather than all patients with LCH, as it is these patients who develop endocrinopathy rather than those who present with isolated bony lesions. As Great Ormond Street Hospital is a tertiary referral centre with multiple specialities available, it is possible that referral bias may also contribute to the difference. However, it is also likely that careful monitoring of our patients' growth and prompt investigation, have led to a higher ascertainment.

Anterior pituitary dysfunction is nearly always associated with DI and there are very few patients with GHI in the absence of DI as in Pt. No. 11. Tabarin et. al. describe a patient who had panhypopituitarism who was confirmed to have 'histiocytosis X' on biopsies of both skin and a hypothalamic mass. They performed detailed endocrine stimulation tests, which confirmed that the patient had panhypopituitarism secondary to loss of hypothalamic releasing factors. Up to the time of reporting this patient had not developed any evidence of DI, so the association of anterior pituitary deficiency and DI is not invariable (Tabarin, Corcuff, Dautheribes, Merlio, Cochet, Maire, Louail, & Roger 1991). However, it is possible that this patient may have had undocumented partial DI, which might not have been identified unless vasopressin levels were measured. It must also be remembered that patients with cortisol deficiency have an impaired ability to excrete a water load. Therefore patients with combined anterior and posterior pituitary dysfunction might not manifest symptoms of DI until they receive replacement with hydrocortisone and may need to be retested at that stage.

Although it is felt that GH deficiency and diabetes insipidus occur as a result of a single hypothalamic lesion (Braunstein & Kohler 1972), other authors have suggested that GH deficiency is not a direct complication of histiocytosis, unless irradiation has been given (Dean, Bishop, & Winter 1986). Of the 7 patients in our cohort who had received irradiation to the region of the hypothalamus and pituitary (doses 10 to 12 Gy), only 5 have anterior pituitary dysfunction, of whom 4 had had GHI diagnosed prior to the radiotherapy. Of these 5 patients, 4 also had DI,

indicating that damage may have resulted from a primary hypothalamo-pituitary lesion. Those with panhypopituitarism presented with a hypothalamic mass and multiple endocrine deficiency at diagnosis. Only one of the patients (Pt. No. 29) had an evolving endocrinopathy with GHI and gonadotrophin deficiency at diagnosis and later developed ACTH deficiency. In our patients the doses of radiotherapy used were lower than those used in the study reported by Dean *et al.*, in which some patients received up to 30Gy in fractions, a dose which is well recognised as resulting in pituitary dysfunction. It therefore appears that anterior pituitary dysfunction, in our cohort, is a consequence of hypothalamo-pituitary involvement by LCH rather than secondary to radiation, at least in these relatively low doses.

The time from diagnosis of LCH to the development of anterior pituitary endocrinopathy can vary widely. In our cohort this ranged from 0 to 10 years. In a recent study of adults with LCH, it was found that anterior pituitary deficiencies may develop up to 22 years after diagnosis of LCH(Kaltsas et al. 2000). It is therefore imperative that all patients have careful 'long term' follow up through adult hood with an endocrinologist.

Growth

Poor growth is a recognised sequela of LCH and can be caused by one or more factors including chronic illness, vertebral collapse following infiltration by LCH tissue, prolonged steroid therapy and growth hormone deficiency. In our study the height SD score at diagnosis of LCH was below that expected for target height in most patients, whether or not they were growth hormone insufficient. This finding suggests that the disease itself may affect growth, possibly due to chronic ill health and poor feeding prior to diagnosis, especially since our patients without growth hormone insufficiency eventually showed catch-up growth after the disease had remitted. Although they reach a final height close to target height, the median final height SDS corrected for target height SDS was not statistically different from the patients who were GH insufficient, suggesting that there is a direct and permanent effect of LCH on growth. There are few studies of growth outcome in LCH and reports on final height are needed before the true impact of the disease on growth can be determined. This study is the first to address the question of the final height outcome after LCH and provides a basis for further studies.

The few studies of the use of GH replacement in LCH have shown that treatment is beneficial and safe (Braunstein, Raiti, Hansen, & Kohler 1975;Howell, Wilton, & Shalet 1998). Howell et al retrospectively analysed data from the Kabi (Pharmacia and Upjohn) International growth database (KIGS). They found that patients with LCH showed a response to GH similar to that seen in children with idiopathic growth hormone deficiency with an increase in median height SDS from –2.0 to –0.8 after 3 years of treatment. Final height data were however not available. There was no recurrence of LCH and no side effects were seen apart from benign intracranial hypertension in one patient. Our patients did not have any side effects on GH therapy and no patient had recurrence of LCH after commencing GH.

The GH insufficient patients in our study showed catch-up growth similar to that reported in these previous studies, but did not reach their expected target height. Several factors have been identified which influence the long-term response to GH therapy in GH deficient children (Blethen et al. 1997;Rappaport et al. 1997). Early treatment before the onset of significant growth failure has consistently been found to be a critical factor in optimising final height (Blethen et al. 1993;Boersma, Rikken, & Wit 1995). The earlier treatment is started, the more likely it is that the patient will attain his/ her full growth potential. However, even then not all GH deficient children reach their target height as the effects of GH therapy seem to wane with time (Arrigo et al. 1998;Rappaport, Mugnier, Limoni, Crosnier, Czernichow, Leger, Limal, Rochiccioli, & Soskin 1997). In our study GH therapy was commenced when most patients had already suffered severe growth failure with a mean height SD score of –2.2 and therefore might not have attained their expected target height. The advent of biosynthetic GH has promoted the use of higher doses, which can bring about dramatic improvements in the final height of GH deficient subjects. However, the optimum dose is a controversial issue. It has been shown that doses as high as 25 IU/m^2/wk can normalise final stature in GH deficient children with ultimate attainment of target height (Blethen, Baptista, Kuntze, Foley, LaFranchi, & Johanson 1997). Our patients received the usual recommended dose of 15-20 IU/m^2/wk and we do not know whether higher doses would have significantly altered the final height outcome. GH treatment does not appear to be sufficient to normalise final stature in this group of patients especially in those with dramatic growth failure at the time of active disease.

One patient, with panhypopituitarism, hyperphagia and gross obesity, grew normally without growth hormone replacement. This phenomenon is not yet

understood, but has been reported by several authors in patients with craniopharyngioma (Bucher et al. 1983;Kenny et al. 1968). In these patients it has been postulated that hyperinsulinism associated with hyperphagia and obesity, due to hypothalamic damage, contribute to continued growth in the absence of growth hormone. In some patients, prolactin hypersecretion may have been responsible for maintaining normal IGF I values. This phenomenon of "growth without growth hormone" has never been described in LCH before, but it is likely that a similar mechanism operates.

"Hypothalamic syndrome"

Most reports of hypothalamic involvement by LCH over the years have focused on the endocrine manifestations of hypothalamo-pituitary involvement with less mention of other aspects (Jinkins 1987;O'Sullivan et al. 1991;Ober et al. 1989;Tabarin, Corcuff, Dautheribes, Merlio, Cochet, Maire, Louail, & Roger 1991;Tibbs, Challa, & Mortara 1978). The LCH-related syndrome of behavioural abnormality, appetite imbalance and temperature instability is a relatively newly recognised phenomenon, and has been discussed as part of personal communications, rather than having been reported in the literature. As 5 (12.5%) of our patients had evidence of such problems, it may be more common than has been appreciated. In the younger child, these symptoms are often mistaken for temper tantrums and in the young adolescent may be regarded as being "teenage behaviour". It is therefore crucial that the combination of features – aggressive, often unprovoked outbursts, abnormal eating patterns with binge eating and obesity and temperature instability - are recognised as a possible 'hypothalamic syndrome'. Loss of thirst sensation is very rare in hypothalamic involvement due to LCH and has only been reported in individual cases (Catalina et al. 1995;Leung & McArthur 1988;O'Sullivan, Sheehan, Poskitt, Graeb, Chu, & Joplin 1991). This contrasts with patients with hypothalamic damage secondary to a craniopharyngioma, who often have adipsia in combination with DI making the control of water balance very difficult.

In conclusion, anterior pituitary dysfunction was more common in our patients than has previously been reported. It is likely that more rigorous follow up in our hospital by a dedicated, multidisciplinary team, with careful monitoring of growth has contributed to an increased and early recognition of patients with endocrinopathy.

Table 3.3. Patients with anterior pituitary dysfunction

This table shows the details of the 10 patients with anterior pituitary dysfunction, including the presenting features of endocrine dysfunction, time between diagnosis of LCH and endocrinopathy, results of endocrine testing and details of irradiation to the brain and pituitary.

Abbreviations: GH = Growth Hormone, LH = Lutenizing Hormone, FSH = Follicle Stimulating Hormone, TSH = Thyroid Stimulating Hormone, TRH = Thyrotropin Releasing Hormone, cGy = centigray (dose of radiotherapy)

Pt. No	Presentation	Time between diag of LCH and GHI	Age at initial test (yrs)	Peak GH (mu/L)	LH Basal/ Stimulated	FSH Basal/ Stimulated	TSH after TRH stimulation	Cortisol nmol/L (peak)	Pituitary radiation Timing/ Dose/ site/
4.	DI, normal growth, CT scan – 15mm mass hypothalamus	5 months	9.7	<0.5	2.5 / 1.5	1 / 2.2	1.2, 3.9, >64	74	1200cGy to hypothalamic mass 3 days after diagnosis of panhypopituitarism
11.	Poor growth	50 months	5.5	1.6	1.1/ 2.3	<0.3 / 1	2.0, 4.3, 3.0	664	2 years after diagnosis of GHI to parietal skull lesion
20	Slow growth, poor pubertal growth	120 months	5	18.4	<0.7 basal	0.9 basal	1.9, 17.6, 10.6	normal	2.5 years preceding GHI, for loss of 1200 cGy orbit vision
21	Poor growth	66 months	8	<2.0	0.8 / 1	0.6 / 1.3	1.2, 3.9, 3	493	No
23	Short stature	108 months	9.3	12.8	8.0 / 2.4	0.9 / 6.3	6.2, 25.6, 16.9	731	No
24	Short stature	8 months	4	12.6	prepubertal	prepubertal	NA	normal	No
25	Slow growth	65 months	8.4	14.7	prepubertal	prepubertal	2.9, 11.3, 8.4	normal	No
26	Slow growth	91 months	11.3	6.3	2.7 / 8.4	<0.8 / 0.9	0.4, 1.9, 2.1	1041	No
27	Slow growth	120 months	12.8	18.6	<0.5 / 3.9	<0.2 / 2.1	3.1 basal	1572	No
29	Fatigue, Wt gain	29 months	18	1.8	2.5 /21.3	<0.5 / 1.7	0.8,3.3,2.5	911	3 years after diagnosis of GHI.
32	Short stature	29 months	5.5	<0.5	<0.8 / 1.4	<0.6 / 0.9	<0.5, 7, 7.8	<55	No
33	Slow growth	99 months	7.8	5.1	NA	NA	Initial normal	normal	
40	Short stature	83 months	8.3	2.8	<0.8 / 1.3	<0.6 / <0.6,	3.4,8.5,4.7	716	2 mths after diagnosis GHI. 1200 cGy whole cranium, 300cGy to occiput

Table 3.4. Reassessment of endocrine function

This table shows the results of endocrine reassessment in 6 patients at the end of their growth.

Abbreviations: GH = Growth Hormone, LH = Lutenizing Hormone, FSH = Follicle Stimulating Hormone, TSH = Thyroid Stimulating Hormone

Pt No.	Age in years at reassessment	Peak GH (mu/L)	LH Basal/ Stimulated	FSH Basal/ Stimulated	TSH Basal/ Stimulated	Peak Cortisol
20	17.3	4.4	3.1 basal	3.2 basal	1.8 basal	448
21	16.5	2.3	2.4 basal	2.3 basal		480
23	17.8	8.4	3.9 / 30.6	3.7/ 7.6	2.3/ 17.6	693
25	16.8	1.9	6.7/ 31.7	6.1/ 8.7	2.2/ 10.6	768
26	17.8	16.5	<0.7/ 8.2	2.2/ 3.4	0.3/ 2.0	507
40	18.9	<0.1	<0.7/ 2.4	0.9/ 1.3	0.1/ 0.3	270

Table 3.5. Growth data for group 1a

This table shows the growth data for Group 1a (patients with GH insufficiency who have reached final height)

Pt No	Endocrine abnormality	Treated with GH	Chronological Age (CA) at assessment (years)	Final Height (cm)	Final Ht SDS	HtSDS corrected for TH	Target Height (cm)	Target Ht SDS
4.	DI, panhypopit	No	23.1	172.4	1.44	2.24	159	-0.79
11.	GHI	Yes	18.6	165.9	-1.5	-1.12	174.9	-0.4
20.	DI,GHI	Yes	16.3	163.5	0.01	-0.78	168.5	0.79
21.	DI,GHI, Gndef	Yes	16.9	181.1	0.83	-0.06	183.7	0.89
23.	DI,GHI	No	16.4	151.5	-1.95	-2.77	168.5	0.79
24.	DI, GHI	No	24.0	155	-1.46	-1.18	162.1	-0.29
25.	DI,GHI, Gndef	Yes	19.2	151.5	-2.02	-1.69	161.8	-0.34
26.	Partial DI, GHI	Yes	17.1	166	-1.34	-1.2	176.7	-0.14
29.	DI, panhypopit	Yes, as adult	31.1	171.4	-0.92	0.28	169.5	-1.2
32.	DI, panhypopit	Yes	18.1	148.9	-2.44	-1.98	161.0	-0.46
33.	DI, GHI, Gndef hypothyroid	Yes	18.0	164.9	0.22	-0.16		
40	DI, GHI, Gndef hypothyroid	Yes	17.3	166.5	-1.31	-0.16	178.5	0.13

Table 3.6. Growth data for group 1b

Growth data for the 1 patient in Group 1b (patient with GH insufficiency who has not reached final height)

Pt No	Endocrine abnormaiity	Treated with GH	Chronologicai Age (CA) at assessment (years)	Ht at last visit (cm)	Ht SDS	HtSDS corrected for TH	Target Height (cm)	Target Ht SDS
27	DI, GHI	Yes	15.6	164.4	-0.94	-1.63	182.3	0.69

Table 3.7. Growth data for group 2a

This table shows growth data for Group 2a (patients without GH insufficiency who have reached final height)

Patient No	Endocrine abnormality	Chronological Age (CA) at assessment (years)	Final Height in cm	Final Ht SDS	HtSDS corrected for TH	Target Height	Target Ht SDS
5.	None	16.3	159	-0.69	-0.65	163.5	-0.04
7.	DI	20.0	178.9	0. 33	1.16	172	-0.83
8.	DI	19.5	155	-1.4	-1.4	163.5	-0.04
10.	None	18.7	183.3	0.97	0.77	179	0.2
12.	None	19.2	166.8	-1.41	-0.06	168.5	-1.35
13.	None	24.8	173	-0.68	-1.07	180.3	0.39
14.	None	16.6	172	1.42	-0.04	172.5	1.46
15.	None	30.9	175.3	-0.34	-1.21	183.5	0.87
16.	None	27.0	165.5	0.29	0.33	163.5	-0.04
31.	DI	15.2	140.6	-3.47	-2.32	156.9	-1.15
35.	None	16.8	167.4	-1.04	-0.28	172.5	-0.76
37.	None	17.7	162.5	-0.18	1.2	155.5	-1.38
38.	None	9.9	138.4	0.33	0.53	161.4	-0.4
39.	None	26.6	149.0	-2.46	-1.42	157.5	-1.05

Table 3.8. Growth data for group 2b

This table shows the growth data for group 2b (patients without GH insufficiency who have not reached final height).

Patient No	Endocrine abnormality	Chronological Age (CA) at assessment (years)	Height (Ht) in cm	Ht SDS corr CA	HtSDS corrected for TH	Target Height (cms)	Target Ht SDS
1.	DI	9.6	135.2	-0.11	-1.24	170.6	1.13
2.	None	12.5	158.9	0.95	1.83	158.5	-0.88
3.	DI	9.4	127.3	-1.31	-1.88	181.5	0.57
6.	None	9.7	142.5	0.95	-0.73	189	1.68
9.	None	10.7	131.2	-1.65	-0.36	156.1	-1.29
17.	None	14.3	152.8	-1.41	-0.87	174	-0.54
18.	DI	13.9	160.0	0.57		Unavailable	
19.	None	15.9	157	-2.07	-1.09	171.0	-0.98
22.	None	6.9	122.5	0.43	0.65	162.4	-0.22
28.	None	13.7	165.9	0.67	0.71	177.4	-0.04
30.	None	11.7	136.2	-1.47	-0.94	174.1	-0.53
36.	None	13.8	173.6	1.58	0.79	183	0.79

Chapter 4. Central Nervous System Involvement

Introduction

This chapter describes the clinical abnormalities of the central nervous system (CNS), cognitive outcome and correlates the findings with the MRI appearances of the brain.

The association between histiocytosis and the brain has been recognised from early descriptions of the disease, and in a comprehensive review, Kepes discusses the clinical and pathological features of involvement of the central nervous system (Kepes 1979). The regions most commonly involved are the hypothalamo-pituitary axis, the meninges, the cerebellum and the cerebral hemispheres, while the basal ganglia, brain stem and spinal cord are affected less often. There is increasing awareness of the CNS manifestations of LCH, in particular the late onset "cerebellar syndrome" which often appears several years after active disease has 'burnt out'. Patients present with ataxia, incoordination and clumsiness and on MRI scan have bilateral signal change in the cerebellar hemispheres and nuclei (Grois, Favara, Mostbeck, & Prayer 1998).

Neuropsychological sequelae of LCH have been recognised for some time but few studies have systematically assessed the cognitive outcome of children with LCH. To date most studies have reported either single cases or small numbers of patients (Braunstein, Whitaker, & Kohler 1973;Cervera, Madero, Penas, Diaz, Gutierrez-Solana, Benito, Ruiz-Falco, & Villa 1997;Hayward, Packer, & Finlay 1990). Long term follow up studies published to date only occasionally and briefly mention the intellectual outcome of patients (Komp, El Mahdi, Starling, Easley, Vietti, Berry, & George 1980) (Sims 1977). There are only 2 reports of neuropsychological assessments in children with LCH (Ransom, Powazek, Goff, Anderson, & Murphy 1978;Whitsett et al. 1999).

We undertook clinical neurological examination and detailed neuropsychological testing as part of this long term follow up study.

Section 4.1. Methods

4.1.1. Clinical examination and cerebellar score

All patients had a detailed clinical neurological examination. Cerebellar function was graded according to the International Co-operative Ataxia Rating Scale (Trouillas et al. 1997). Severity of symptoms was graded from 0 to 100; the higher the score the greater the abnormality. A copy of the scoring sheet is shown in **Appendix 3**. Specific history was obtained regarding behavioural and psychological disturbance, and children with problems were assessed by the Child Psychology team. Children with learning difficulty were identified from the history of school performance and requirements for special educational help.

4.1.2. Methodology for Neuropsychological Evaluation

Formal neuropsychological assessment was performed by designated research neuropsychologists, Ms Claire Chapman, Ms Louise Parry and Ms Leasha Lillywhite from the Neurosciences Unit at the Wolfson Centre, Great Ormond Street Hospital for Children and the Institute of Child Health, London.

Different aspects of cognitive function including intelligence, memory and learning, language, and academic attainments were assessed using the following tests as described by Vargha-Khadem et al and Christie et al (Christie et al. 1994;Christie et al. 1995;Vargha-Khadem F. et al. 1992).

a. **Intelligence** The age-appropriate Wechsler Intelligence scales were administered to evaluate intellectual ability.

*i) **The Wechsler Intelligence Scale for Children – Third edition UK (WISC–III)*** for children aged 6 years to 16 years and 11 months (Wechsler 1992)

*ii) **The Wechsler Adult Intelligence Scale – Revised UK (WAIS–R)*** for patients aged 17 years and over (Wechsler 1986)

The Wechsler Scales of Intelligence provide verbal, performance and full scale intelligence quotients (IQ). The average IQ is 100 (range 90 to 110). Mild learning difficulty was graded as IQ of 80 to 89, moderate learning difficulty IQ 70 to 79 and severe learning difficulty IQ <70 (<-2SD from the mean). Nineteen of the 28 children were assessed using the WISC–III and the 9 older patients using the WAIS–R. Five subtests are used to calculate the VIQ and the PIQ which have a mean of 100 and a standard deviation of 15. The scaled scores for each subtest yield standard scores with a mean of 10 and standard deviation of 3 (range 1 -19).

b. Memory and Learning.

(i) The Wechsler Memory Scale (Wechsler 1945), with age corrections for children, was used to assess memory and learning. The overall memory quotient, was calculated according to the WMS manual. In addition, two subtests were selected to provide measures of immediate and delayed recall for verbal and visual information (Logical Memory and Visual Reproduction), and one subtest to provide a measure of verbal learning and delayed recall (Paired Associate Learning).

Logical Memory. For children over the age of 12 years (n=20) the two standard Wechsler stories constituting the Logical Memory subtest (Form 1) were used, containing 24 and 22 units of information, respectively. For children below the age of 12 years (n=8), two children's stories developed by Taylor (Kimura & McGlone 1979) were substituted for the standard Wechsler stories. Each contained 18 units of information. Whichever set was used, recall of each story was obtained immediately after its presentation and an average score was calculated for the pair. Following a 90 minute interval filled with unrelated tasks, delayed recall of each story was obtained and an average score again calculated.

Paired Associate Learning. This subtest was administered as described in the WMS manual and scored for immediate recall after each of the three presentations of the 10 paired associates. The set of 10 pairs consists of six pairs of related items (e.g. up-down) and four pairs of unrelated items (e.g. cabbage-pen). The related and unrelated items were scored separately. Recall was also measured after a 90 minute filled delay. Delayed recall was scored out of 10.

Visual Reproduction. The immediate reproduction of geometric designs was scored as described in the WMS manual. In addition, following a 40 minute delay filled with other tasks, participants were again asked to draw the geometeric designs from memory.

(ii) ***The Children's Auditory Verbal Learning Test -II Ed (CAVLT-II)*** (Talley 1993) was administered to provide measures of immediate memory span, level of learning, interference with learning, recognition accuracy, and immediate and delayed recall. The test involves a list of 16 words (List A) being presented five times for immediate recall. An interference list of 16 words (List B) is then presented for immediate recall before the child is asked to recall the original list (List A). The child is also asked to recall the words (List A) after a 20 minute delay. This test provides standard scores which have a mean of 100 and a standard deviation of 15.

c. Language.

(i) ***The British Picture Vocabulary Scale (BPVS)*** (Dunn 1982) was administered to provide a measure of receptive vocabulary for words and concepts. This test does not require the child to read, write, or speak as he or she is instructed to point to one of four pictures that best matches the word spoken by the examiner. Raw scores are then converted to standard scores which have a mean of 100 and standard deviation of 15.

(ii) ***The Wechsler Objective Language Dimensions (WOLD)*** (Wechsler 1996a) comprises several subtests. The Listening Comprehension subtest examines the child's understanding of orally presented words and passages. In the Words subtest, the child is presented with a page of four pictures and is instructed to point to the picture that corresponds to the word. For the Passages subtest, a related picture is shown and the participant is asked to answer questions relating to the passages heard. The Oral Expression subtest assesses the ability to describe a target word, describe a scene, give directions and explain steps. Scores are converted to age-graded standard scores which have a mean of 100 and a standard deviation of 15. The Written Expression subtest of the WOLD was not administered.

d. Academic Attainments.

(i)***The Wechsler Objective Reading Dimensions (WORD)*** (Wechsler 1993) comprises three subtests: Basic Reading, for which the child has to read the words of increasing difficulty; Spelling, which requires the child to write the spelling of verbally presented words of increasing difficulty; and Reading Comprehension, in which the child has to read a passage aloud and answer questions on it. Scores are converted to age-graded standard scores with a mean of 100 and a SD of 15.

(ii) ***The Wechsler Objective Numerical Dimensions (WOND)*** (Wechsler 1996b) comprises two subtests: Mathematical Reasoning which taps the ability to reason mathematically, and Numerical Operations which assesses the ability to write dictated numerals and solve calculation problems involving basic operations. Scores are converted to age-graded standard scores which have a mean of 100 and a SD of 15.

MRI was performed according to standard protocol (described in Chapter 5).

Section 4.2. Results

Ten (25%) of the 40 patients had clinical and/ or MRI evidence of CNS involvement. The neurological abnormalities and relevant MRI appearances in these 10 patients are summarised in **Table 4.1**. A detailed description and discussion of MRI findings is given in Chapter 5.

Clinical CNS abnormalities included ataxia and incoordination, psychological problems and learning difficulty reported by parents and /or teachers. These problems were not evident at diagnosis of LCH, and were unusual during the "acute" phase of the illness. The time from diagnosis of LCH to the first symptom suggestive of CNS damage ranged from 8 to 240 months (mean 112 months, median 108 months). Only 1 child presented with severe behavioural problems within the first year of diagnosis of LCH and was later noted to have learning difficulty. All the rest of the patients developed symptoms/ signs of CNS damage as "late" sequelae.

4.2.1. Cerebellar involvement

Seven patients (70% of patients with CNS involvement, 17.5% of entire cohort) had clinical evidence of cerebellar involvement, with incoordination and /or ataxia. The degree of disability ranged from mild incoordination on clinical testing to gross ataxia requiring support to walk. In 4 of these 7 patients (10% of the entire cohort) the ataxia and incoordination caused functional impairment. The clinical status of these 4 patients appears stable at present with no obvious deterioration in function. Two of the 4 patients occasionally require the use of wheel chairs to travel between classes at college or on long trips to prevent fatigue.

Scores on the Ataxia Rating Scale ranged from 0 to 54 (mean 6.9, median 0) in the entire cohort. Twenty-five of 40 patients (62.5%) had no detectable abnormality of cerebellar function - scores of 0. Seven (17.5) had scores of <9, 1 had a score of 18 and the 7 patients (17.5%) with clinically detectable cerebellar dysfunction, as described above, had scores of >20.

MRI of the cerebellum showed bilateral signal change in the hemispheres and the dentate nuclei in 5 of the 7 patients with the most severe clinical findings. One of the remaining 2 patients had prominent cerebellar folia, while in the other the cerebellum had a normal appearance. Conversely, 1 patient with no ataxia/ incoordination on examination, had bilateral signal change in the cerebellar hemispheres and thalamus on MRI scan.

4.2.2. Motor Abnormalities

One patient (Pt. No. 15) developed an intracranial Aspergillus infection, with several space-occupying lesions, secondary to chronic steroid treatment. He has a residual hemiparesis, a seizure disorder requiring anticonvulsant therapy, and psychological problems. However, as these handicaps are not a direct consequence of the LCH, we have not included this patient in the 'CNS group'. None of the other patients had seizures.

4.2.3. Behavioural and Psychological abnormalities

Eleven of 40 patients (27.5%) had abnormalities of behaviour or psychological problems. Five patients had evidence of hypothalamic damage, manifesting as one or more of the following: behavioural change, abnormal eating patterns and temperature instability. These patients are discussed in more detail in Chapter 3. Four of these 5 patients have additional psychological problems. One has intermittent symptoms requiring psychological help, one has periods of depression secondary to the chronic disability due to severe lung involvement, a third has exhibited anti-social behaviour and problems with inter-personal relationships while the fourth patient has very marked psychological abnormalities including violent thought processes, a fascination with "fire-setting", and a tendency to cross dressing. Four of the other 6 patients have moderate to severe learning difficulties affecting their behaviour and the ability to care for themselves and to lead independent lives. Pt. No. 15, who has a residual hemiparesis, has had intermittent depression and has required psychotherapy. One patient, now aged 20 years, suffered from a depressive illness with agoraphobia and claustrophobia, requiring anti depressive medication and psychotherapy. As a result, he has not been able to work.

Table 4.1. CNS abnormalities and MRI changes

This table shows details of behavioural and learning difficulty, intelligence quotient (FSIQ), degree of cerebellar dysfunction and related MRI changes in the 10 patients with abnormalities of the central nervous system.

Pt No	Age (yrs)	Behaviour and psychological problems	FSIQ	Ataxia Scale (0-100)	MRI Abnormality	
					Cortical Atrophy	Cerebellar Signal
11	18.6	Abnormal behaviour, learning difficulty, impaired ability to lead independent life	72	54	Moderate	Abnormal
19	14.4	Learning difficulty	77	24	Mild	Normal
21	17.6	Learning difficulty, marked psychological problems preventing employment and affecting ability to lead independent life	83	6	Moderate	Normal
22	7.0	Mild learning difficulty	77	18	Mild	Normal
24	23.8	No problems	Not done	20	Mild	Prominent folia
26	15.7	Severe behavioural and psychological problems, learning difficulty	75	40	Moderate	Abnormal
27	13.8	Learning difficulty, depression, behavioural abnormality	80	0	None	Normal
31	14.6	Severe learning difficulty, abnormal behaviour, rage attacks, impaired ability to lead independent life	61	40	Severe	Abnormal
32	18.0	Learning difficulty, abnormal behaviour, problems with interpersonal relationships and integration into society	Not done	27	Moderate	Abnormal
40	16.5	Learning difficulty, impaired ability to lead independent life	63	44	Severe	Abnormal

Risk factors

Nine of the 10 of the patients with CNS involvement in this study had had skull involvement during the acute phase. Five of the 10 patients had had orbital involvement. There was no obvious association between the degree of damage to the CNS and the use of radiotherapy. Only 2 of the 10 patients with CNS involvement had received cranial irradiation, while none of the patients who had received radiation to the hypothalamo-pituitary region or orbit developed CNS damage.

There did appear to be a relationship between the duration of therapy for the acute illness and the presence of CNS sequelae, but this difference was not statistically significant. The total dose and duration of steroid therapy in the CNS group was also greater than that in patients without CNS involvement. Again, this difference was not statistically significant.

These findings are tabulated in **Table 4.2**

4.2.4. Cognitive outcome

Twenty-eight (13 male, 15 female) of the 40 patients had psychometric evaluation at follow-up assessment, using standardised tests of intelligence, memory, language and academic attainments (see above). Twelve patients were not tested either because they could not attend the session due to educational or work commitments, or due to failure to attend several appointments.

The mean IQ of the whole group was within the normal limits when compared to the hypothetical mean of 100 (range 90 to 110) for the normal population, but there were wide ranges. The mean Full Scale IQ (FSIQ) was 93.6 (range 61.7 to 134), the mean Performance IQ (PIQ) was 92.2 (range 46 to 136) and the mean Verbal IQ (VIQ) was 93.7 (range 64.2 to 126). In an attempt to understand these variations in intelligence we performed a regression analysis. This showed that there was a significantly lower (<0.001) mean FSIQ, PIQ, VIQ and MQ in the patients with CNS involvement as judged by clinical and/or MRI evidence compared to patients without any CNS involvement. Other factors such as the presence of diabetes insipidus, gender and the use of radiotherapy made no significant difference.

These results are shown in **Tables 4.3 and 4.4.**

Table 4.2. Risk factors in the patients with and without CNS involvement

This table compares the 2 groups of patients – with and without clinical CNS involvement. There was no statistically significant difference between the 2 groups with regard to possible risk factors, including skull and orbital involvement, radiotherapy to the cranium, duration of active disease as assessed by years of treatment or the dose of steroids received.

	CNS involvement (n=10)	**No CNS involvement** (n=30, including DI n=11)	**Significance**
Skull involvement	9 (90%)	25 (83%)	ns
Orbit	5 (50%)	7 (23%)	ns
Radiotherapy to the head	2 (20%)	6 (20%)	ns
Years of treatment for active disease	Mean 4 Median 2.6 Range 0.34 to 13.5	Mean 2.25 Median 1.2 Range 0 to 20	ns
Cumulative dose of steroid in milligrams/ kilogram body weight	Mean 380 Median 300 Range 56 to 1000	Mean 230 Median 100 Range 0 to 2000	ns

Table 4.3. Regression analysis of Full Scale Intelligence Quotient

This table shows the results of a linear regression model where Full scale IQ (FSIQ) is the dependent variable. The predictors were CNS involvement (0=no, 1=yes), DI (0=no, 1=yes), gender (0=male, 1=female) and cranial / pituitary radiotherapy (0=no, 1=yes). The only significant factor was the presence of clinical CNS involvement.

Variable	Coefficient (confidence intervals)	p value
CNS	-29.15 (- 42.5 to –15.86)	<0.0005
Diabetes insipidus	0.284 (-12.45 to 13.018)	0.964
Gender	-4.91 (-16.3 to 6.49)	0.382
Radiotherapy	-1.29 (-18 to 15.41)	0.87

Regression analyses for Verbal IQ and Performance IQ were similar with the only significant variable being CNS involvement (p <0.0005)

Table 4. 4. Regression analysis of Memory Quotient

This table shows the results of a linear regression model where Memory Quotient (MQ) is the dependent variable. The predictors are as above. Again CNS involvement was the only significant factor.

Variable	Coefficient (confidence intervals)	p value
CNS	-29.7 (-44.06 to –15.35)	<0.0005
Diabetes insipidus	-3.05 (-16.74 to 10.63)	0.65
Gender	-5.38 (-18.08 to 6.43)	0.33
Radiotherapy	1.81 (-16.15 to 19.77)	0.84

The confidence intervals for the patients with diabetes insipidus and those who had received radiotherapy are wide, as there are only 6 and 4 patients respectively in these 2 groups. There were 13 males and 15 female patients.

We looked at individual patient FSIQ scores (see **Appendix 4**) and found that all but 4 of the patients with scores below the normal range had identifiable CNS involvement. We then went on to divide the patients into groups depending on their clinical status and neuroimaging findings into those with and without CNS involvement. Although patients with hypothalamo-pituitary involvement have traditionally been classified as having 'CNS disease', we found that those with isolated diabetes insipidus (DI) had a neuropsychological outcome similar to that of patients without any evidence of CNS involvement at all. We therefore divided the patients into 3 groups – those with no CNS or hypothalamo-pituitary involvement ('No CNS' n =14), those with isolated DI ('DI' n=6) and those with other CNS involvement, with/ without DI ('CNS' n=8). The CNS group included patients with cerebellar ataxia, abnormal behaviour and/or MRI abnormality such as cerebellar signal change, hydrocephalus, meningeal infiltration and cerebral atrophy. Some of the patients with abnormal imaging had no clinical evidence of CNS involvement. None of the patients in 'No CNS' group had received cranial irradiation, 2 of the patients in the 'DI only' group had received radiotherapy to the hypothalamo-pituitary region, while 2 of the patients with CNS involvement had received irradiation to the skull.

Six of the 8 patients in the CNS group had a history of learning difficulty. Pt. No 22 was the youngest patient in the group, being 6 yrs at the time of testing. She was included in the CNS group as she was noted to have subcortical white matter streaking in the left temporal lobe with minimal cortical enhancement and some supratentorial cortical atrophy on MRI scan. One patient (Pt. No 27) had abnormal behaviour suggestive of hypothalamic damage and learning difficulty. However, he had no detectable abnormality on clinical neurological examination and a normal MRI appearance of the cerebral cortex and cerebellum, the only abnormality on imaging being minimal thickening of the pituitary stalk. The other 6 patients in this group had both clinical and imaging abnormalities of the CNS and the 2 most severely affected patients, with IQ < 65 (1^{st} percentile), showed evidence of gross neurological damage.

The assumptions of normality and homogeneity were checked for all data before parametric analyses were conducted on standard scores and percent correct values. One-way analysis of variance (ANOVA) indicated no significant group differences on the variables - age at diagnosis of LCH, age at assessment and time elapsed (**Table 4.5**)

Table 4.5. Cognitive function - Patient details

This table shows the Number of patients in each group, Mean and Standard Deviation for Age at Diagnosis, Age at Assessment and the Time Elapsed between diagnosis and assessment.

The 3 groups are

'No CNS' – patients without any CNS involvement or diabetes insipidus

'DI' – patients with isolated diabetes insipidus

'CNS' – patients with clinical and /or MRI evidence of brain involvement

There was no significant difference in these parameters between the 3 groups.

Group	N	Age at diagnosis Mean (SD)	Age at assessment Mean (SD)	Time elapsed Mean (SD)
No CNS	14	1.6 (1.0)	16.2 (5.6)	14.7 (5.2)
DI	6	2.1 (1.0)	13.6 (4.5)	11.9 (4.3)
CNS	8	1.0 (0.9)	14.6 (3.11)	13.6 (3.9)

There was a significant difference in neuropsychological outcome between the groups. Patients without CNS involvement had IQs within the normal range – mean FSIQ 102.3 (SD 4.16), mean PIQ 102 (SD 4.6), mean VIQ 101.5 (SD 34.2) as did those with isolated DI – mean FSIQ 100 (SD 5.98), mean PIQ 97 (SD 3.98), mean VIQ 98.17 (SD 7.36). The patients with CNS involvement had significantly lower IQ with mean FSIQ 73.59 (SD 2.71), mean PIQ 71.38 (SD 4.26) and mean VIQ 76.8 (SD 3.22) [$p<0.001$]. Of the 8 patients in the 'CNS' group 2 had 'mild' learning difficulty (IQ 80 to 90), 4 had 'moderate' learning difficulty (IQ 70 to 79) while 2 had severe learning difficulty (IQ <70). Only 2 of 14 (14%) patients in the 'No CNS' group and 2 patients (33%) in the 'DI' group had a 'mild' learning difficulty.

Table 4.6 shows the group means and standard deviations on each of the test measures and indicates the level of significance (ANOVA) for differences between groups on individual measures. The 'CNS' group differed significantly from both the 'No CNS' and isolated DI groups on a number of specific measures including Verbal and Non Verbal (Performance) IQ, Verbal and Non Verbal Memory, Interference in Learning, Reading Comprehension, Mathematical Reasoning and Numerical Operations. The results of these tests are depicted graphically in Figures 4.1 to 4.9. In addition, the 'CNS' group differed significantly from the 'No CNS' group on Level of Learning, and significantly from the Isolated DI group on Delayed Paired Associates, Receptive Vocabulary and Word Reading. There were no significant differences between groups on Trial 3 Paired Associates, Immediate and Delayed Recall in Learning, Listening Comprehension or Word Spelling. *Post hoc* investigation (Scheffe) revealed that for each of these differences the 'CNS' group performed significantly below that of the other groups. There was a significant difference for gender on Word Reading ($t=2.47$; $p=0.022$) and Reading Comprehension ($t=3.44$; $p=0.002$); girls performed significantly better than boys. However there were no significant interactions between Group and gender on test performance.

A significant linear relationship between Full Scale IQ (FSIQ) Scores and performance on the majority of tests in other cognitive domains was observed (**Table 4.7**). This relationship was similar for each group. The test scores were then adjusted for FSIQ scores to look for differences, independent of intelligence, between the groups (ANCOVA). The 'CNS' group's performance remained significantly different from that of both the 'No CNS' and 'DI' groups on Immediate Non Verbal Memory ($F(2,21)=5.66$; $p=0.011$), Immediate Memory Span ($F(2,17)=3.88$; $p=0.041$), Interference in Learning ($F(2,17)=4.63$; $p=0.025$), Oral Expression ($F(2,11)=8.54$; $p=0.006$), and Reading Comprehension ($F(2,19)=4.75$; $p=0.021$).

Table 4.6. IQ scores

This table shows the Mean (SD) scaled scores for IQ, memory, learning, language and academic attainments in the 3 groups – patients with no CNS involvement (No CNS), isolated diabetes insipidus (DI) and with CNS involvement (CNS) -compared with the hypothetical mean of 100 for the normal population and the Level of Significance (One-way ANOVA) for Group Differences

		No CNS Mean (SD)	DI Mean (SD)	CNS Mean (SD)
Intelligence (Standard Scores)				
Verbal IQ	a	101.50 (12.81)	98.17 (18.04)	76.80 (9.12)
Non Verbal IQ	a	102.00 (17.23)	97.00 (9.76)	71.38 (12.05)
Full Scale IQ	a	102.29 (15.56)	100.00 (14.66)	73.59 (7.67)
Memory (Percent Correct)				
Immediate Stories	a	40.83 (15.41)	51.02 (20.56)	19.18 (8.14)
Delayed Stories		32.54 (14.45)	41.50 (16.12)	17.20 (4.07)
Immediate Verbal Memory	a	51.95 (10.94)	59.22 (9.56)	39.67 (6.77)
Delayed Verbal Memory	a	46.16 (11.60)	54.04 (7.00)	30.63 (9.65)
Immediate Non Verbal Memory	a	87.09 (10.57)	80.95 (12.09)	55.86 (9.57)
Delayed Non Verbal Memory	a	80.77 (15.81)	69.05 (18.02)	42.03 (13.98)
Trial 3 Paired Associates		87.14 (17.73)	95.00 (12.25)	80.00 (18.97)
Delayed Paired Associates	c	85.71 (19.89)	96.67 (8.17)	66.67 (24.22)
List Learning (Standard Score)				
Immediate Memory Span	a	107.25 (18.20)	114.60 (5.77)	75.27 (11.33)
Level of Learning	b	108.92 (15.26)	104.40 (13.67)	82.12 (21.41)
Interference in Learning	a	112.17 (14.72)	110.00 (10.72)	79.31 (8.25)
Immediate Recall		98.50 (21.75)	101.80 (4.76)	80.25 (23.98)
Delayed Recall		103.93 (15.57)	98.20 (9.65)	81.26 (22.84)
Language (Standard Scores)				
Receptive Vocabulary	c	108.56 (18.64)	99.80 (21.52)	68.12 (4.74)
Listening Comprehension		102.31 (18.08)	104.75 (8.34)	85.25 (7.50)
Oral Expression	a	104.00 (4.04)	104.25 (5.44)	80.31 (7.78)
Academic Attainments (Standard Scores)				
Word Reading	c	98.08 (12.82)	105.80 (11.90)	84.80 (15.43)
Word Spelling		92.83 (17.24)	110.20 (11.03)	83.27 (21.17)
Reading Comprehension	a	94.08 (12.52)	98.80 (4.92)	70.15 (8.18)
Mathematical Reasoning	a	101.58 (14.21)	97.40 (14.99)	70.60 (6.30)
Numerical Operations	a	97.92 (14.32)	98.60 (13.56)	76.60 (6.11)

a CNS group perform significantly below both 'No CNS' and 'DI' groups, $p<0.05$.

b CNS group perform significantly below 'No CNS' group, $p<0.05$.

c CNS group perform significantly below 'DI' group, $p<0.05$.

Table 4.7. Correlation of FSIQ with other test scores

This table correlates the Full Scale IQ (FSIQ) with test scores in other cognitive domains.

		r
Memory (Percent Correct)		
Immediate Stories	a	0.46
Delayed Stories		0.36
Immediate Verbal Memory (cprime)	a	0.57
Delayed Verbal Memory (c.)	a	0.65
Immediate Non Verbal Memory (dprime/14)	a	0.69
Delayed Non Verbal Memory (d/14)	a	0.72
Trial 3 Paired Associates (Trial 3/10)	a	0.53
Delayed Paired Associates (Delayed/10)	a	0.58
List Learning (Standard Scores)		
Immediate Memory Span	a	0.54
Level of Learning		0.41
Interference in Learning	a	0.54
Immediate Recall	a	0.56
Delayed Recall	a	0.44
Language (Standard Scores)		
Receptive Vocabulary	a	0.63
Listening Comprehension	a	0.71
Oral Expression	a	0.75
Academic Attainments (Standard Scores)		
Word Reading	a	0.61
Word Spelling	a	0.48
Reading Comprehension	a	0.64
Mathematical Reasoning	a	0.76
Numerical Operations	a	0.63

a = p value <0.05.

Figure 4.1. Individual scores for Full Scale IQ (FSIQ)

This graph depicts the full scale IQ of individual patients in the 3 groups. The hypothetical mean score for the normal population (solid line) and the range (dotted lines) are shown. All patients with CNS involvement had scores below normal. Only 2 patients in the 'No CNS' group and 2 in the DI group had low IQs.

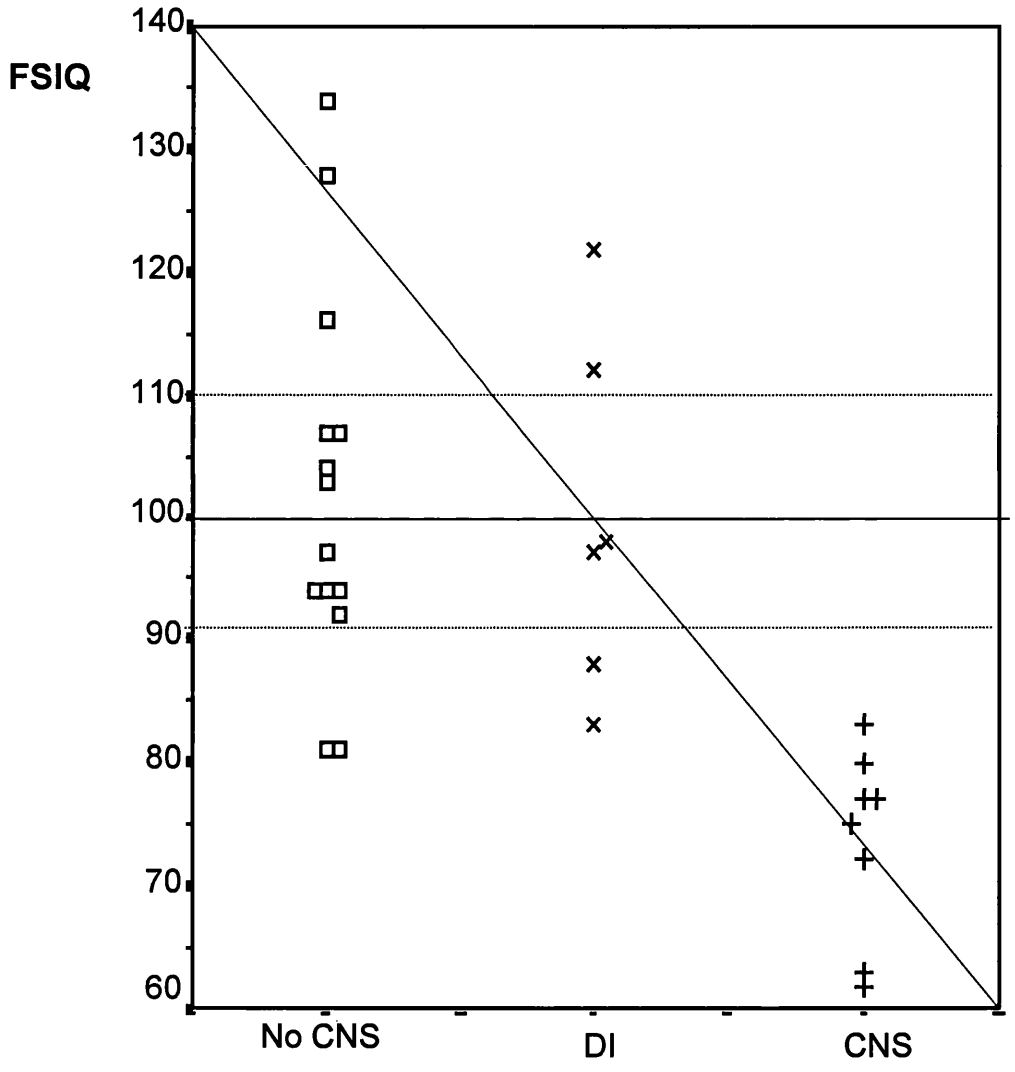


Figure 4.2. Intelligence Quotients

This bar graph depicts the mean verbal, performance and full scale IQs in the 3 groups – 'No CNS', 'DI' and 'CNS'. There was a significantly ($p<0.05$) lower IQ for all 3 measures in the CNS group.

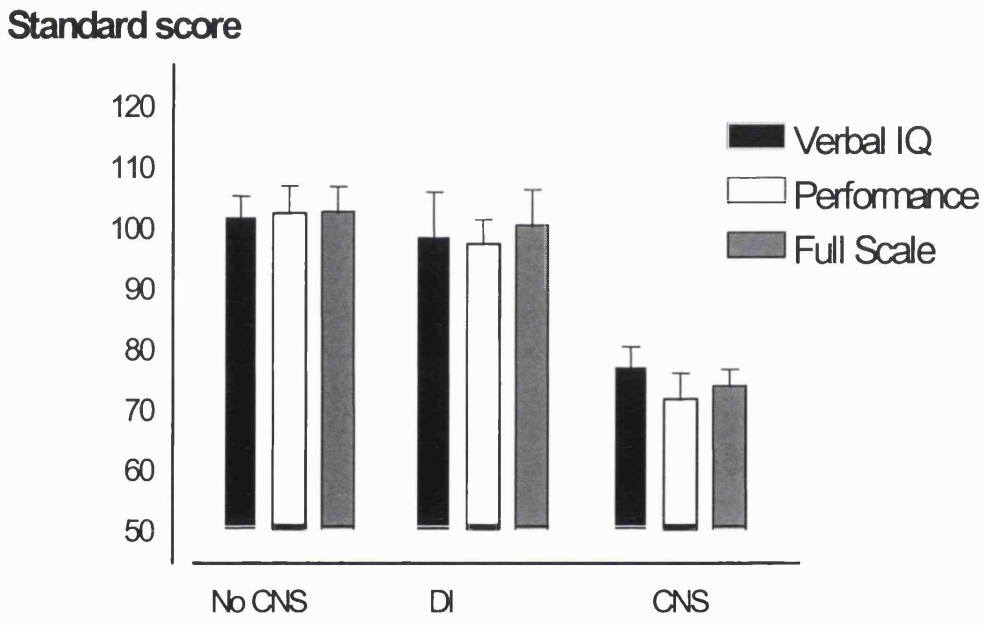


Figure. 4.3. Verbal Memory

This bar graph depicts the immediate and delayed verbal memory in the 3 groups – 'No CNS', 'DI' and 'CNS'. There is significantly reduced verbal memory in the CNS group, which is more pronounced in delayed recall (* p =<0.05)

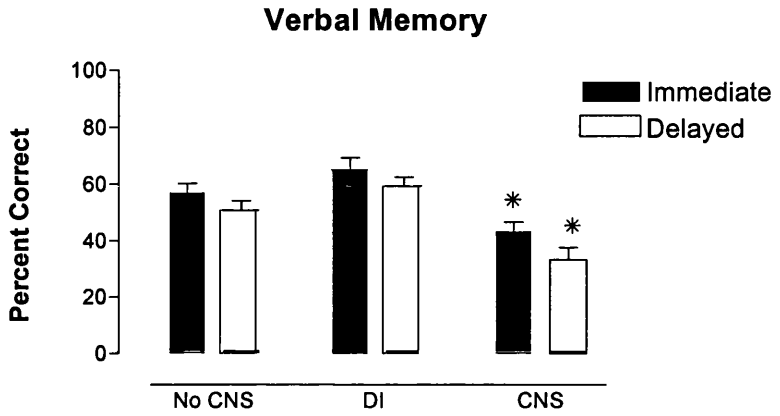


Figure 4.4. Visual Memory

This bar graph depicts the visual memory in the 3 groups There is significantly reduced visual memory in the CNS group, especially in delayed recall (* p =<0.05)

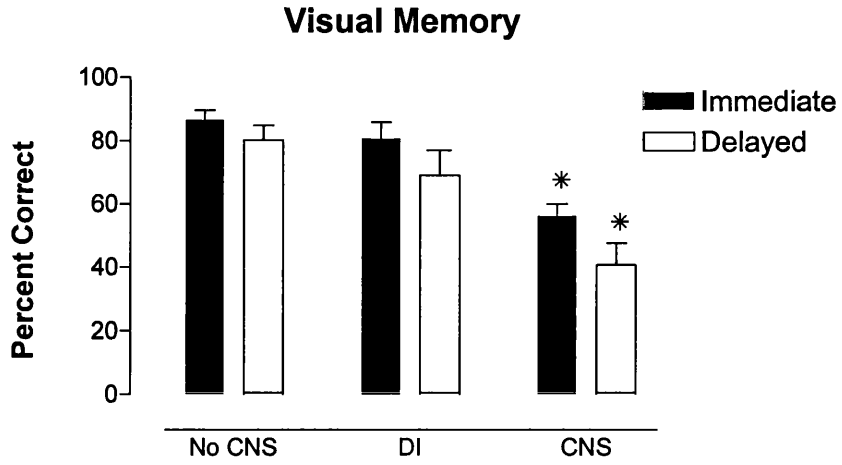


Figure 4.5. Learning

This bar graph depicts the level of learning in the 3 groups The tests of level of learning show significant reduction in the CNS group (* p =<0.05)

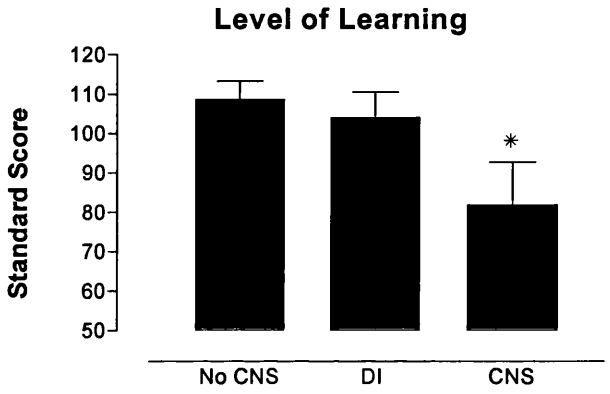


Figure 4.6.Language abiiity

This bar graph depicts the results for Language ability in the 3 groups. Patients with CNS involvement showed a significant reduction in both listening comprehension and oral expression (* p =<0.05)

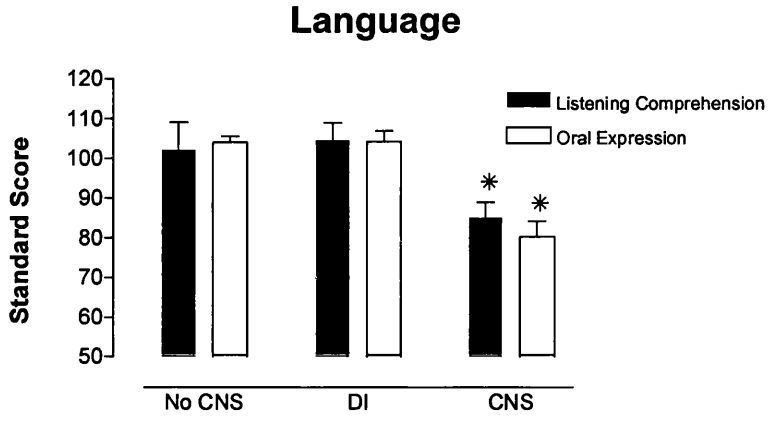


Figure 4.7. Vocabulary

This bar graph shows the results of vocabulary testing using the BPVS in the 3 groups. Receptive vocabulary showed significantly lower scores in the CNS group (* p =<0.05)

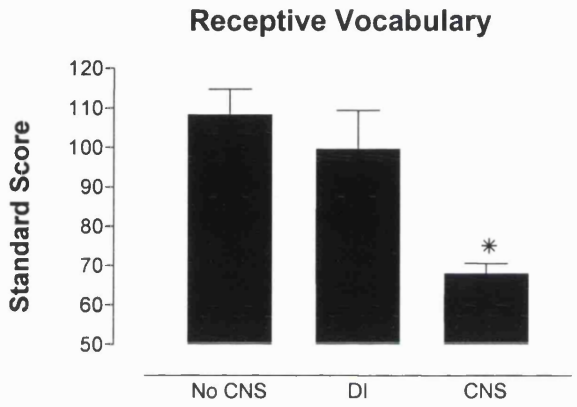


Figure 4.8. Reading Ability

This bar graph depicts the results for Reading, Spelling and Reading comprehension in the 3 groups. The CNS group had significantly lower scores for Reading comprehension (* p=<0.05)

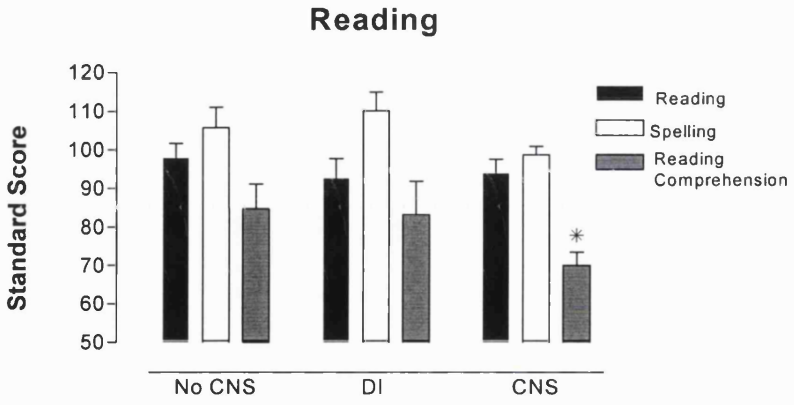
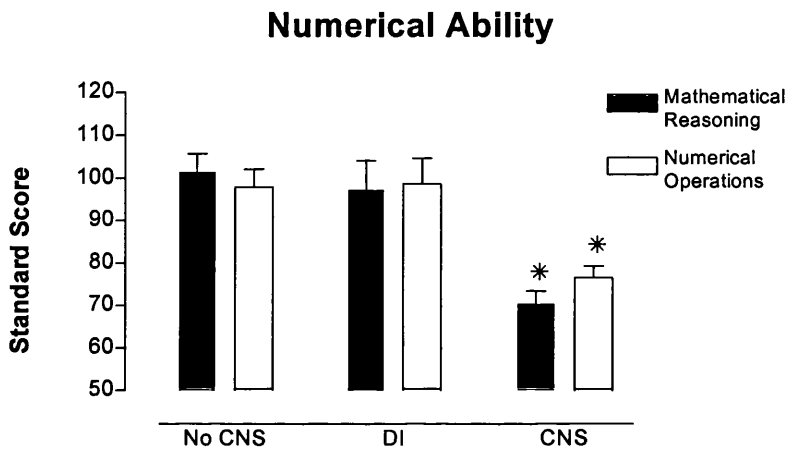


Figure 4.9. Numerical Ability

This bar graph depicts the results for Mathematical reasoning and Numerical operations in the 3 groups Patients in the CNS group showed significantly lower scores for both mathematical reasoning and numerical operations (*p=<0.05).



Section 4.3. Discussion

This is the first study, in our knowledge, to investigate in detail, neurological and cognitive function in children who survive multisystem LCH. Our study reveals significant impairment of brain function in this group of patients, much higher than had been previously recognised. Ten patients (25%) had CNS involvement, of whom 7 had clinical signs of cerebellar involvement. Of the 28 patients who had neuropsychometry performed, 12 (30% of the entire cohort) had evidence of cognitive deficit.

Although it has been recognized for many years that LCH can affect the brain, over recent years there has been a growing interest in CNS involvement in LCH, in particular with regard to the natural history, outcome and the possible pathogenetic pathways. CNS LCH can either be due to infiltration of structures by 'active' LCH, presenting with symptoms of a space occupying lesion, or due to the more common degenerative changes affecting the cerebellar-pontine region causing ataxia, dysarthria and tremor and the cerebral cortex resulting in intellectual impairment (Grois, Favara, Mostbeck, & Prayer 1998). The true incidence is not known but has been estimated to be between 1-3% (Grois, Favara, Mostbeck, & Prayer 1998). Most publications are descriptions of single case reports (Hayward, Packer, & Finlay 1990;Iraci, Chieco-Bianchi, Giordano, & Gerosa 1979) (Haslam & Clark 1971) or small numbers of patients, ranging from 2 to 4 (Braunstein, Whitaker, & Kohler 1973;Kepes & Kepes 1969;Rube, De La Pava, & Pickren 1967) (Cervera, Madero, Penas, Diaz, Gutierrez-Solana, Benito, Ruiz-Falco, & Villa 1997). In the recent LCH I study of the Histiocyte Society, over an observation period of 6 years, 6 patients with multisystem involvement (3 %) have been diagnosed as having symptoms/ signs of 'neurodegenerative' CNS disease (N. Grois, personal communication).

In our series of 40 patients with multisystem involvement, we found evidence of CNS involvement in 10 patients (25%). Some of this difference in prevalence from other follow up studies may be explained by referral bias, but it is more likely that careful assessment, both clinically and on MRI, have increased the sensitivity of detection. We feel that CNS disease in LCH is probably still under-diagnosed, as not all patients have sufficiently detailed clinical examination and neuroimaging.

With increasing use of MRI, it is likely that more patients will be found to have CNS lesions, some even before symptoms develop. The clinical significance of isolated imaging abnormalities and the outcome for these patients is yet to be defined.

The retrospective LCH CNS study of 38 patients with CNS-LCH (Grois, Favara, Mostbeck, & Prayer 1998), revealed that patients with multisystem disease with multiple skull, orbital, temporal bone and skull base lesions were more likely to develop CNS complications. This association with cranial lesions was not found in our study. DI was the most common feature of the patients in that study, developing at a median interval of 3 months after diagnosis of LCH and preceding the appearance of other CNS manifestations by a median interval of 3 years. We feel that DI is not a true manifestation of CNS disease as the hypothalamo-pituitary region lies outside the CNS, and do not include all patients with DI in the group with CNS involvement. Neurological symptoms in the LCH CNS study developed before the diagnosis of LCH in some patients, but the median time was 4½ years after diagnosis, with a maximum interval of >20 years. Findings included extraparenchymal lesions in 42% and cerebellar lesions in 60%, with some patients having combinations of different manifestations. It must be remembered that this study was looking exclusively at patients with CNS involvement, unlike our study, which assessed all patients with multisystem LCH.

Prominent findings in our study were a high incidence of cerebellar abnormality and learning difficulty. None of the patients had infiltrative mass lesions of the parenchyma, but that was not surprising as this type of lesion is usually due to infiltration with 'active' CD1a +ve tissue, and to qualify for our study, patients must have had no active LCH for >5 years at the time of assessment. There were no specific risk factors that could be associated statistically with the development of CNS sequelae, including the presence of skull and orbital lesions in the active phase or duration of active disease. The time to development of CNS symptoms and signs ranged from 8 to 240 months (mean 112, median 108 months). It does therefore appear that CNS damage can reveal itself decades after the active phase.

Cerebellar involvement

The true incidence of cerebellar changes is not known, although it has been suggested that 60% of patients with CNS involvement may have cerebellar abnormalities (Grois, Favara, Mostbeck, & Prayer 1998). In our series, 7 patients

(70% of patients with CNS involvement, 17.5% of entire cohort) had clinical signs of cerebellar involvement. A further patient had changes on MRI scan with no detectable clinical abnormality. The natural history of these lesions has not been studied, so this patient will now be followed up closely with serial clinical examination and MRI. It is, of course, possible that other patients in our cohort may show clinical signs or imaging evidence of CNS involvement in the future, so this is a minimum figure.

Cognitive outcome

The neuropsychological outcome of survivors of childhood malignancies, especially leukaemia, has been studied extensively but not much is known about the consequences of LCH and its treatment. As treatment for childhood cancer has improved and more children survive, the identification of long term sequelae has become a priority. The most commonly recognised neuropsychological late effects after cancer include deficits in intelligence, attainment and memory, along with behavioural abnormalities (Copeland 1992;Mulhern 1994). The causes for this deterioration in function are predominantly related to treatment, such as cranial irradiation (for brain tumours and leukaemia), both intravenous and intrathecal chemotherapy and surgery for brain tumours. However in patients with LCH, neuropsychological deficits can develop in the absence of the use of neurotoxic treatments like these and are likely to be a direct consequence of the disease.

There are a few isolated case reports which have described low IQ in patients with CNS involvement due to LCH (Braunstein, Whitaker, & Kohler 1973;Cervera, Madero, Penas, Diaz, Gutierrez-Solana, Benito, Ruiz-Falco, & Villa 1997;Hayward, Packer, & Finlay 1990) and long term follow up studies noted intellectual impairment in LCH survivors (Sims 1977) (Komp, El Mahdi, Starling, Easley, Vietti, Berry, & George 1980;Komp 1981) but this aspect has never been studied systematically in larger cohorts of patients.

We have found only 2 reports of detailed intellectual testing in patients with LCH. The first reported study of neuropsychological sequelae is an abstract from the journal 'Pediatric Research' (Ransom, Powazek, Goff, Anderson, & Murphy 1978). In this study intellectual functioning was found to be below average (IQ <89) in 7 of 15 patients with 'histiocytosis X' using the Wechsler Adult Intelligence Scale or Wechsler Intelligence Scale for Children. These patients were also shown to have

below average results in spelling and arithmetic. There was evidence of cortical dysfunction in 4 patients, while 2 had truncal ataxia, pyramidal tract signs and behavioural changes. Although this report does give the prevalence of DI and clinical CNS involvement in these patients and also mentions the treatments they had received for 'active' disease, no correlation was made between these factors and the intellectual outcome. A recent report describes cognitive deficits in 2 patients with CNS involvement by LCH with progressive deterioration (Whitsett, Kneppers, Coppes, & Egeler 1999). In both patients there were global deficits of intellectual functioning (below the 20th percentile) as assessed by the WISC-III. This was felt to be a significant decrease in IQ in comparison to their pre-morbid condition. The patients showed poor perceptual organization, verbal comprehension and "freedom from distractablity". The patients also had some deficit in short term memory, but this was a less obvious feature and more difficult to interpret. The authors also reported behavioural abnormalities.

In our cohort, 12 of the 28 patients (42%) studied showed deficits in cognitive performance (intelligence, memory, language and attainment) and 8 of the 12 had either clinical and/or MRI evidence of neurological impairment. The patients with the most severe learning deficit appeared to be those with gross neurological damage, but in the patients who have milder problems the association was less obvious. Only 4 patients without CNS involvement had learning difficulty and in each case it was of a 'mild' degree (FSIQ 80 to 89). Although this deficit may be a result of the LCH, we would need to assess the IQ of their siblings and parents to rule out an underlying familial or environmental cause for the low IQ. If the abnormalities in these patients are apparently related to the disease, cognitive assessment may well provide a more sensitive measure of functional brain impairment in LCH, than neurological examination or MRI.

It was also interesting to find that our patients with CNS involvement had other specific cognitive abnormalities, over and above those that could be accounted for by low intelligence alone. The affected domains included immediate non verbal (visual) memory, immediate memory span, Interference in list learning, oral expression, and reading comprehension. It is believed that these functions are performed by the peri-sylvian grey matter of the cerebral cortex and it is likely that patients with LCH have widespread damage to these regions of the brain. However, no specific MRI abnormalities of the cerebral hemispheres, apart from

cortical atrophy, were detected in our patients. The advent of new, functional imaging techniques such as magnetic resonance spectroscopy (MRS) and volumetric measures of the cerebral cortex may, however, improve our understanding of these problems.

In conclusion long standing, and probably permanent damage to the CNS occurs in at least 25% of survivors of multisystem LCH, resulting in significant functional impairment. It is important to diagnose CNS involvement as early as possible as this can have implications for the management of the patient. Although, as yet, no specific treatment has been found which can reverse or halt the degenerative changes in the brain, interventions can be made to improve the patient's 'quality of life'. Referral to the appropriate specialist should be made as soon as possible - physiotherapists and occupational therapists who can assess and ameliorate physical handicap, psychologists and psychiatrists to deal with the behavioral and psychological problems and neurologists who can deal with the neurological manifestations of the disease. Measures instituted to address learning deficit will improve the outcome for these patients. All patients should therefore have regular assessments of neurological status, including objective measures such as the ataxia rating scale, neuroimaging by MRI and cognitive function.

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Chapter 5. Neuroimaging

Introduction

This chapter outlines the findings on Magnetic Resonance Imaging (MRI) of the brain and 3-Dimensional (3-D) computerised tomography (CT) of the cranio-cervical skeleton. These findings are correlated with the associated clinical abnormalities in the relevant chapters.

The advent of MRI scanning in the 1980's has led to great improvements in imaging of the brain and pituitary. The ability to scan in the sagittal plane meant that hypothalamo-pituitary morphology could now be studied in detail and accurate measurements of structures could be made (Broadbent, Dunger, Yeomans, & Kendall 1993). The discovery of a posterior pituitary hyperintensity on T-1 weighted images in the normal population brought forward the suggestion that this may represent the presence of Vasopressin (AVP) in the cells of the posterior pituitary. The use of Gadolinium for enhancement has an added benefit in the detection of 'active' stalk lesions. MRI scanning therefore helps in studying not just the structure, but also the function of the pituitary region (Rosenfield, Abrahams, & Komp 1990).

MRI is more sensitive than CT at detecting lesions in the other regions of the brain such as the cerebrum, cerebellum and brain stem. The granulomatous lesions of 'active' LCH enhance with gadolinium. More commonly cerebellar signal change is caused by gliosis as a "late effect" of the disease (Grois, Favara, Mostbeck, & Prayer 1998). Although the association of ataxia with LCH was well known, the changes on imaging were not recognised until the advent of good quality MR scanning. In addition, changes in the thalamus and brain stem can also be delineated on MRI as can dural infiltration and scarring.

Three dimensional CT involves computer reconstruction of 2 dimensional images into a 3D image. It is particularly useful for delineating the anatomy of the bony skeleton and we have used it to assess the skull, including the petrous temporal bones and cervical vertebrae and in particular the cranio-cervical junction.

Section 5.1. Methods

5.1.1. Magnetic Resonance Imaging (MRI)

Cranial MRI was performed on a 1.5 Tesla scanner (Magnetom SP 4000, Siemens, Erhlangen, Germany). Coronal and sagittal T1-weighted images, using slice thickness of 2 to 5mm, TR of 530 – 680 milliseconds and TE of 14 –22 milliseconds, were acquired pre and post enhancement with intravenous gadopentetate dimeglumine (Gd-DTPA, Magnevist, Schering Health Care Ltd). Axial T2-weighted coronal images were also obtained with TR of 5400 and TE of 90 milliseconds. Images were assessed for pituitary gland and stalk abnormalities, meningeal enhancement, cerebellar signal change, cerebral atrophy and/or parenchymal lesions and hydrocephalus.

All assessments and measurements were made by two observers (Dr. K. Miszkiel, Consultant Neuroradiologist and the author) and consensus reached.

The width of the pituitary stalk was measured both at its upper end (median eminence) and at its midpoint in the coronal and sagittal planes and compared to established normal ranges (Maghnie, Arico, Villa, Genovese, Beluffi, & Severi 1992a) (Tien et al. 1990). Maximum pituitary gland height (PGH) was measured perpendicular to the sella turcica on midline images and also correlated with normal values for age (Argyropoulou et al. 1991). The appearance of the posterior pituitary bright spot was assessed on sagittal T-1 weighted, unenhanced images and correlated with absence or presence of diabetes insipidus.

An incidental and novel finding of basilar invagination (Nanduri et al. 1998) in some of our patients prompted us to evaluate the skull base in the entire cohort. Relevant radiological definitions are as follows:

1. Basilar invagination (inversion of the margins of the foramen magnum) was quantified on the midline sagittal image using Chamberlain's line (a line joining the posterior end of the hard palate to the posterior border of the foramen magnum). Normally less than 2 mm of the odontoid peg should protrude above this line. (**see Fig.5.4**)

2. Presence or absence of platybasia (flattening of the skull base) was determined from the midline sagittal image by estimating the 'basal angle', which is the

angle between lines drawn from the anterior lip of the foramen magnum and the nasion to the tuberculum sellae. The normal angle ranges from 120-140^0, and an angle of >148^0 indicates platybasia.

3. Herniation of the cerebellar tonsils below the level of the foramen magnum was measured directly on coronal views. It is usually regarded as 'pathological' if more than 3mm of the cerebellar tonsils lie below the foramen magnum, although some authors allow up to 6mm between the ages of 0-10 yr and up to 5mm between 10-20 yrs. (Aboulezz et al. 1985;Mikulis et al. 1992).

Originally, the degree of basilar invagination and platybasia were defined from lateral skull radiographs (Shapiro & Janzen 1960) but midline sagittal MR images demonstrate the same anatomical structures and relationships.

5.1.2. 3-Dimensional CT scan

3-D CT scans of the cranio-cervical skeleton were performed in a helical mode on a Siemens Somatom Plus 4 helical scanner with a 2mm slice thickness with a pitch of 1.5, reconstructing in 2mm slices using a CH20 (soft tissue) algorithm. Three dimensional constructions were made using these data.

The anatomy of the skull vault, orbits, mastoids, middle and inner ear and skull base were assessed. Chamberlain's line and basal angle were measured as defined above and correlated with values obtained from MR images.

Section 5.2. Results

5.2.1. MRI scan

Thirty eight of the 40 patients had an MRI of the brain. One patient was unable to have a scan because the family lived abroad and the second was not scanned because of technical problems. Eleven patients had already had one or more scans, either CT or MRI, prior to entry into the study (the usual indication was the onset of DI). These images were retrospectively assessed for hypothalamo-pituitary morphology and compared to the scans carried out as part of this study.

5.2.1.1. Hypothalamo-Pituitary Morphology

The appearance of hypothalamo-pituitary region and measurements of the stalk and pituitary gland in the entire cohort are tabulated in **Table 5.1**.

Hypothalamus

There are no established standards for correlating hypothalamic morphology with the kind of clinical findings observed in our patients. Four patients had a hypothalamic mass at diagnosis of endocrinopathy. The masses reduced in size on follow up scans in all of them. In 1 patient the MRI appearance of the hypothalamus returned to normal, while 3 of the patients showed only residual thickening of the median eminence of the hypothalamus. Not all the patients with symptoms of hypothalamic involvement or of panhypopituitarism had a hypothalamic abnormality on imaging.

Pituitary stalk

Stalk measurements in the coronal and sagittal planes were compared to the normal range. Retrospective pituitary stalk measurements were available in 11 patients. The mean (range) measurements at this initial examination were - coronal width 5.2 mm (2 to 13mm), sagittal width 5.6 mm (0 to 15mm), both were significantly greater ($p < 0.05$) than the mean for normal controls – coronal 1.92mm (1.37 to 2.63mm), sagittal 1.85 mm (1.45 to 2.51). There was a wide variation in stalk thickness with 4 patients having measurements of < 2.5 mm. In 2 of the older scans the stalk was not visible, but this might have been a result of the poor quality of these scans. Two patients had grossly enlarged enhancing pituitary stalk masses of 15mm each, in diameter. In one of these patients (Pt No 4) the stalk was indistinguishable from an enhancing hypothalamic mass lesion. On excluding these 2 patients with stalk masses, we still found that the mean stalk thickness in the remaining 7 patients was above normal, with a mean coronal width of 3.1mm and a sagittal width of 2.54 mm.

From this study, stalk measurements were available in 38 patients. There was a reduction in stalk thickness in those 11 patients with previously noted enlargement, but the mean stalk diameter remained slightly above - coronal width 2.5mm (1.6 to 3.3), sagittal width 2.3 mm (0 to 2.8 mm) - the normal range. The stalk dimensions in the entire cohort of patients - coronal width 2.7mm (1.6 to 5), sagittal width 2.5

mm (0 to 5mm) - were also slightly above the normal range. These differences however were not statistically significant. These data are depicted graphically in **Fig. 5.1**. It appears that during the active phase of the disease and particularly in patients with DI, MR scans may show thickening of the stalk but, this relationship is variable. Initial scans usually showed enhancement of the stalk with contrast injection, but this was not consistent on the follow up scans.

Pituitary gland and sella

The appearance and dimensions of the pituitary gland varied greatly in individual patients. PGH measurements at follow up assessment in the whole cohort showed a mean PGH of 6.03 mm (2.5 to 10mm). There was no correlation between endocrine status and PGH, with no statistically significant difference in PGH in patients with and without diabetes insipidus or growth hormone insufficiency. Patients with DI – PGH mean 5.5mm (4 to 10 mm), no DI – mean 6.5mm (2.5 to 9 mm), patients with GHI – mean 5.3 mm (2.5 to 10 mm), without GHI – mean 6.3 mm (5 to 9 mm). PGH changes according to age in the normal population (PGH in mm, mean ± SD) age 5.1 to 10 yrs – 4.5 ± 0.6, age 10.1 to 15.1 yrs – 5.3 ± 0.8, age 15.1 to 20 yrs – 6.1 ± 0.3 (Argyropoulou, Perignon, Brunelle, Brauner, & Rappaport 1991). Data for individual patients were therefore compared to the normal for that age group and no statistically significant difference was found. At final assessment, 3 patients had a 'partially empty' sella with a small pituitary gland <4mm. Twelve patients had a bulky pituitary gland for their age, with a PGH > 7mm. A representative MRI showing a thickened stalk and a bulky pituitary gland is depicted in **Fig. 5.2**.

Posterior pituitary bright spot

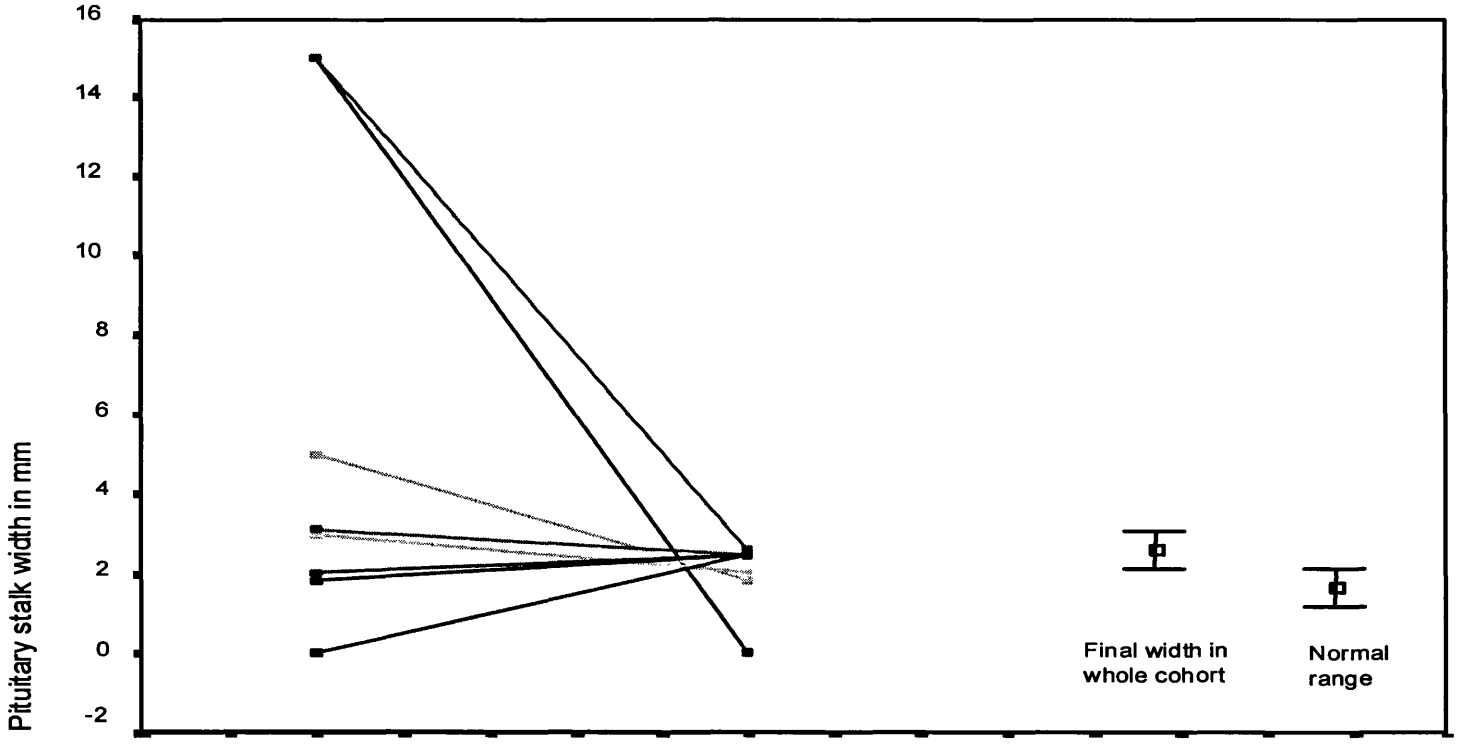
The hyperintensity in the region of the posterior pituitary was assessed on pre-contrast T1-weighted images. There was a very close correlation between the presence of diabetes insipidus and the absence of the posterior pituitary bright spot. All patients with DI lacked the posterior pituitary hyperintensity, whereas 19 of the 21 patients without DI had a visible bright spot.

Pineal Gland

None of the patients in this study had abnormality of the pineal gland and in particular no pineal cysts were found.

Figure 5.1. Changes in pituitary stalk width

The graph on the left depicts the change in maximum pituitary stalk width from the initial CT or MRI scan (for details see Table 5.2) to the final assessment in the 11 patients with two sequential measurements. The scans were performed 6 to 13 years apart (mean, median 9yrs). The lines connect points for the individual patients. The error bars on the right show the mean value and 95% CI for measurements in the entire cohort and in the normal population (Maghnie, Arico, Villa, Genovese, Beluffi, & Severi 1992a). The Y axis shows stalk measurements in millimetres. The difference between stalk width in the patient group and the normal range was not statistically significant.



MRI scans of the brain

Details of the imaging findings of the rest of the brain including cerebellum, cerebrum, ventricular system, meninges and the skull are tabulated in **Table 5. 2.**

5.2.1.2. Cerebellum

Seven patients had abnormalities of the cerebellum on MRI scan. Cerebellar signal change (high T-2 and low T-1 signal) was present in 6 patients. It was bilateral in all and involved both the cerebellar hemispheres and dentate nuclei. A representative MRI is shown in **Figure 5.3**. Five of the 6 patients had clinical evidence of cerebellar involvement. Despite careful testing the 6th patient (Pt. No 1) had no clinical abnormality. The 7th patient (Pt. No 35) had cerebellar atrophy, but no clinically detectable abnormality of cerebellar function. The converse was also seen in 2 instances. Pt. No. 24 had moderate ataxia and dysdiadochokinesis, but on MRI, only had prominent cerebellar folia with no signal change. A second patient (Pt. No. 22) had no MRI abnormality in the cerebellum despite ataxia and incoordination. The association of changes in the cerebellum on imaging and clinical findings therefore may not always be consistent. The clinical features of cerebellar involvement are discussed in more detail in Chapter 4.

5.2.1.3. Cerebral cortex

Ten patients had cerebral atrophy, manifested by prominent cortical sulci and ventricles. Six of these 10 patients also had neuropsychological assessment and were found to have reduced IQ and memory. One patient (Pt. No 4) had a small <5mm cystic lesion with a fluid level, in the left temporal region, of unknown significance. None of the patients have had or currently have a seizure disorder.

5.2.1.4. Ventricular system

Hydrocephalus was present in 3 patients, all of whom required surgical intervention. Two patients (Pt. Nos. 31, 32) had ventriculo-peritoneal shunts inserted while the 3rd (Pt. No. 26) needed a 3rd ventriculostomy to bypass stenosis of the aqueduct of Sylvius. Pt. No. 31 had basilar invagination and cerebellar tonsillar herniation resulting in hydrocephalus with an associated syrinx (syringohydromyelic cavity) of the cervical spinal cord (**see Fig. 5.5**). Two patients (Pt. Nos. 19, 40) had mild dilatation of the ventricles, but this was secondary to cortical atrophy, rather than true hydrocephalus.

Figure 5.2. Thickened pituitary stalk and enlarged gland

Midline sagittal MRI of the hypothalamo-pituitary region showing an enhancing thickened pituitary stalk and enlarged pituitary gland

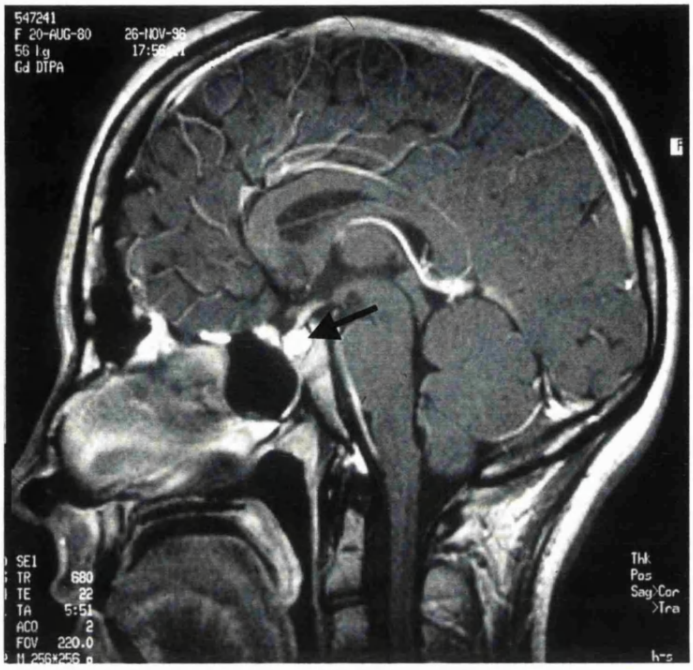
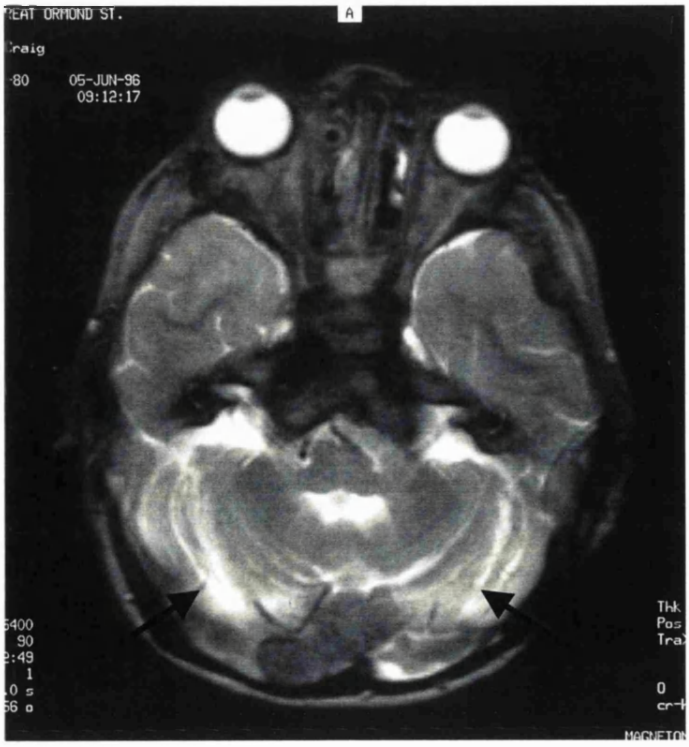


Figure 5.3: Sagittal MRI showing bilateral cerebellar signal change

T-1 weighted MRI coronal section showing bilateral cerebellar signal change



5.2.1.5. Meninges

Dural thickening was identified in 4 patients. Two patients (Pt. Nos. 31 and 40) had marked, widespread, dural thickening and enhancement involving the tentorium and falx in one and over the cerebral convexities in the second (**see Fig. 5. 6**). The third (Pt.No.12) had minimal thickening along the clivus, while Pt.No.29 had thickening of the dura around the cavernous sinus and overlying the temporal lobe and middle cranial fossa.

5.2.1.6. Skull, inciuding orbits and temporal bones

Although MRI is not considered the ideal imaging modality for assessment of bone, we were able to identify abnormalities of the skull on imaging, which correlated well with CT findings. Thirteen patients had asymmetry of the skull vault or face and 9 of them had persistent deficiencies in the skull vault reflected by loss of the diploic space. Ten had residual proptosis with soft tissue thickening in the orbits and displacement of one or both globes. Eight patients had decreased aeration, sclerosis or poor development of the mastoid air cells.

5.2.1.7. Skull base

Seven patients had an unexpected abnormality of the skull base – basilar invagination – with protrusion of the odontoid peg above Chamberlain's line (a line joining the posterior end of the hard palate to the posterior border of the foramen magnum- **Fig 5.4**). This appearance had never previously been described in LCH. It was an acquired abnormality, as it was not present on the initial skull X Ray at diagnosis of LCH or in any of the initial scans. Two patients (Pt. No 31& 32), who had had serial scans showed progression of the abnormality, with worsening invagination from 2.5mm to 9mm and 0mm to 6mm respectively. The invagination was associated with narrowing of the foramen magnum in 2 patients, with a cervical syrinx in one patient (**Fig. 5.5**) and kinking of the brainstem in the second (**Fig. 5.6**). Four patients had herniation of the cerebellar tonsils, of between 5mm and 12mm, through the foramen magnum, 2 of whom had associated basilar invagination.

The measurements of the skull base on MRI scan are given in **Table 5. 3**. The degree of basilar invagination ranged from 'mild' (4mm) to 'gross' (30mm) abnormality (mean 11.3mm, median 8mm). The basal angle also varied widely, with only 1 patient having platybasia (basal angle 165^0). Six patients had basal angles at the lower end of normal (120^0) and 1 an angle below normal (118^0).

Figure 5.4. Chamberlain's line

This is a line drawing of the skull in sagittal section. Chamberlain's line is depicted as a dotted line extending from the posterior tip of the hard palate to the posterior margin of the foramen magnum. The tip of the odontoid (black arrow) normally lies below this line.

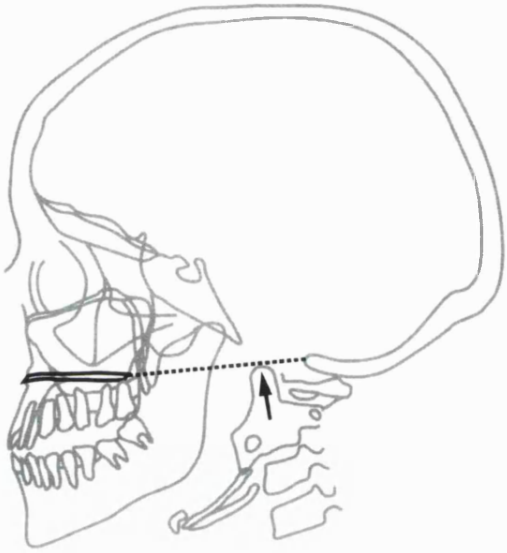


Figure 5.5. Tonsillar herniation, basilar invagination, cervical syrinx

Sagittal MRI showing herniation of the cerebellar tonsils, basilar invagination and a syrinx of the cervical cord (white arrow). Chamberlain's line is depicted in black.

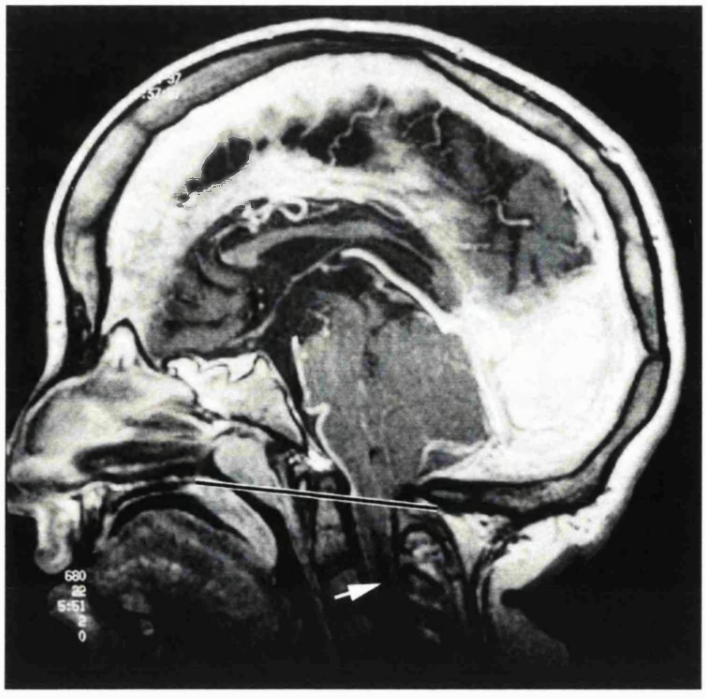
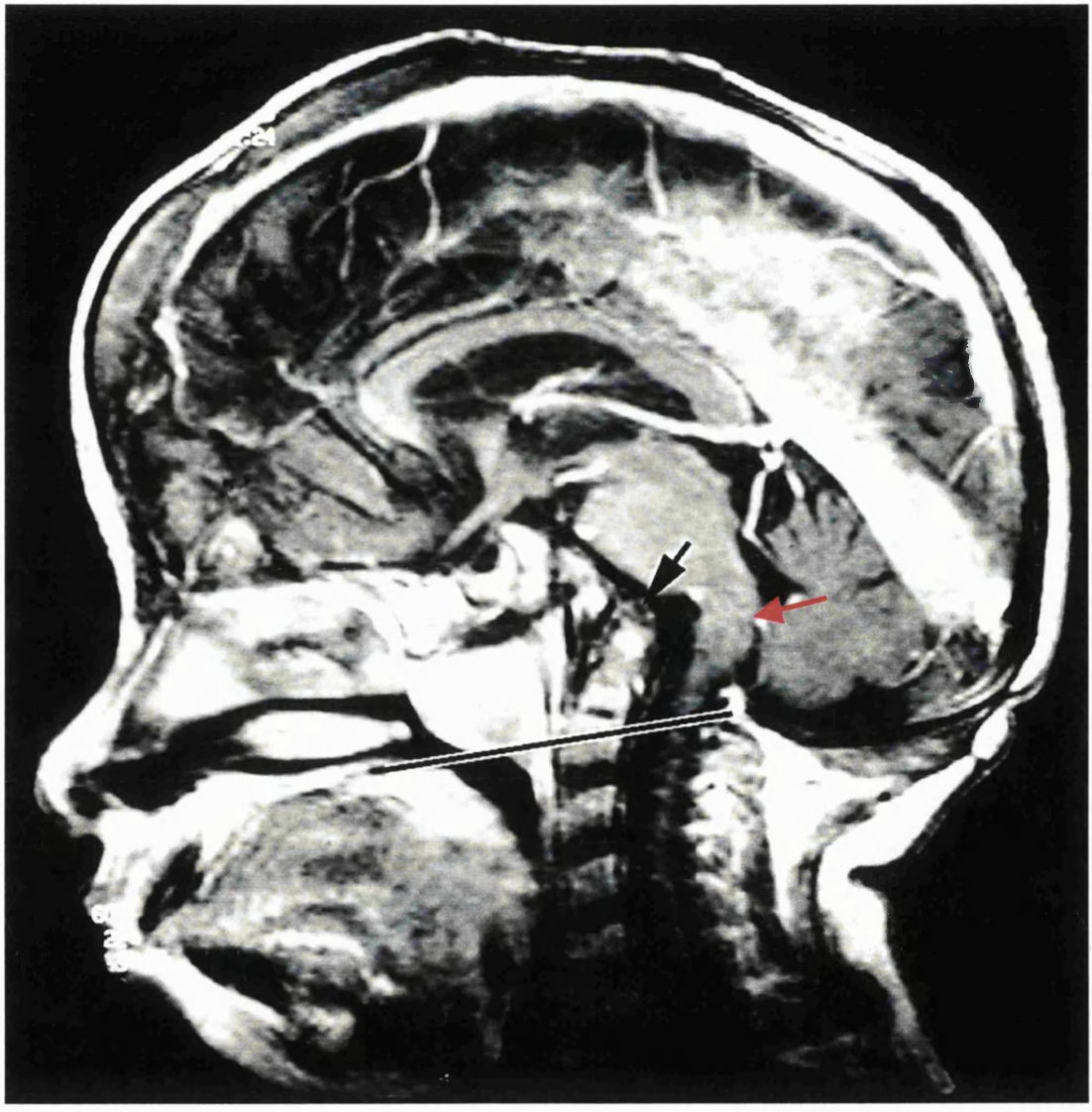


Figure 5.6. Midline sagittal MRI showing gross basilar invagination

This MRI shows several of the features of brain involvement by LCH. There is gross basilar invagination as demonstrated by the protrusion of the odontoid process (black arrow) above Chamberlain's line (black line). The foramen magnum is narrow and the brain stem kinked (red arrow). There is an enhancing dural plaque overlying the cerebral hemisphere. There is also cortical atrophy and loss of diploic space of the skull.



5.2.2. 3-Dimensional CT scan

Twenty of the 40 patients underwent a 3-D CT of the cranio-cervical region. This investigation was added to the assessment protocol after the unexpected abnormal skull base findings on the MRI scans. Therefore some patients who had already attended for the assessment were not recalled for this one test.
The findings on 3-D CT are tabulated in **Table 5. 3**.

Skull vault: Residual abnormalities of the skull vault were noted in 12 patients (60% of patients who had a 3-D scan). All had asymmetry of the skull, 4 had full thickness lytic vault lesions, 4 had depressed lesions, with an intact inner table, while 2 patients had excessive thickening of the skull. Another patient (Pt. No. 40) had several bilateral, large, residual deficiencies of the skull in the parieto-temporal and occipital regions (**Fig. 5.7**). He also had gross asymmetry of the skull and basilar invagination.

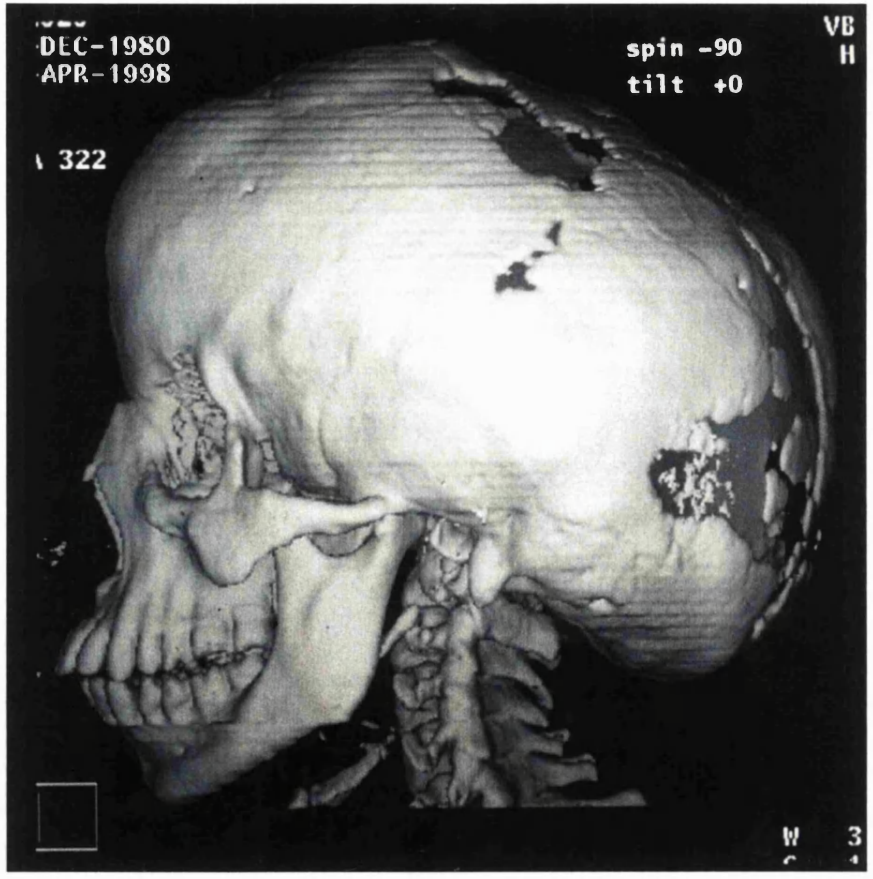
Skull base: Basilar invagination was confirmed in all the patients in whom the abnormality had been noted on MRI. The measurements of both the degree of invagination and of the basal angle correlated very closely with those made on MRI scan, confirming that MRI can be used to assess the anatomy of the skull base.

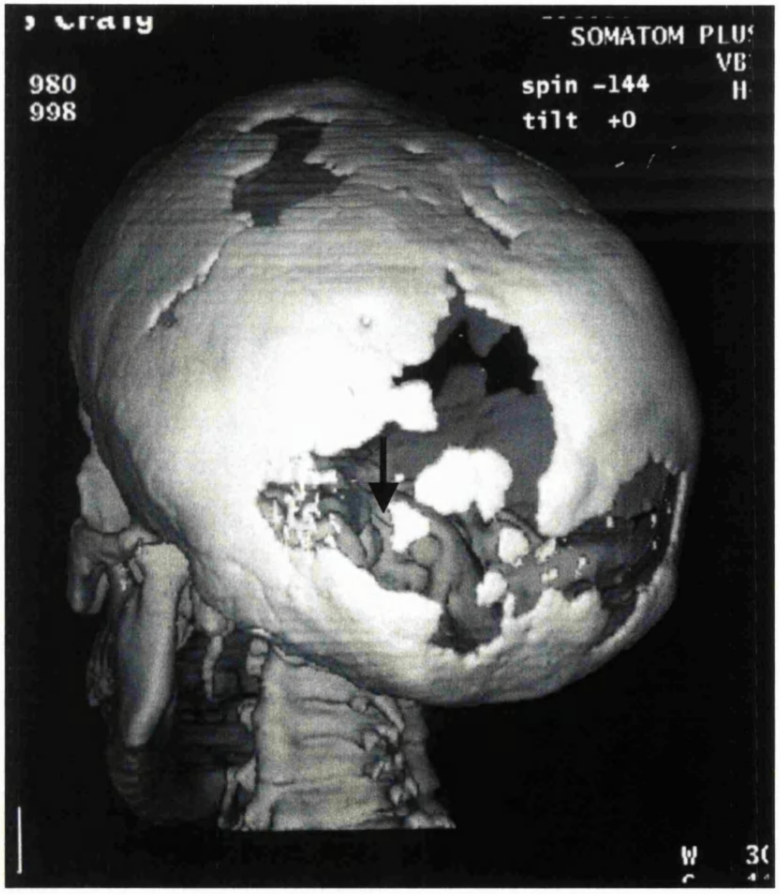
Orbits: Five patients had abnormalities of the orbits including thickening of the bony margins and residual proptosis.

Temporal bone and sinuses: Twelve of the 19 patients showed poorly pneumatized and/ or underdeveloped mastoids. The scans also showed middle ear opacification in 3 patients and destruction of the ossicular chain in 3 patients. These abnormalities are correlated with findings on audiology in Chapter 6. Five patients had underdeveloped and opacified sinuses – maxillary, ethmoid and/ or frontal.

Figure 5.7. Three-Dimensional CT of the skull

3 –D CT of the skull performed 15 years after initial diagnosis of LCH and 8 years from the end of treatment. The skull vault shows persistent, multiple, large lytic lesions with 'full-thickness' loss of bone. There is superior translocation of the cervical spine through the foramen magnum - basilar invagination (black arrow). As a consequence the occipital region 'overhangs' the spine.





Section 5.3. Discussion

5.3.1. Hypothalamo-pituitary region and pineal gland

Abnormalities of the pituitary stalk and gland were seen in half the patients in our cohort and correlated with clinical findings and with reports in the literature. The pituitary stalk, gland and hypothalamus are recognised to be the commonest site of intracranial involvement in patients with LCH. The main reported abnormalities on imaging studies are thickening of the pituitary stalk and absence of the posterior pituitary bright spot. Tien et al described the MR images in 4 adults with LCH who had acute onset of DI. Three patients had a uniformly thickened enhancing pituitary stalk and all 4 had loss of the posterior pituitary bright spot (Tien, Newton, McDermott, Dillon, & Kucharczyk 1990). Maghnie et al studied 14 children with LCH, aged 1 to 15 yrs. They showed that the pituitary stalk was thicker than normal in 7 of the 14 children, but that only 3 had DI. They concluded that patients with LCH and a thickened stalk were probably at a higher risk of developing DI (Maghnie, Arico, Villa, Genovese, Beluffi, & Severi 1992a). These changes have been reported by several other authors (Broadbent, Dunger, Yeomans, & Kendall 1993;Rosenfield, Abrahams, & Komp 1990;Schmitt et al. 1993). We found that the pituitary stalk was often thickened at initial diagnosis of DI in our patients. Although the thickening often decreased with time, the stalk width remained above the normal range at follow up times ranging from 6 to 13 years.

The posterior pituitary hyperintensity (the so-called 'bright spot') is felt to represent the presence of Vasopressin in the posterior pituitary and is usually absent in patients with DI, whatever the underlying cause (Brooks, el Gammal, Allison, & Hoffman 1989;Chiumello et al. 1989;Colombo, Berry, Kucharczyk, Kucharczyk, de Groot, Larson, Norman, & Newton 1987;Gudinchet, Brunelle, Barth, Taviere, Brauner, Rappaport, & Lallemand 1989;Tien, Kucharczyk, & Kucharczyk 1991). The 'bright spot' was consistently missing in all patients with DI in this study. Two of the 21 patients without DI lacked the posterior pituitary bright spot. The significance of this finding in patients without DI is not understood but has been noted in up to 10% of the normal population (Colombo, Berry, Kucharczyk, Kucharczyk, de Groot, Larson, Norman, & Newton 1987).

The pituitary gland height (PGH) in the normal population increases with age, reaching a maximum during puberty (Argyropoulou, Perignon, Brunelle, Brauner, &

Rappaport 1991). The PGH measurements in our cohort were similar to the reported normal range. There was no statistical correlation between PGH and any endocrine abnormality.

Cystic lesions of the pineal gland have been reported as occurring more frequently in patients with LCH, than in the normal population (Grois et al personal communication, report of LCH-CNS group at the Histiocyte Society meeting). This finding was not seen in our cohort and has not been reported in the literature.

5.3.2. Cerebellum

The incidence of cerebellar changes on MRI scans was 17.5% of all the patients in our study. The MRI scans showed bilateral, symmetric signal changes of the cerebellum as have been reported previously (Cervera, Madero, Penas, Diaz, Gutierrez-Solana, Benito, Ruiz-Falco, & Villa 1997;Grois, Favara, Mostbeck, & Prayer 1998;Grois et al. 1994;Rosenfield, Abrahams, & Komp 1990). No other study has as yet imaged all patients with LCH to assess the incidence of cerebellar change on MRI. The LCH-CNS study group of the Histiocyte Society found that 23 of 38 patients (60%) with CNS involvement with LCH had clinical evidence of cerebellar dysfunction and that 50% of patients had MRI abnormalities in the cerebellar region. This was however a selected group of patients with known CNS involvement and the high incidence of abnormality is therefore not surprising.

It is important to note that clinical features of cerebellar involvement were not consistently associated with imaging changes in our cohort, as has been reported by others (Grois, Favara, Mostbeck, & Prayer 1998;Rosenfield, Abrahams, & Komp 1990). This could be explained by the fact that all the patients in our study had a scan rather than just those with clinical neurological abnormalities. Sub-clinical or early involvement could therefore probably have been picked up in some of our patients. Not enough is known at present about the natural history of cerebellar disease in LCH and therefore no conclusions can be made regarding the clinical outcome for asymptomatic patients.

5.3.3. Supratentorial abnormalities

Atrophy of the cerebral cortex may be seen in patients with LCH (Grois, Favara, Mostbeck, & Prayer 1998;Grois, Tsunematsu, Barkovich, & Favara 1994) and may be associated with reduced intelligence as was seen in our patients. Infiltration of the meninges has been recognised and may represent "active" disease. None of our patients who had meningeal thickening had evidence of active disease and this

appearance is therefore more likely to represent residual scarring. "Space-occupying" lesions were not present in any of our cohort.

Classification of imaging abnormalities:

The LCH-CNS study group of the Histiocyte Society in 1994 recommended a classification of the changes seen on imaging. The lesions were classified according to morphology, site (supra or infratentorial), white or grey matter involvement and the presence or absence of enhancement into 6 main forms – (Grois, Favara, Mostbeck, & Prayer 1998).

Type	Morphology
Ia	White matter lesions - enhancement
Ib	White matter lesions + enhancement
IIa	Gray matter lesions - enhancement
IIb	Gray matter lesions + enhancement
IIIa	Extraparenchymal dural based
IIIb	Extraparenchymal arachnoidal based
IIIc	Extraparenchymal plexus choroid based
IVa	Infundibular thickening
IVb	(Partial) empty sella
IVc	Hypothalamic mass lesion
Va	Atrophy diffuse
Vb	Atrophy localized
VI	Therapy–related +/- enhancement

This is a rather arbitrary division and we prefer to classify abnormalities predominantly according to the site of involvement. We have found that clinical abnormalities relate to the location of the lesion rather than to whether or not the white or grey matter is involved. Thus hypothalamo-pituitary abnormalities, especially a thickened stalk and loss of the posterior pituitary bright spot, were related to endocrine abnormalities, cerebellar ataxia was seen in those patients with cerebellar signal change, and patients with learning deficit had cerebral atrophy. We further found the subdivision into subtypes a, b and c was confusing and did not contribute to understanding either the pathogenesis, or the clinical implications of these lesions. We therefore did not use this classification for this study and propose that a simpler classification using the presence or absence of the following features may be more useful to clinicians –

Hypothalamo-Pituitary involvement
Cerebellar involvement
Cerebral Atrophy
Cerebral mass lesions
Meningeal infiltration

The LCH-CNS group has recently proposed a simpler classification, dividing lesions into axial and extra-axial abnormalities depending on the site. This classification has however not yet been published.

5.3.4. Skull base changes

We report a new and unexpected abnormality - basilar invagination- in long term survivors of multisystem LCH (Nanduri, Jarosz, Chong & Pritchard 2000). The term 'basilar invagination' is used to describe bulging of the upper cervical spine and the skull base around the foramen magnum into the posterior fossa of the cranial cavity. It may be developmental or acquired. As a developmental anomaly, it is most often associated with a small foramen magnum and occipitalization of the atlas vertebra - the Klippel-Feil syndrome. Acquired basilar invagination is caused by bone-softening diseases or causes of delayed or defective cranial ossification such as osteomalacia, osteogenesis imperfecta, Paget's disease, fibrous dysplasia, achondroplasia, untreated hydrocephalus and acro-osteolysis (Williams 1977). Basilar invagination may be associated with platybasia (flattening of the skull base), cerebellar tonsillar herniation and syringo- or hydro-myelia, features seen in some of our patients Basilar invagination has never before been described in LCH.

Although the skull is the most common site of 'active' bony disease in LCH, lesions of the base of the skull are rare. In our patients, basilar invagination cannot be explained as a simple consequence of localised bone softening since, with one exception (Pt 40), there were no demonstrable lytic LCH lesions in the skull base during the 'active phase'. None of the patients had biochemical or radiological evidence of any of the other causes of acquired basilar invagination, such as osteomalacia or Paget's disease. Long term corticosteroid therapy can cause osteopenia and many of the patients in this study had received steroids for treatment of the acute phase of their LCH. However, we found no apparent correlation between the dose and/ or duration of steroid therapy and the development of the skull base abnormalities. Also, acquired basilar invagination has never been described in other conditions where long term steroid therapy has been used.

Irradiation to the skull or cervical spine has not been reported to cause basilar invagination. Only 1 (Pt 40) of the 7 affected patients had received radiotherapy to

the skull, in a dose of 30Gy. Two other patients had received radiotherapy to cervical lymph nodes in relatively small doses of 10 and 12 Gy respectively.

Basilar invagination causes symptoms via compression of the medulla oblongata or upper cervical cord and has been implicated as a factor contributing to death in patients with acro-osteolysis (Williams 1977) and osteogenesis imperfecta (McAllion & Paterson 1996). Basilar invagination in association with the Arnold-Chiari type I malformation has been reported to cause 'sneeze syncope' (Corbett, Butler, & Kaufman 1976). None of our patients had evidence of problems like these, but symptoms may not be manifest until adult life and patients should therefore remain under regular surveillance for life. There are also implications for the provision of general anasthaesia, in particular during management of the airway, for these patients, as this could result in significant damage due to pressure on the brainstem.

To summarise, this study confirms previous reports of thickening of the pituitary stalk in patients with LCH and loss of the posterior pituitary 'bright spot' in patients with DI. Cerebellar signal change and cerebral atrophy can occur and may be associated with clinical cerebellar abnormalities and learning difficulties respectively. These changes can appear several years after the end of treatment, and may be seen in asymptomatic patients. Dural thickening and hydrocephalus are less common, but significant, abnormalities. Skull base abnormalities may be clinically significant sequelae. Changes on MRI can be described simply according to the site of abnormality, avoiding the need for complicated classification.

Table 5.1. MRI/ CT appearance of the hypothalamo-pituitary region

This table gives the dates and type of scan, appearance and measurements of pituitary stalk and gland, presence or absence of the 'posterior pituitary bright spot' and the appearance of the hypothalamic region in the 40 patients in this study.

sag = sagittal, cor = coronal

Pt. No.	Date /type of scans	Appearance of stalk	Maximum stalk Width	Sella and gland	Pituitary gland height	Post. pituitary bright spot	Hypothalamus
1	1992 MRI 1998 MRI	Thickened, fusiform Normal	5mm-sag 4.8mm-cor 1.8mm-sag 2.5mm-cor	Normal Normal	 5mm	Absent Absent	Normal Normal
2	1997 MRI	Thickened, enhancing	5mm –sag 5mm – cor	Normal	7.5 mm	Present	Normal
3	1997 MRI	Normal	2.3mm-sag 2.5 mm-cor	Normal	5mm	Present	Normal
4	1985 CT 1997	Incorporated into large suprasellar mass Thread-like	Indistinguishable from hypothalamic mass 0mm-sag 2mm-cor	Normal Partial empty sella	Could not be distinguished from mass 4mm	---------- Absent	Enhancing suprasellar mass. Ht 15mm, 15mm-sag, 13mm-cor Mass smaller, residual thickening median eminence
5	1996	Normal	4mm-sag 4mm-cor	Normal for puberty	9mm	Present	Normal
6	1997	Fusiform	2.5mm sag 3.2 mm cor	Normal	5mm	Absent	Normal
7	1987 CT 1997 MRI	Thickened Normal	3.1mm sag 3mm cor 2.5mm sag 2.5 mm cor	Small gland Normal	3.3mm 6mm	------ Absent	Normal Normal

Table 5.1. MRI/CT appearance of the hypothalamo-pituitary region (contd)

Pt. No.	Date of scans	Appearance of stalk	Maximum stalk Width	Sella and gland	Pituitary giand height	Post. pituitary bright spot	Hypothalamus
8	1988 MRI	Normal	1.8mm sag 2.2mm cor	Normal	3.5mm	Absent	Normal
	1996 MRI	Very thin at lower end	2.5mm sag 2.6mm cor	Normal	5mm	Absent	Normal
9	1997 MRI	Normal	2.5mm sag 2.5mm cor	Normal	5mm	Present	Normal
10	1997 MRI	Normal	2.5mm sag 2.8mm cor	Normal	6mm	Present	Normal
11	1999 MRI	Normal	2.5mm sag 2.6mm cor	Partially empty sella, flat fossa	2.5mm	Present, but very small	Normal
12	1998 MRI	Normal	3mm sag 3mm cor	Normal	6mm	Present	Normal
13	1997 MRI	Normal	3mm sag 2.5mm cor	Normal	7.5mm	Present	Normal
14	1998 MRI	Slight fusiform thickening	3mm sag 2.8mm cor	Normal	7.5mm	Present	Normal
15	1992 MRI	Normal	2mm sag 2mm cor	Normal	6.6 mm	Present, small	Normal
16	1998 MRI	Normal	2.4mm sag 2.5mm cor	Normal	7.5mm	Present	Normal
17	1997 MRI	Normal	2.5mm sag 3.5mm cor	Normal	6mm	Present	Normal

Table 5.1. MRI/CT appearance of the hypothalamo-pituitary region (contd)

Pt. No.	Date of scans	Appearance of stalk	Maximum stalk Width	Selia and gland	Pituitary giand height	Post. pituitary bright spot	Hypothalamus
19	1997 MRI	Thin	2.5mm sag 2.5 mm cor	Normal	5mm	Present	Normal
20	1996 MRI	Thin stalk, not enhancing	2.6mm sag 2 mm cor	Shallow fossa	5mm	Absent	Normal
21	1996 MRI	Normal	2.4mm sag 2.5mm cor	Normal	5mm	Absent	Normal
22	1997 MRI	Normal, not enhancing	2.5 mm sag 2.5 mm cor	Normal	8mm	Present	Normal
23	1989 MRI 1997 MRI	Normal Normal	2mm sag 2.6mm cor 2.5 mm sag 2.5 mm cor	Normal Normal	6mm 7.5mm	Absent Absent	Normal Normal
24	1997 MRI	Normal	2.5mm sag 2.6mm cor	Normal	6mm	Absent	Normal
25	1997 MRI	Slightly bulky, fusiform stalk	2.8mm sag 2.8mm cor	Normal	5mm	Absent	Normal
26	1986 CT 1989 MRI 1993 MRI 1998 MRI	Thickened upper end of stalk and hypothalamus Bulky at top Less bulky Normal	15mm AP(sag) 11mm cor 2.7mm sag 8 mm cor 5 mm sag 6mm cor 2.6 mm sag 2.5 mm cor	Merging with stalk Small gland Small gland Small gland	---------- 4mm 5mm 5mm	---------- Absent Absent Absent	Hypothalamic mass Ht 10mm, width 11mm, AP diam 15mm Bulky hypothalamus Less bulky Normal appearance

Table 5.1. MRI/CT appearance of the hypothalamo-pituitary region (contd)

Pt. No.	Date of scan	Appearance of stalk	Maximum Stalk Width	Sella and gland	Pituitary giand height	Posterior pit bright spot	Hypothaiamus
27	1989 MRI	Slightly thickened	3.3mm sag 3.5mm cor	Small	Not measurable	Absent, but nodule of high signal in sella	Normal
	1995 MRI	Thick at top	2.8mm sag 3.2 mm cor	Small	4mm	Absent	Normal
28	1998 MRI	Normal	2.5mm sag 2.8 mm cor	Normal	6mm	No definite bright spot, but considerable movement artefact	Normal
29	1997 MRI	Normal	2.5 mm sag 2.6 mm cor	Normal	10mm	Absent	Normal
30	1998 MRI	Normal	2.5 mm sag 2.5 mmcor	Normal	5mm	Probably normal	Normal
31	1988 MRI	Thin	Not seen sag 2mm cor	Shallow fossa, small gland	4mm	Absent	Normal
	1997 MRI	Normal	2.5 mm sag 2.5 mm cor	As above	5mm	Absent	Normal
32	1989 MRI	Thickened	3 mm sag 3.2 mm cor	Normal	6mm	Absent	Thickening of region
	1994 MRI	Merging with pituitary mass	--	Pituitary mass	12.5 mm	Absent	Mass lesion
	1998 MRI	Thin, deviated to Rt	2mm sag 1.6 mm cor	asymmetric	7mm	Absent	Slightly bulky

Table 5.1. MRI/CT appearance of the hypothalamo-pituitary region (contd)

Pt. No.	Date of scan	Appearance of stalk	Maximum Stalk Width	Sella and gland	Pituitary gland height	Posterior pit bright spot	Hypothalamus
33	1997 MRI	Normal	2.5 mm sag 2.5 mm cor	Gland slightly small for age	5mm	Absent	Normal
34	1999 MRI	Normal	2.5 mm sag 2.5 mm cor	Normal	5mm	Absent	Normal
35	1996 MRI	Mild fusiform stalk thickening	2.8mm sag 3 mm cor	Gland asymmetrical bulky for age	7.5mm	No definite spot	Normal
36	1996 MRI	Normal	2.2mm sag 2.5 mm cor	Small gland		Absent	Normal
37	1990 MRI 1997 MRI	Normal Slightly bulky	No sag view 2mm cor 2.5mm sag 3.7mm cor	Normal Normal	6mm 8mm	Present Present	Normal Normal
38	1991 MRI 1997 MRI	Normal Normal	2.5 mm sag 2.5mm cor 2.5 mm sag 2.5mm cor	Normal Normal	5mm 5 mm	Present Present	Normal Normal
39	1998 MRI	Normal	2.5mm sag 2.5mm cor	Normal	7mm	Present	Normal
40	1996 MRI	Bulky at top	2.5mm sag 3.3 mm cor	Partial empty sella	5mm along the margin	Absent	Mild thickening

Table 5.2: Abnormalities of the brain and skull on MRI scan

This table includes the findings on MRI in the cerebellum and cerebral cortex, the presence or absence of hydrocephalus and dural involvement and changes in the skull including the vault and mastoid temporal regions.

Pt. No.	Cerebellar change	Cerebral atrophy	Hydrocephalus	Dural abnormality	Other abnormalities
1	Bilateral T2 high signal change	None	None	None	Bilateral T1 high signal in thalamus
2	None	None	None	None	None
3	None	None	None	None	High signal in Rt mastoid air cells
4	None	None	None	None	Small lesion lt temporal lobe
5	None	None	None	None	Residual proptosis, facial asymmetry
6	None	None	None	None	None
7	None	None	None	None	None
8	None	None	None	None	Rt frontal skull vault defect
9	None	None	None	None	None
10	None	None	None	None	None
11	Bilateral signal change in dentate nuclei	None	None	None	Asymmetric skull, lytic lesion Rt temporal region Bilateral proptosis
12	None	None	None	Minor dural thickening along clivus	Prominent cisterna magna Bilateral loss of mastoid aeration
13	None	None	None	None	Mild prominence of parietal sulci, but not true atrophy. Vault asymmetry with Rt frontal flattening
14	None	None	None	None	None

Table 5.2. Abnormalities of the brain and skull on MRI scan (contd).

Pt. No.	Cerebellar change	Cerebral atrophy	Hydrocephalus	Dural abnormality	Other abnormalities
15	None	Moderate supratentorial and mild infratentorial atrophy	None	None	Bilateral flattening in parietal regions; defect in diploic space Rt mastoid opacification
16	None	None	None	None	Lt occipito-parietal thinning of skull with overlying scalp defect
17	None	None	None	None	Asymmetric skull vault; focal bulge in Rt parietal region with thickening of underlying diploe
18	---	---	---	---	---
19	None	Mild	Prominent 3rd and lateral ventricles	None	Inflammatory change in sinuses, Lt mastoid opacification
20	None	None	None	None	1984 CT – bilateral bony destruction of orbital margins with soft tissue component in contact with optic nerve. Lt proptosis, with globe pushed down 1996 MRI Rt mastoid opacification Residual orbital roof thickening
21	None	Moderate atrophy, prominent sulci, lateral ventricles	None	None	Slightly asymmetric skull vault, bilateral residual proptosis Rt mastoid less pneumatized
22	None	Mild supratentorial atrophy	None	None	Abnormality in Lt temporal lobe subcortical white matter-streaking. ? cortical enhancement Lt temporal
23	None	None	None	None	Slight prominence of cortical sulci

Table 5.2. Abnormalities of the brain and skull on MRI scan (contd).

Pt. No.	Cerebellar change	Cerebral atrophy	Hydrocephalus	Dural abnormality	Other abnormalities
24	Prominent cerebellar folia	Prominent sulci and lateral ventricles	None	None	Skull vault asymmetry; residual vault lesions; under pneumatized mastoids, minimal proptosis
25	None	Mild prominence of cortical sulci and ventricles with perivascular spaces	None	None	Marked skull vault deformity
26	1989 Bilateral signal change 1992 PD Axial 1998 MRI Bilateral signal change	None Some atrophy Cortical sulci prominent	Mild prominence 3rd and lateral ventricles Marked 3rd ventricular dilatation, aqueduct stenosed 3rd and lateral ventricles prominent 3rd ventriculostomy	None None None	Signal change in pons and midbrain, Multiple vault lesions, Lt proptosis As above Brain stem signal change
27	None	None	None	None	None
28	None	None	None	None	None
29	None	Mild prominence of sulci	None	Dural thickening around cavernous sinus Lt temporal lobe	Bilateral proptosis; thickening of greater wings of sphenoid and skull base with heterogeneous enhancement . Asymmetric skull vault
30	None	None	None	None	None

Table 5.2. Abnormalities of the brain and skull on MRI scan (contd).

Pt. No.	Cerebellar change	Cerebral atrophy	Hydrocephalus	Dural abnormality	Other abnormalities
31	Bilateral change	Marked supratentorial atrophy	3rd and lateral ventricles enlarged, Rt occipito-parietal shunt in-situ	Extensive dural thickening along falx, tentorium	Bilateral proptosis, micrognathia, absent frontal sinuses, hypoplastic maxillary antra, thickened skull vault Cervical syrinx
32	1994 Bilateral white matter change, high signal change in dentate nuclei 1995 no change 1998 Change less obvious	Cortical sulci prominent Cortical sulci less prominent Cortical atrophy	All ventricles enlarged Rt occipito-parietal shunt , ventricles less prominent As before	None None None	Patchy signal change in basal ganglia Patchy signal change in basal ganglia Basal ganglia more homogeneous appearance New skull vault lesions – frontal and parietal regions
33	None	None	None	None	Inflammatory change Rt maxillary antrum, Rt ethmoid and frontal sinuses
34	None	None	None	None	Bilateral hearing aids
35	Mild atrophy	None	None	None	Decreased pneumatization Lt mastoid
36	None	None	None	None	None
37	None	None	None	None	Defect in skull vault;asymmetry occipital region; residual enhancing tissue around Lt orbit with displacement of globe; mastoids poorly pneumatized
38	None	None	None	None	Absent frontal sinuses
39	None	None	None	None	Choroid plexus cyst
40	Signal change in region of dentate	Bilateral, asymmetric atrophy	Mild bilateral ventricular dilatation	Widespead dural plaques	Multiple skull vault deficiencies, asymmetry of skull, mild residual Rt proptosis, medullary kinking

Table 5.3. Skull base anatomy on MRI scan

The basal angle, degree of basilar invagination and tonsillar herniation on MRI scans are shown in this table. The abnormal findings are highlighted in **bold** type.

Pt. No.	Basal angle	Protrusion of odontoid above Chamberlain's line	Herniation of cerebellar tonsils
1	135^0	0mm	None
2	132^0	0mm	None
3	125^0	0mm	None
4	138^0	0mm	None
5	120^0	0mm	None
6	120^0	0mm	None
7	120^0	0mm	None
8	135^0	0mm	None
9	131^0	0mm	None
10	122^0	0mm	None
11	132^0	1mm (normal)	None
12	130^0	**4mm**	None
13	133^0	0mm	2.5mm (normal)
14	120^0	0mm	None
15	122^0	**8mm**	None
16	124^0	0mm	None
17	128^0	0mm	None
19	128^0	0mm	**9mm**
20	120^0	0mm	**6mm**
21	127^0	0mm	None
22	130^0	0mm	None
23	138^0	**17.5mm**	**5mm**
24	139^0	0mm	None
25	130^0	0mm	None
26	124^0	0mm	None
27	130^0	0mm	None
28	125^0	0mm	None
29	120^0	0mm	None
30	150^0	0mm	None
31	135^0 130^0	2.5 mm **9mm**	None **12mm**
32	130^0 130^0	0mm **6mm**	None None
33	124^0	1mm (normal)	None
34	118^0	0mm	None
35	125^0	**5mm**	None
36	122^0	0mm	None
37	132^0	0mm	None
38	129^0	0mm	None
39	132^0	0mm	None
40	165^0	**30mm**	None

Table 5.4. 3-D CT scan of skull and cervical spine

Findings in the cranio-cervical skeleton in the 20 patients who had 3-D CT scans.

Pt. No.	Skull vault abnormalities	Other abnormalities	Basal angle	Protrusion of odontoid
5	Marked asymmetry; Areas of thickening	Middle ear and mastoid opacification, destruction of ossicles on Lt	118^0	0mm
10	No skull vault lesions	None	120^0	0mm
11	Skull asymmetry; lytic lesion Rt temporal	Bilateral proptosis; lytic lesion Rt mandible; soft tissue of face abnormal		
12	No skull vault lesions	Bilateral poorly pneumatized mastoid	130^0	5mm
14	No skull vault lesions	Poorly pneumatized Rt mastoid	*No reformat available*	0mm
16	Lt occipito-parietal skull lesion with scalp defect	None	128^0	0mm
19	Mild asymmetry with flattening Lt tempero-occipital region	Opaque frontal and Lt sphenoid sinuses; inflammatory change in maxillary antra; sclerotic Lt mastoid air cells.	128^0	0mm
20	Mild asymmetry; residual Lt proptosis with thickened orbit al margin; bone thinning in temporal regions.	Sclerotic mastoids and middle ear cleft	*No reformat available*	0mm
21	Asymmetry, Lt frontal Depression	Bilateral proptosis; Poorly pneumatized mastoids	131^0	1mm
22	Normal	Lt maxillary and ethmoid opacification	135^0	1mm
23	Lt frontal depression	Poorly pneumatized Lt mastoid	140^0	17.5mm
28	Normal	Poorly pneumatized Lt mastoid	125^0	0mm
29	Lytic lesion Lt frontal	Poorly pneumatized Lt mastoid	126^0	0mm
30	Normal	Poorly pneumatized mastoids	128^0	0mm
31	Marked vault thickening and irregularity	Bilateral proptosis; hypoplastic antra, petrous bones and mastoids very sclerotic and anatomy distorted	128^0	9mm
32	Lytic lesion Rt parietal region and 2 frontal lesions	Poorly pneumatized mastoids and maxillary antra; absent frontal and sphenoid sinuses, opacified Lt middle ear	138^0	4mm
34	Asymmetry Lt parietal region with bony depression	Sclerosis and thickening Rt orbit; poorly pneumatized mastoids; opacification of Rt middle ear cleft with soft tissue around malleus	120^0	0mm
37	Deformity and thinning of occipital bone,	Deformity Lt superior orbital fissure; lateral wall and roof of Lt orbit thickened, residual Lt proptosis; poorly pneumatized mastoids; no ossicles in Rt middle ear	135^0	0mm
39	Normal	Lt mastoidectomy - sclerotic underpneumatized residual mastoid with large single cavity; ossicles absent apart from tiny residual head of malleus. Hypoplastic frontal sinus. Calcified falx	128^0	0mm
40	Multiple large, full thickness lytic defects with areas of sclerosis	Very small hypoplastic mastoids, mastoid and middle ear cleft opacified, some ossicular destruction	165^0	30mm

Chapter 6. Other Systems

LCH causes long term sequelae, affecting not only the hypothalamo-pituitary region and the brain, as described in earlier chapters, but also other tissues such as bone, skin, lungs and liver. This chapter discusses these other sequelae including bony deformity, oro-dental abnormalities, hearing loss, skin changes and chronic lung and liver damage. A summary of the sequelae in the entire cohort of patients is given in **Appendix 1**.

Section 6.1. Bony deformities

Introduction

Bony abnormalities are the most common sequelae of LCH, and can result in limb deformity, loss of vertebral height and facial asymmetry. Loss of dentition is usually secondary to involvement of the maxilla and mandible and is discussed in this section. Hearing deficit, also often due to bony involvement, is discussed in the next section of this chapter.

Methods

Patients were assessed by clinical examination of the face, including teeth, skull, spine and limbs. Anthropometry including measurement of sitting height was performed. Abnormalirties of the cranio-facial skeleton were also assessed on MRI scans and 3-dimensional CT as described in the previous chapter.

Results

Thirty-six of the 40 patients (90%) had had 1 or more recognised bone lesions during the 'active' phase of the illness - 35 (70% of cohort) had skull lesions, 18 had limb lesions and 6 had involvement of vertebrae. These figures are likely to be an underestimate because a) skeletal surveys were not regularly repeated after diagnosis unless the patients had symptoms and b) skeletal surveys are not 100% sensitive and may miss some lesions.

Twenty-four patients (60% of the entire cohort, and 66% of those with bony involvement in the 'active' phase) had 1 or more residual bony abnormality at follow up.

Limb and vertebral Involvement

None of the patients had evident limb abnormalities on follow up assessment.

Three of the 6 patients with vertebral involvement had near complete reconstitution of the vertebral bodies, while the remaining 3 patients had residual collapse of 1 or more vertebral bodies. Patients with spinal involvement had shorter spines with a median sitting height SDS of –2 (range –2.97 to –0.44) compared to those without spinal involvement who had a median sitting height SDS of –0.98 (range –2.15 to 1.16) ($p<0.05$). However, as 3 of the patients with spinal involvement also had acquired basilar invagination (see Chapter 5), it is conceivable that some of the loss in upper segment measurement could be accounted for by the invagination of the cervical spine into the foramen magnum.

Abnormalities of the cranio-facial skeleton

Abnormalities of the skull and/ or face were noted on clinical examination and on MRI scan and 3-D CT of the head in 24 of the 40 patients (60%). Facial asymmetry was the most common anomaly (**Figure 6.1**). Ten patients had asymmetry of the skull vault. Seven patients had residual defects of the skull and in 1 patient (Pt. No 40) these defects were so extensive that they were easily visible and palpable (**Figure 6.2**). Three had areas of localised thickening of the vault and 2 had areas of thinning of the skull table. Seven of the 10 patients (70%) who had proptosis during the 'active' phase of the disease had residual proptosis at follow up. Four patients have marked facial abnormalities, which will require reconstructive surgery for correction.

Oro-dental abnormalities

Fifteen of the forty patients (37.5%) had loss of permanent dentition ranging from loss of 1 to 8 teeth (**Figures 6.3 and 6.4**). Ten patients (17.5%) have had or are planned to have orthodontic correction. Three patients had micrognathia with malocclusion and two have asymmetry of the lower jaw. One patient had marked prognathism with incorrect alignment of teeth requiring reconstructive surgery to the lower jaw.

Figure 6.1. Facial asymmetry following skull involvement by LCH

This is a photographic reconstruction of a patient demonstrating asymmetry following involvement of the left side of the skull by LCH resulting in poor growth of that half of the face. The image at the top is the actual appearance of the patient. On the right is a reconstruction using mirror images of the right side of the face, and on the left a reconstruction using mirror images of the left. The asymmetry of the face is thereby accentuated and the abnormality made obvious.

The patient's written consent has been obtained for publication of this photograph.

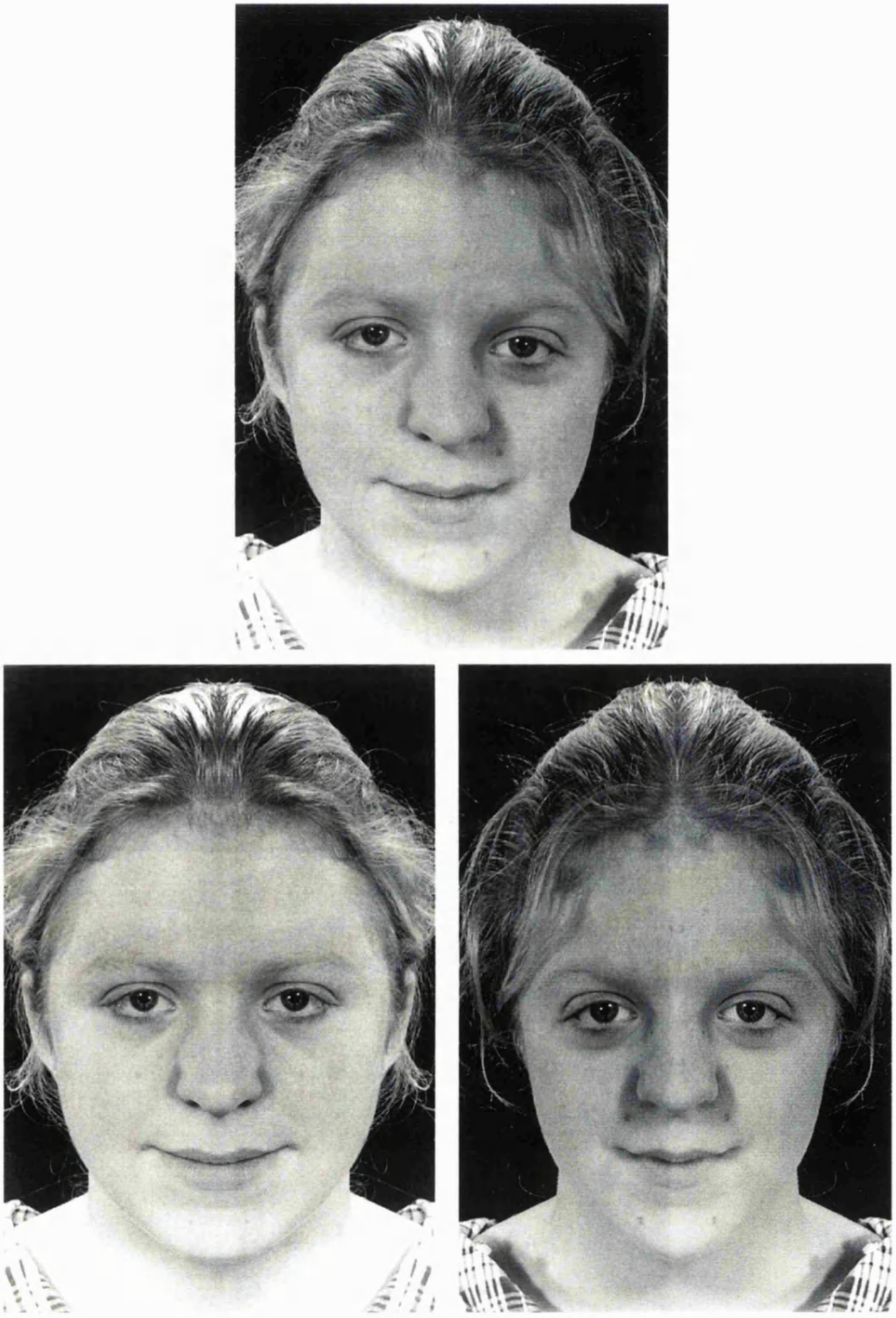
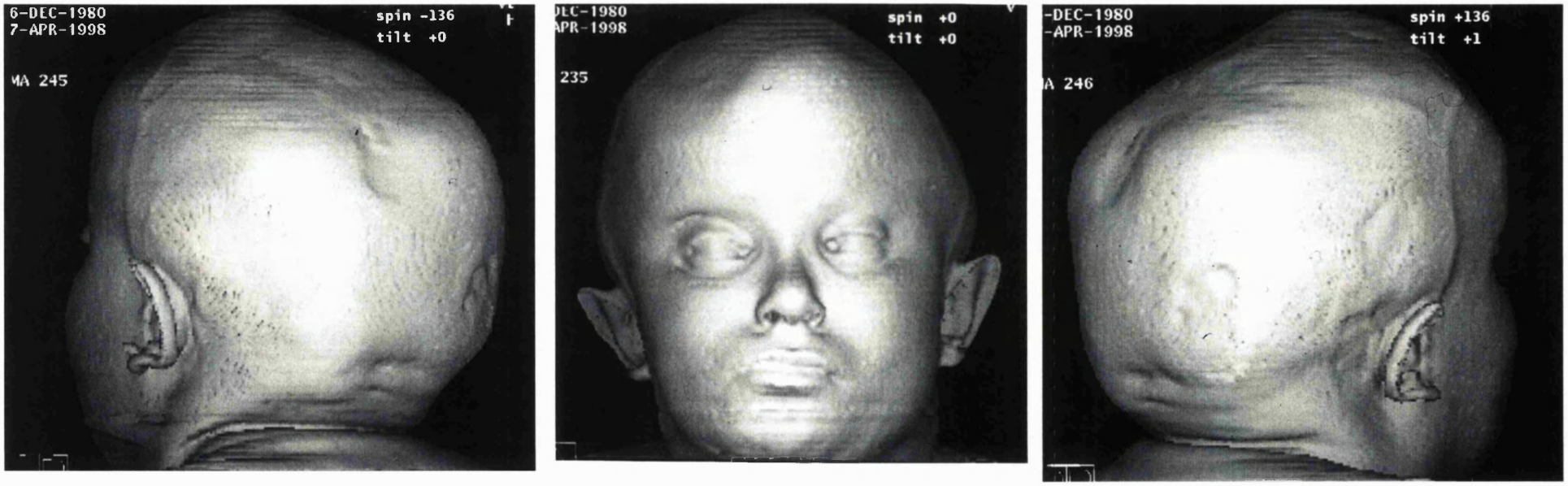


Figure 6.2. Skull vault defects and asymmetry

This is a 3-dimensional soft tissue reconstruction of the face and skull of patient no.40 demonstrating defects of the skull with depression of the overlying scalp. Right and left oblique posterior views and the face are shown.



Discussion

Our study shows that a considerably larger proportion (60%) of survivors than previously recognised have residual bony abnormalities. The reported incidence of skeletal late sequelae varies widely. The highest incidence was in 42% of patients in one series (Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996), including pathological fractures, bony malformations, scoliosis and vertebral compression with missing or malformed teeth in 30% of patients. In the French collaborative follow up study, vertebra plana and other orthopaedic sequelae were seen in just 2.5% and dental loss in 0.6% (Donadieu & French LCH Study group. 1996). Braier et al reported bony sequelae in 9% of their cohort (Braier et al. 1999b).

The most common bony abnormality in our patients was facial asymmetry, which has not been reported by other authors. This high incidence is possibly a reflection of the use of both clinical examination and the more sensitive imaging studies to assess facial structure. Cranio-facial anomalies are common after LCH and can be disfiguring, affecting the patient's 'body image' and self-confidence. Although, in most patients in this study these sequelae were considered to be relatively 'mild', 4 patients had more gross abnormality. It is difficult to assess the impact of these sequelae on the patient but important to consider the cosmetic implications for the patient's "quality of life". Once facial growth has been completed reconstructive plastic surgery needs to be considered in certain patients.

Persistence of lytic lesions of the skull has not been described in long term follow up studies. It may be that they are missed, as the defects may not always be palpable. Although it is unlikely that the residual skull defects are clinically significant in most patients, in the occasional patient the presence of large areas of bone loss may be an indication for surgical correction. In our patient the presence of several other sequelae, including basilar invagination precluded surgical reconstruction of the bony defects.

Loss of teeth can be a real handicap and can lead to difficulty in chewing food. Patients with jaw involvement may have asymmetric growth of 1 side leading to malocclusion and abnormalities of the "bite" which can cause long term problems including pain and muscle spasm. Patients need regular dental and orthodontic assessments. Some require operative procedures to correct these abnormalities and may need dentures to replace missing teeth to improve mastication.

Figure 6.3. Loss of teeth from permanent dentition

This photograph shows several teeth missing from both the upper and lower jaws. The patient required corrective orthodontic procedures.

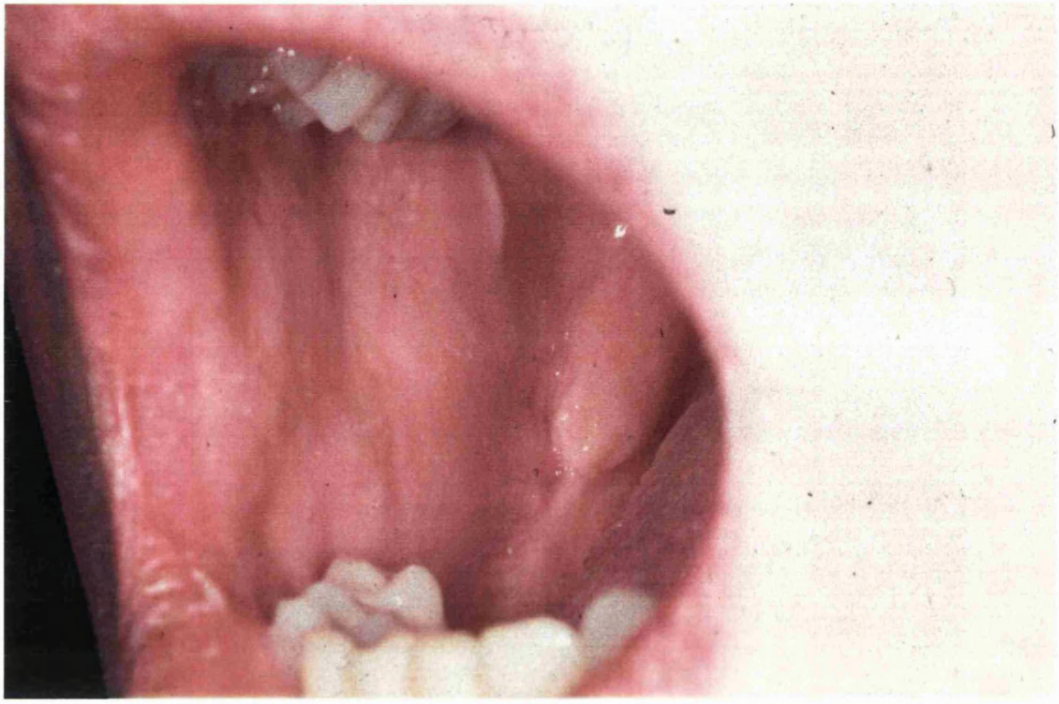
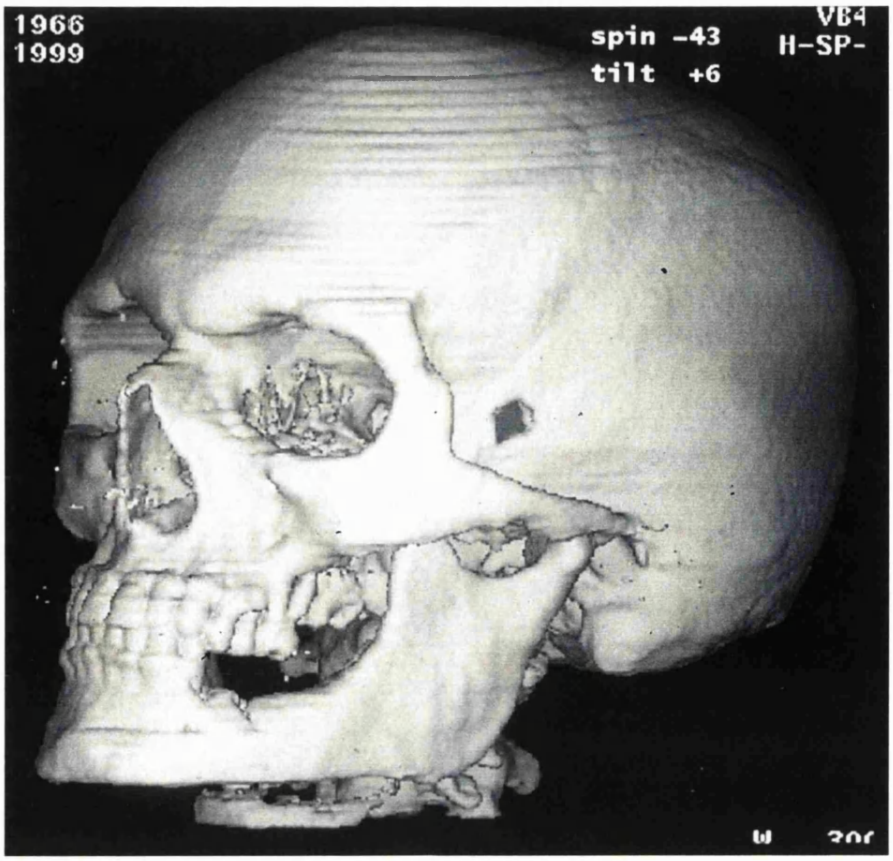


Figure 6.4. Loss of dentition

Three- dimensional CT scan of skull showing loss of several teeth from the lower jaw Also note the persistent lytic lesion of the left side of the skull



Section 6.2. Hearing

Introduction

Involvement of the ears is relatively common in LCH during the 'active phase'. Symptoms include aural discharge, swelling over the mastoid region and either conductive or sensorineural deafness due to middle or inner ear involvement, respectively. Less is known about long term damage to hearing in these children.

Methods

Hearing was tested by pure-tone audiometry as recommended by the British Society of Audiology (1981). Bone conduction (BC) and Air Conduction (AC) were measured and the Air Bone gap (AB gap) calculated. The definitions for level of hearing and type of hearing loss (HL) used here have been established by the European Work Group on Genetics of Hearing impairment (Milan, 1996) and are as follows:

Hearing Level		**Frequency Range**	
Normal	< 20 decibel (dB) HL	Low	< 500 Hertz (Hz)
Mild loss	20 – 39 dBHL	Mid	500 < < 2 K Hz
Moderate	40 – 69 dBHL	High	2K < < 8 K Hz
Severe	70 – 94 dBHL	Extended High	8 < K Hz
Profound	95 < dBHL		

Type of Hearing Loss

Conductive HL	BC < 20 dBHL, AB gap < 15dB averaged over 0.5, 1 & 2K
Sensorineural HL	AB gap <15dB averaged over 0.5, 1 & 2K
Mixed HL	BC ≥ 20dBHL, AB gap < 15dB

Tympanometry was also performed according to the recommendations of the British Society of Audiology (1992).

Results

Audiology and Tympanometry

Thirty nine of the 40 patients had audiology, as well as tympanometry, performed as part of the follow up study. The results are shown in **Table 6.1**. One patient could not have audiology performed due to technical reasons. Twenty four patients had normal hearing and tympanometry. Fourteen patients (35% of cohort) had documented residual permanent hearing loss. Of them, 6 had unilateral mild to moderate hearing loss, while 9 had bilateral hearing loss. Four patients (10% of cohort) had bilateral severe to profound hearing loss and have hearing aids (Pts. No 31, 34, 37, 40). Hearing loss was conductive in 6, purely sensorineural in 1 and mixed in 8.

Of the 28 patients (70% of the cohort) who had had ear involvement in the 'active' phase, 14 had normal hearing on follow up, and 1 patient was not tested. Thirteen of the 28 (53%) had documented hearing loss. Only 1 patient who did not have recognised ear involvement in the 'active' phase was found to have mild unilateral sensorineural loss on testing.

Petrous bone morphology

MRI and CT scans of the petrous temporal bones revealed unilateral or bilateral mastoid opacification, underpneumatization, or sclerosis in 17 patients. Patients who had had a mastoidectomy showed a large single mastoid air cell often with loss of ossicles. In 10 (59%) of these 17 patients there was an associated hearing loss. By contrast, in 5 (33%) of the 15 patients with hearing loss, the mastoid appeared normal. Of the 28 patients with ear involvement at diagnosis, 14 had mastoid changes, and 14 had normal imaging appearances at follow up.

Table 6.1. Audiology assessment

This table shows the presence or absence of ear involvement in the 'active' phase of the disease, the results of audiometry and tympanography and MRI/ CT appearances of the petrous temporal bones on follow up assessment. Hearing loss on follow up is shown in **Bold** type

Ear involvement in the 'active' phase had been diagnosed by the presence of aural discharge, hearing loss and mastoid disease.

Abbreviations: dB = decibels, LF= low frequency, HF = high frequency

Pt No.	Ear Involved in 'active' phase	Results of Audiology and Tympanometry on follow up assessment	MRI / CT abnormalities of the petrous bones
1	Yes	**Unilat.eral (left) mild hearing loss.** 20dB hearing loss left, Normal hearing right. Tympanograms normal bilaterally	None
2	No	Normal hearing and tympanograms bilaterally	None
3	Yes	**Bilateral mild hearing loss.** –Mild conductive hearing loss (25 to 35dB) bilaterally, more HF than LF. Normal bone conduction bilaterally.	High signal in right mastoid
4	Yes	**Unilateral (right) mild to moderate hearing loss -** Right sensorineural loss (BC) 40 dB low frequency, 30dB mid and high frequency. Normal hearing left.. Tympanograms normal bilaterally	None
5	Yes	**Bilateral moderate hearing loss** – Right 20dB LF sensorineural loss + 40dB HF loss in air conduction. Left 20dB LF sensorineural loss + 60 dB LF and 40dB HF loss in air conduction.	None
6	Yes	Normal hearing bilaterally. Tympanogram suggests bilateral eustachian tube dysfunction.	None
7	No	Normal hearing and tympanograms bilaterally	None
8	No	Normal hearing and tympanograms bilaterally	None
9	No	Normal hearing and tympanograms bilaterally	None
10	Yes	Normal hearing and tympanograms bilaterally	None
11	Yes	Normal hearing and tympanograms bilaterally	None
12	Yes	**Unilateral mild to moderate hearing loss** – details not available	Bilateral loss of mastoid aeration

Table 6.1. Audiology assessment - contd

Pt No.	Ear Involved in 'active' phase	Results of Audiology and Tympanometry on follow up assessment	MRI / CT abnormalities of the petrous bones
13	No	Normal hearing and tympanograms bilaterally	None
14	No	Normal hearing and tympanograms bilaterally	Right mastoid underpneumatized
15	Yes	**Bilateral moderate hearing loss** –details not available	Right mastoid opacificaftion
16	No	Normal hearing and tympanograms bilaterally	None
17	Yes	Normal hearing and tympanograms bilaterally	None
18	No	Normal hearing and tympanograms bilaterally	None
19	Yes	Normal hearing and tympanograms bilaterally	Left mastoid opacification
20	Yes	Normal hearing and tympanograms bilaterally	Right mastoid opacification
21	Yes	Normal hearing and tympanograms bilaterally	Right mastoid underpneumatized
22	Yes	**Unilateral (right) moderate hearing loss.** –Right conductive loss LF 40dB, HF 30dB, mild 20dB sensorineural loss. Left hearing and tympanogram normal.	None
23	Yes	Normal hearing and tympanograms bilaterally	Poorly pneumatized left mastoid
24	No	**Unilateral mild (left) hearing loss.-** Left sensorineural 30dB loss, flat tympanogram. Right normal hearing and tympanogram.	Underpneumatized mastoids bilaterally
25	Yes	Normal hearing and tympanograms bilaterally	None
26	Yes	**Bilateral mild hearing loss –** 20 to 30 dB hearing loss bilaterally	None
27	Yes	Normal hearing and tympanograms bilaterally	None
28	Yes	Normal hearing and tympanograms bilaterally	None
29	No	Normal hearing and tympanograms bilaterally	None

Table 6.1. Audiology assessment - contd

Pt No.	Ear Involved in 'active' phase	Results of Audiology and Tympanometry on follow up assessment	MRI / CT abnormalities of the petrous bones
30	Yes	**Bilateral mild to moderate hearing loss** – Right 20 to 30dB loss HF more than LF. Left normal bone conduction, moderate 60 dB LF and mild 30dB HF conductive loss.	Poorly pneumatized mastoids
31	Yes	**Bilateral mild to moderate conductive hearing loss.** –Right mild 30dB loss both HF and LF. Left mild 20 dB HF loss, moderate 40dB LF loss. Hearing aids. Normal bone conduction bilaterally.	Petrous bones and mastoids very sclerotic
32	Yes	Not performed	No mastoid pneumatization, opacifed left middle ear
33	Yes	Normal hearing bilaterally, flat tympanograms	None
34	Yes	**Bilateral severe to profound mixed hearing loss.** -Profound hearing loss right ear >>95 dB. Left severe 70dB hearing loss, mixed conductive and sensorineural. Bilateral hearing aids	Poorly pneumatized mastoids, opacification Rt middle ear cleft with soft tissue around malleus. Bilateral hearing aids visualised
35	No	Normal hearing and tympanograms bilaterally	Left mastoid underpneumatized
36	Yes	Normal hearing and tympanograms bilaterally	None
37	Yes	**Bilateral hearing loss**. – Right BC normal LF, moderate 50dB HF loss. Right air conduction LF severe 80dB loss, HF profound loss. Left no LF loss, mild 30dB HF sensorineural hearing loss. Left tympanogram flat, right tympanogram large external ear canal, possible perforation. Bilateral aids.	Both mastoids poorly pneumatized. No ossicles seen in right middle ear.
38	No	Normal hearing and tympanograms bilaterally	None
39	Yes	**Unilateral (Left) moderate conductive hearing loss.** –Left normal bone conduction. Air conduction LF 40dB loss, HF 60dB hearing loss. Left tympanogram reveals perforation of drum. Right normal audiometry and tympanogram.	Left mastoidectomy, sclerotic underpneumatized, residual single large cavity. Ossicles absent apart from tiny residual head of malleus
40	Yes	**Bilateral moderate to severe hearing loss. – Hearing aids** Mixed conductive and sensorineural hearing loss bilaterally 50 – 80dB	Underpneumatized mastoids, hearing aids in situ bilaterally

Discussion

Detailed audiological assessment was useful for quantifying permanent hearing loss in our patients, an aspect that has not been previously studied as thoroughly as the acute abnormalities. Involvement of the ear by histiocytosis in the 'active' phase is well recognised and relatively common. The original patients described by Schüller (Schuller 1915) and Letterer (Letterer 1924) had clinical evidence of ear involvement and the first report of otologic manifestations by 'histiocytosis X' appeared in 1935 (Lederer, Poncher, & Fabricant 1935). Since then there have been several reviews of aural involvement, the incidence ranging from 15-61% (Hudson & Kenan 1969;Irving, Broadbent, & Jones 1994;McCaffrey & McDonald 1979;Quraishi et al. 1995;Quraishi, Blayney, & Breatnach 1993;Smith & Evans 1984;Tos 1966). This variation probably reflects the use of different diagnostic criteria and the different specialities reporting the problem, with resultant selection bias. In our cohort the incidence of ear involvement in the acute phase was 70%, but this high incidence is probably a reflection of a combination of factors including a referral bias, our selection of patients with multisystem involvement and the more careful audiological testing undertaken in patients seen at our centre. In the 'active' phase, patients may develop conductive hearing loss due to the presence of granulation tissue in the middle ear, mastoiditis and/or perforation of the drum. When the disease process subsides, the hearing often improves.

Long term hearing loss is generally regarded as much less common, the reported incidence ranging from 1% to 16% of patients (Braier, Chantada, Rosso, Bernaldez, Amaral, Latella, Balancini, Masautis, & Goldberg 1999b;Ceci, Terlizzi, Colella, Loiacono, Balducci, Surico, Castello, Testi, Bernardi, Indolfi, Macchia, Madon, Mancini, & Rosati 1993;Donadieu & French LCH Study group. 1996;Gadner, Heitger, Grois, Gatterer-Menz, & Ladisch 1994;Komp, El Mahdi, Starling, Easley, Vietti, Berry, & George 1980;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996). These papers predominantly report results from questionnaire studies. There are no studies reporting detailed audiological findings in long term survivors of LCH. Fifteen of 40 patients (37.5%) in our cohort had a long term, perhaps permanent, hearing deficit. This incidence is much higher than previously reported and is possibly a reflection of careful assessment, enabling recognition of the loss, in our series. It is likely that hearing loss is not recognised sufficiently often because the possibility of permanent impairment is not considered and/or assessed at follow up.

Imaging techniques such as 'fine slice' CT scan and MRI of the petrous bones enable better resolution of the anatomy of the middle and inner ear structures, not only in the early stages but also at follow up. Invasion of the labyrinth is rare in the 'active' phase but should be suspected in any child with LCH who has sensorineural hearing loss, nystagmus, vertigo or behavioural change. Destruction of the labyrinth can result in permanent hearing loss. Early recognition and treatment may prevent permanent damage and reduce the long - term morbidity due to deafness (Nanduri et al. 1999c). It is possible that destruction of inner ear structures was responsible for sensorineural hearing loss in our patients.

Hearing deficit has major implications on the ability of children to learn and to speak and early recognition and correction of loss is essential. Bilateral hearing loss causes serious disability and needs to be addressed as early as possible to reduce the handicap. It is therefore imperative that all children with ear involvement in multisystem LCH have regular audiometry and imaging of the petrous temporal bones during the acute phase and those with any abnormality detected have long term follow up of hearing. All children with significant hearing loss, especially if bilateral, should have appropriate intervention, including hearing aids.

Section 6.3. Skin Changes

Introduction

Skin involvement is seen in the 'active' phase in up to 50% of patients with LCH (Munn and Chu 1998). Although long term scarring has been recognised, again, no specific prevalence has been reported. We assessed the long term cutaneous sequelae of the primary skin lesions and the possible effect of the topical treatments used. The scars from interventional procedures including biopsy and insertion of chest drains or lines are often overlooked when assessing scarring, so we also addressed this point.

Method

Clinical examination was used to detect skin changes. No biopsies of affected areas were performed, apart from one in the patient with xanthogranulomatous

change. Patients who had had topical mustine applied to the lesions were studied in more detail including assessment of the area of skin treated, duration of treatment and any skin changes in the site of application.

Results

Thirty three (82%) of the 40 patients had skin involvement in the 'active' phase. Scarring was noted at follow up in 15 patients (37.5% of the entire cohort). Eight patients (24% of the 33 with skin involvement) had scars at sites of previous skin rash, while the other 7 had scars from surgical procedures including biopsy, curettage, insertion of chest drains or orthopaedic and thoracic surgery. In 5 of the patients who had had a skin rash, scars were faint and seen at skin creases (**Fig 6.5**). One patient had chronic discharging sinuses overlying involved lymphnodes with resultant scarring (**Fig. 6.6**). The 7th patient (Pt. No 31) had lipid- filled scars of juvenile xanthogranuloma, most obvious in the creases of the neck (**Fig 6.7**). She and her parents found these scars disfiguring and were considering cosmetic surgery. The final patient (Pt. No. 40) has several scars on the scalp with hair loss and underlying skull deficits and deep scars in the axillae (**Fig.6.8**) and groin. Most of the surgical scars were on the limbs and chest wall. Two patients had facial scars, which were not very obvious, 1 of which was from cosmetic surgery to remove a deep scar resulting from a discharging bony lesion. Eight patients had been treated with topical mustine hydrochloride (nitrogen mustard) to the skin rash during the 'acute' phase, with a good, prompt response. These patients have been reported earlier (Sheehan, Atherton, Broadbent, & Pritchard 1991). At follow up, only 1 of these 8 patients (Pt. No 31) had severe scarring, felt to be secondary to the LCH rash rather than due to the mustine therapy. There were no other 'late effects' of mustine treatment, such as the development of malignant or premalignant lesions in the areas of treated skin. It therefore appears that topical mustine is a safe and effective treatment for cutaneous LCH (Hoeger et al. 2000)

Discussion

Although scarring is recognised after LCH, skin changes are not usually discussed as long term sequelae of LCH and have not been reported in the several outcome studies of these patients. Possibly, this is because scars do not affect vital functions or mobility and are therefore not felt to be clinically

significant. However, the impact of scarring on a person's "quality of life" must not be forgotten. Severe scars can be disfiguring and contribute to morbidity. In our cohort, several adolescents and their parents have considered, or already had, cosmetic surgery to improve appearance. Although not affecting body function, skin damage must be assessed as part of follow up and appropriate cosmetic intervention offered.

Figure 6.5. Faint scars

Faint scars in the creases of the neck as a sequela of skin rash of LCH

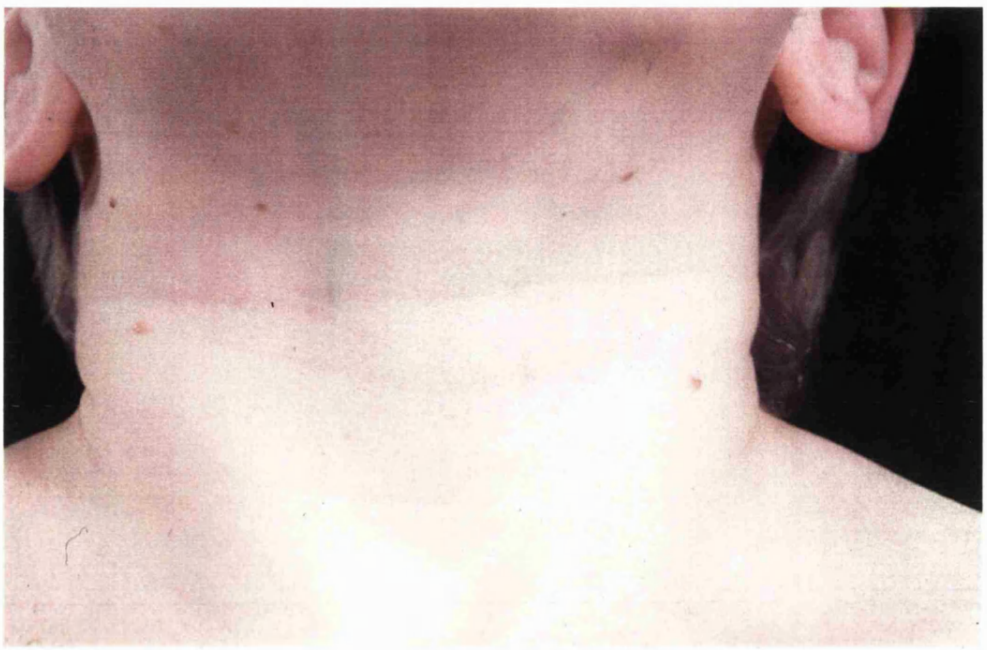


Figure 6.6. Chronic discharging sinuses

Chronic discharging sinuses overlying cervical lymph node involvement

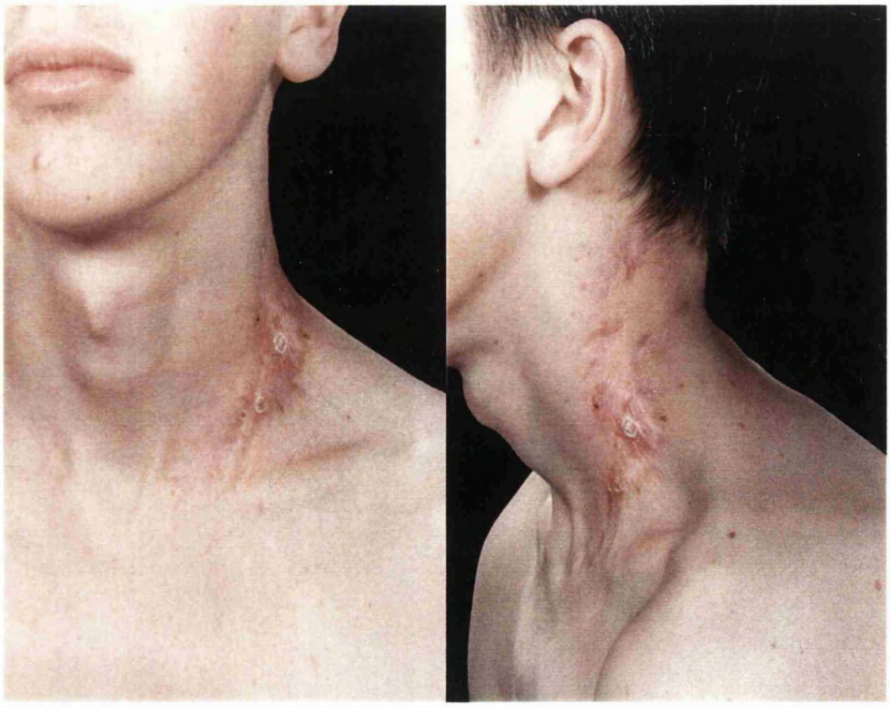


Figure 6.7. Xanthomatous lesions

Xanthomatous lesions in an area of previous active LCH skin rash

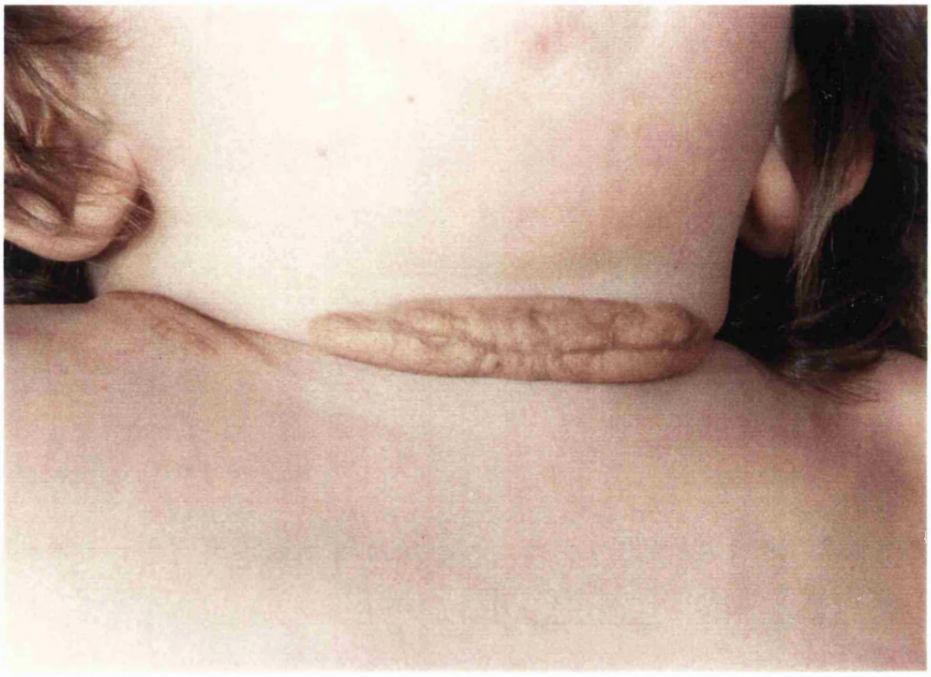
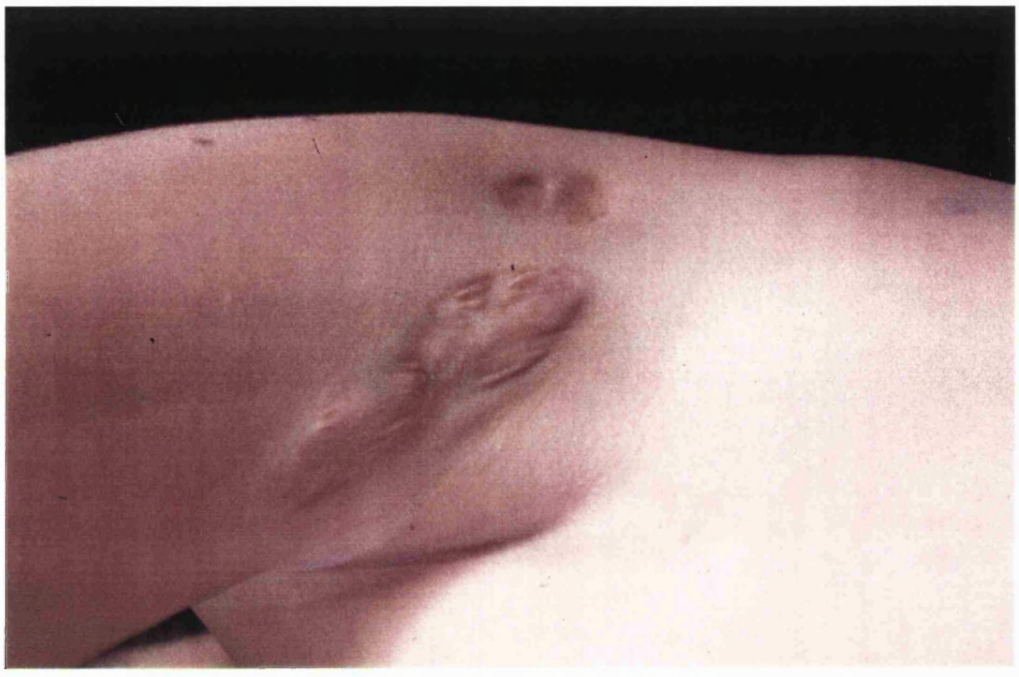


Figure 6.8. Axillary scarring

Deep disfiguring scars in the axilla as a result of severe skin involvement



Section 6.4. Pulmonary sequelae

Introduction

Lung involvement is common in children with multisystem LCH but is often asymptomatic and resolves without sequelae (Ha, Helms, Fletcher, Broadbent, & Pritchard 1992). Lung fibrosis can be the consequence in some patients but is more commonly seen in adults, especially smokers. Few studies have assessed long term lung function in survivors of LCH and most of these authors have reported results from questionnaire- based studies. (Willis et.al 1996, French Langerhans' Study Group 1996).

We assessed pulmonary function by respiratory function tests in this cohort with additional radiological investigations as indicated clinically.

Methods

Respiratory Function tests

Peak Flow rate (PFR) was performed using a Wright's Peak Flow meter and the best of three attempts was used. Spirometric variables measured were the Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC), Peak Expiratory Flow Rate (PEFR) and the Maximum Expiratory Flow at 25% of FVC (MEF_{25}). Three to six attempts were measured and the best effort recorded. The results were compared to the mean expected for height, weight and gender (Rosenthal et al. 1993). The percentage of predicted value was calculated.

Chest X Ray

Chest X Ray was performed on patients with abnormal lung function i.e. below 70% of predicted values.

High Resolution CT (HRCT) scan

High resolution CT scan of the chest was performed in those patients who had an abnormal chest X Ray.

Results

Lung Function tests

The results of lung function tests are tabulated in **Table 6.2.** Fifteen patients (37.5% of the cohort) had had lung involvement in the active phase of the disease. Of them, 8 (53% of initially afftected patients, 20% of the entire cohort) had abnormal lung function at follow up assessment. In 1 (Pt.No.4) the abnormal result was felt to be secondary to gross obesity and hypoventilation. Although in 4 patients poor technique (due to poor compliance with instructions and reduced understanding secondary to a low IQ) partly contributed to the low results, there was also supporting evidence of underlying lung involvement.

Five (12.5% of cohort) of the 8 patients with abnormal lung function have breathlessness on exertion. Patients No. 15 and 29 have very severe residual lung disease with significant restriction of functional ability and have both been considered for lung transplantation. It is important to note that 2 patients (Pt. No. 15 and 37) developed lung damage only after they started to smoke, having been asymptomatic prior to this.

Chest X Ray

Chest X Ray was performed in 6 of the 8 patients who had abnormal lung function. The other 2 patients (No. 21 and 32) failed to attend several appointments for chest X ray and repeat lung function and could not be reassessed to date. Two of the 6 patients (Pt. No. 4 and 26) had normal chest X rays, 2 (Pt. No. 31 and 37) had bilateral streaky interstitial shadowing, while 2 (Pt. No. 15 and 29) had gross abnormalities including widespread fibrotic shadowing, honeycomb pattern and emphysema with bullous change (**Fig. 6.9**). Patient no. 15 developed an Aspergillus lung infection following prolonged corticosteroid use and had residual radiological changes from the infection in addition to the lung fibrosis. Patient No. 29 had had recurrent pneumothoraces at diagnosis requiring emergency chest drain insertion, and finally had bilateral pleurectomies in an attempt to prevent recorrence of this complication.

CT Scan Chest

Three patients (Pt. No 15, 29 and 31) had high resolution CT scans of the chest. They showed widespread fibrosis, bullous formation and scarring of lung tissue (**Fig. 6.10**).

Table 6.2. Lung Function

This table shows the results of lung function tests and chest X Ray at the time of diagnosis of LCH and the lung function tests at follow up assessment. No CT scans were carried out at diagnosis. Initial lung function test results are reported with normal ranges in brackets. At follow up assessment each result is given as a percentage of normal mean predicted for age (Rosenthal, Bain, Cramer, Helms, Denison, Bush, & Warner 1993). Results below 70 % of expected (highlighted in **Bold** type) were considered to be abnormal and further investigations performed.

Pt No	Lungs Initially involved	Initial Lung Function/ Chest Xray	Lung Function at follow up assessment			
			FVC %Predicted	FEV1 %Predicted	PEFR L/ min %Predicted	MEF25% L/sec % Predicted
1	No	Lung function tests not performed. CXR normal				
2	Yes	Small stiff lungs. TGV 97 (140 to 260), Comp 3.6 (6 to 11.5). CXR patchy shadowing right upper lobe, streaky shadowing left mid and lower zone	84	95	117	146
3	No	Low normal lung volume and compliance. TGV 260mls (240 to 420), Comp 11.9 (9.2 to 15). CXR – normal lungs	109	108	127	80
4	No	Mild hyperinflation, otherwise normal. VC 1800 (1740 to 2890), TLC 2990 (3000), FEV1 1650 (1720 to 2560), PEFR 295 (202 to 380)	**66**	**63**	83	**41**
5	No	Lung function tests not performed. CXR normal	96	101	92	99
6	No	Normal lung volume and compliance. TGV 288 mls (168 to 314), Comp 9 (8 to 14.8) CXR no lung abnormality	88	97	98	107
7	No	VC 1720 (1320 to 2400), FEV1 1600 (1280 to 1920), PEFR 250 (160 to 320) CXR lung fields clear	96	89	89	75
8	No	Lung function tests not performed. CXR normal	97	110	107	163

Table 6.2. Lung Function - Contd.

Pt No	Lungs Initially involved	Initial Lung Function/ Chest Xray	Lung Function at follow up assessment			
			FVC %Predicted	FEV1 %Predicted	PEFR L/ min %Predicted	MEF25% L/sec % Predicted
9	No	Lung function tests not performed. CXR normal	83	83	114	56
10	No	Lung function tests not performed. CXR normal	102	100	93	88
11	No	Lung function tests not performed. CXR normal	92	82	84	68
12	No	Lung function tests not performed. CXR normal	112	93	91	56
13	No	Lung function tests not performed. CXR normal				
14	No	Normal lung volumes, but ↓compliance and↑ resistance. TGV 64 (35 to 70), Comp 6.19 (9 to 20), R 66.6 (20 to 30). CXR normal lung fields	105	94	95	68
15	★Yes	Restrictive defect with interstitial lung involvement. FVC 4.37 (4.67 to 5.14), FEV1 3.53 (3.98 to 4.96), FEV1/FVC 81% (79 to 85%), PEFR 512 (465 to 563). ↓ diffusion of CO – TLCO 6.09 (23.07 to 23.42) CXR – Widespread bilateral lung shadowing, with honeycomb pattern and emphysema	84	**38**	**49**	**15**
16	No	Lung function tests not performed. CXR normal	101	97	104	69
17	Yes	Lung function tests not performed. CXR streaky shadowing both lung fields	94	102	111	104
18	Yes	Small, stiff lungs. TGV 317 (>420), Comp 13 (23 to 35), R 14 (11 to 16). CXR marked reticulonodular shadowing	86	88	100	80
19	Possibly	Normal lung volume, ↓ compliance- TGV 325 mls (235 to 440), Comp11.5 (13 to 22) CXR – normal appearance	**71**	82	85	107
20	Yes	Low normal lung volume with moderate ↓ compliance- TGV 351 (300 to 530), Comp 17.2 (18 to 28) CXR clear	84	91	96	124

Table 6.2. Lung Function - Contd.

Pt No	Lungs Initially involved	Initial Lung Function/ Chest Xray	Lung Function at follow up assessment			
			FVC %Predicted	FEV1 %Predicted	PEFR L/ min %Predicted	MEF25% L/sec % Predicted
21	Yes	Poor technique, uncooperative, lung function reported as probably normal CXR bilateral interstitial shadowing	**57***	**63***	**64***	76*
22	Yes	Low/normal lung volume, compliance at upper limit of expected range, ↑resistance CXR – diffuse infiltrate	84	82	82	66
23	No	Lung function tests not performed. CXR normal	102	102	109	85
24	No	Lung function tests not performed. CXR normal	87	87	82	68
25	No	Normal lung function – VC 1450 (984 to 1748), TGV 1706 (1537 to 2418), FEV1 1250 (887 to 1569), FEV1/FVC 86%, PEFR 250 (130 to 280) CXR clear				
26	Yes	Restrictive defect small, stiff lungs. CXR honeycombing	**58**	**68**	82	143
27	Yes	Small stiff lungs,– TGV 162mls (270 to 420), Comp 10 (17 to 27) CXR normal appearance	89	89	119	73
28	No	Lung function tests not performed. CXR normal	87	90	101	85
29	Yes	Mixed restrictive, obstructive defect. Reduced gas mixing. VC 2120 mls (3200 to 4500), TLC 4991 (4900 to 7000), FEV1 1620 (3300 to 4300), PEFR 405 (420 to 500) CXR bilateral honeycombing ,right pneumothorax	**46**	**27**	**57**	**12**
30	No	Lung function tests not performed. CXR normal	94	103	111	97
31	Yes	Small, stiff lungs – TGV 190 (194 –283), Comp 7 (7 to 13). CXR- coarse linear, reticular lung shadowing	65*	72*	63*	157
32	Yes	Lung function tests not performed. CXR fine linear shadowing, interstitial markings	**64***	**60***	**61***	**42***
33	Yes	Lung function not performed. CXR bilateral multicystic change, bilateral spontaneous pneumothoraces	69	75	120	83

Table 6.2. Lung Function - Contd.

Pt No	Lungs Initially involved	Initial Lung Function/ Chest Xray	Lung Function at follow up assessment			
			FVC %Predicted	FEV1 %Predicted	PEFR L/ min %Predicted	MEF25% L/sec % Predicted
34	No	Lung function tests not performed. CXR normal				
35	No	Lung function tests not performed. CXR normal	91	98	114	100
36	Yes	Normal lung volumes, ↑ resistance, ↓ compliance. TGV 253 (170 to 315), R 68 (13 to 18.5), Comp 6.2 (8.5 to 15). CXR hyperinflated, but otherwise normal	78	73	86	51
37	Yes★	Initial CXR clear. Lung function not performed.	55*	62*	88*	116
38	No	Lung function tests not performed. CXR normal				
39	No	Lung function tests not performed. CXR normal	129	128	127	102
40	No	Lung function tests not performed. CXR normal	81	81	69*	79

* indicated poor technique

★ lung abnormality developed late - at age 23 years and 16 years respectively (after starting smoking)

TGV = thoracic gas volume in millilitres

Comp =Compliance in millilitres/centimetres H_2O

R = Resistance

VC = Vital capacity in Litres

FVC = Forced vital capacity in Litres

FEV_1 = Forced Expiratory Volume in one second

PEFR = Peak Expiratory Flow Rate

MEF_{25} = Maximum Expiratory Flow at 25% of FVC

Figure 6.9. Fibrosis, emphysema and bullous change

Chest X Ray showing interstitial fibrosis, emphysema and bullous change

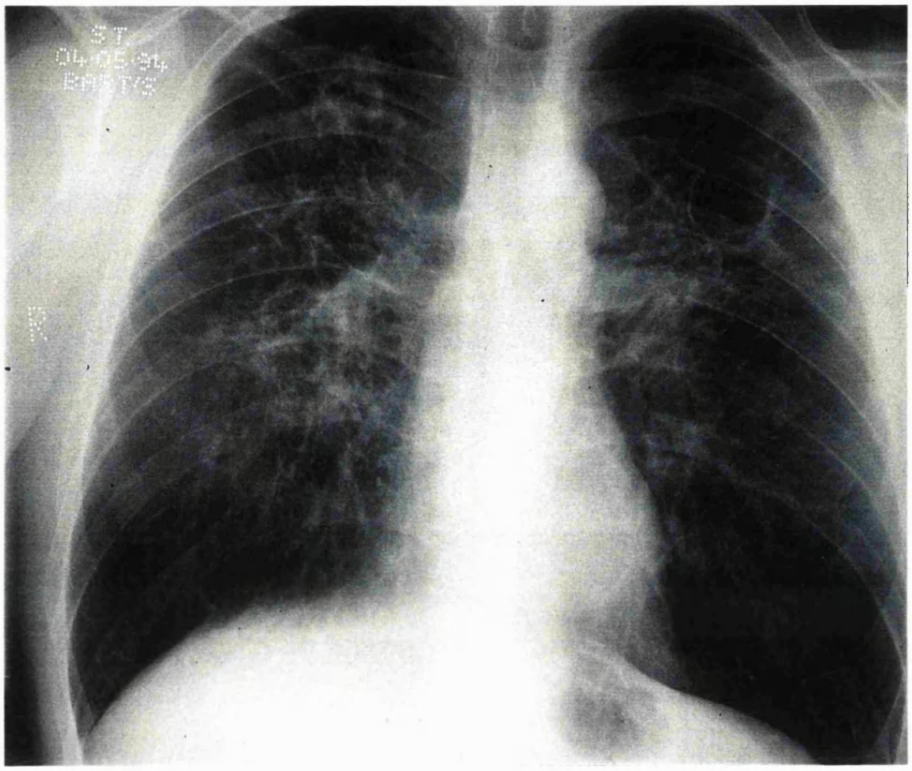
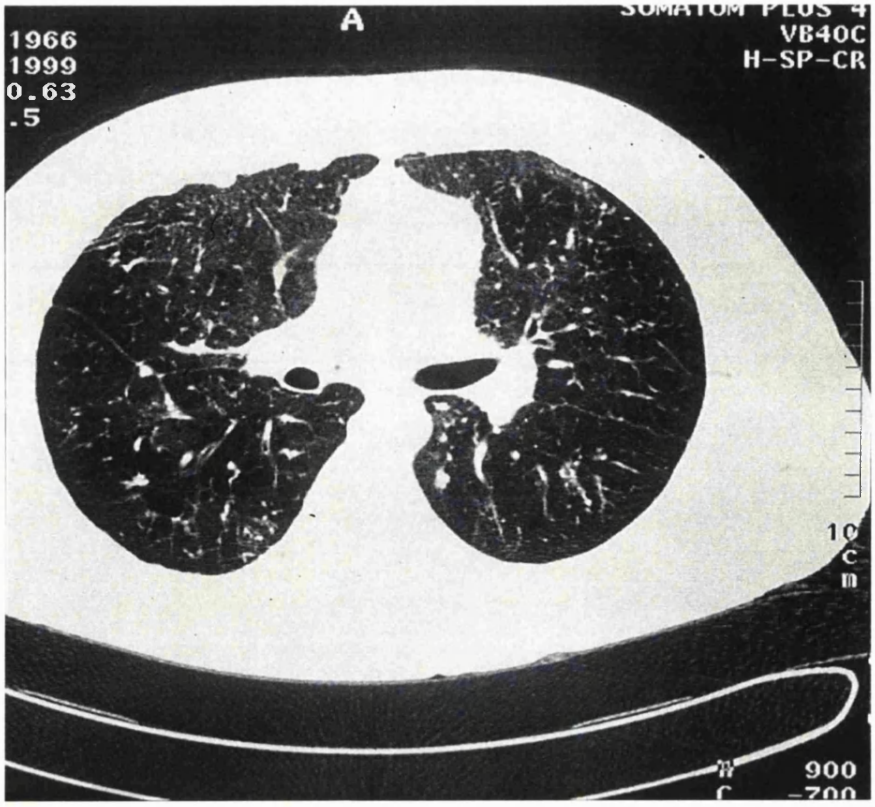


Figure 6.10. Fibrosis and scarring on CT scan

High resolution CT scan of chest showing fibrosis and scarring



Discussion

Abnormal lung function was seen in 20% of long term survivors, with respiratory symptoms in 12.5%. Of great concern is the fact that 2 subjects (5%) of the cohort have developed severe symptoms resulting in a possible need for transplant. Other long term follow up studies report a lower incidence of pulmonary fibrosis - 8% (Willis et.al.1996), while The French Langerhans' Cell Histiocytosis group found that 1% of patients had respiratory distress, and that only 1 patient (0.3%) needed lung transplantation. Both these studies were questionnaire based and did not involve active examination or investigation of patients. The study that compares most closely to ours is that from Stockholm (Bernstrand et al. 2001) where 41 patients who were 5 or more years from diagnosis were assessed clinically and with X ray and high resolution CT scans of the chest. They found that 10 patients (24%) had abnormal radiological findings and of them 7 had been smokers and concluded that it was important for patients with LCH to be advised about smoking-related pulmonary pathology. The main difference between our study and the study from Stockholm is our use of respiratory function tests to assess morbidity, thus reducing the burden of radiation to patients.

Although lung involvement, as diagnosed by the presence of interstitial shadowing on chest X Ray, is common in infants with multisystem LCH, patients are often asymptomatic (Ha, Helms, Fletcher, Broadbent, & Pritchard 1992). Pulmonary involvement in young children appears to be 'benign', often resolving spontaneously or with little treatment, and does not appear to be the primary cause of death in children who die of LCH (Carlson, Hattery, O'Connell, & Fontana 1976). Pulmonary fibrosis is a well-recognised sequela of lung involvement, but this abnormality is more often recognised in adults and adolescents while children with lung involvement often have no long term sequelae. No specific cause for this difference has been identified, but it is possible that the lungs of younger children have some capacity to repair and / or to regenerate damaged tissue. This belief is supported by the finding in this study that of 15 patients who had initial lung disease, only 7 (~50%) had abnormal lung function at follow up. Certainly the 2 patients who have very severe fibrosis developed lung damage in late adolescence and early adulthood, resembling the pattern seen in adults with lung disease. The changes were worse in those patients who smoked as has been reported by other authors (Cederlund, Bernstrand, & Henter 1996) (Bernstrand et al. 2000;Bernstrand, Cederlund, Sandstedt, Ahstrom, Lundell, Dahlquist, & Henter 2001). Lung fibrosis causes dyspnoea and exercise intolerance and can restrict activity.

End stage pulmonary disease causes respiratory failure. In severely affected patients the only treatment option may be lung transplantation (Grossman, Frost, Zamel, Patterson, Cooper, Myron, Dear, & Maurer 1990). However, there is a small chance that LCH may recur in the transplanted lung leading to damage in the donor organ (Habib, Congleton, Carr, Partridge, Corrin, Geddes, Banner, Yacoub, & Burke 1998).

In summary, although unusual in children, lung fibrosis can cause morbidity and affect quality of life. As it is especially common in those who smoke, the importance of abstaining from smoking and avoiding passive smoking must be emphasised to all patients and their parents. All survivors of LCH should have lung function assessed on a regular basis. Respiratory function tests are non-invasive, easy to perform and do not involve radiation and can therefore be used as a screening test before embarking on radiological examination. Patients with abnormal lung function can be further assessed by chest X ray and high resolution CT scan if necessary. Although it is well recognised that HRCT scanning offers high quality imaging of the pulmonary abnormalities, it is necessary to further study the clinical usefulness, financial impact and radiation burden of this investigation before applying it to all patients.

Section 6.5. Liver fibrosis

None of our patients had signs of liver fibrosis or abnormal liver function. Studies have reported sclerosing cholangitis and cirrhosis in 1.3% (The French Langerhans' Cell Histiocytosis Group 1996) and 2% (Willis et.al. 1996) of patients. It is possible that the patients with liver involvement did not survive and therefore were not included in this long term study. In addition, as our cohort consisted of 40 patients, it is possible that a sequela that occurs at a frequency of ~1% may not have been seen.

Summary

The prevalence of long term sequelae involving the bones, teeth, skin, ears and lungs in this cohort of survivors of multisystem LCH is higher than previously reported. We feel that careful assessment, rather than a true increase in sequelae in our patients, was responsible for the higher 'pick up' rate in this series. Most previously published studies have used a questionnaire-based approach, rather than clinical examination and investigation at follow up. Our findings stress the importance of regular dental assessment, audiology and lung function testing in addition to investigations discussed in previous chapters. For a comprehensive list of suggested follow up investigations for LCH patients, see **Appendix 5**.

Chapter 7. Morbidity Scores and Functional Outcome

Patients with Langerhans' cell histiocytosis, especially those with multisystem involvement, are often left with long term sequelae that can impair their quality of survival (Komp, El Mahdi, Starling, Easley, Vietti, Berry, & George 1980). Although this morbidity is well-documented, no uniform, reproducible scale for assessment of the degree of impairment or morbidity has been formulated. As a result, it is difficult to assess patients objectively and to compare outcome in subjects treated with different regimens. As well as the obvious medical needs, such as hospital visits and regular medication, the presence of a chronic condition has several implications for the lives of the child and the family. The stresses that develop can have far-reaching psychological, social and financial consequences for the entire family and need to be taken into consideration when assessing the impact of the disease on 'Quality of Life'.

In this chapter we describe 2 different measures we used to assess the functional outcome of patients who have survived multisystem LCH. The first is a morbidity score, using a numerical scale, we developed to grade the clinical status of the patient. The second is a measure of the patient's perception of the burden of the disease –Heath-related Quality of Life or Health Status as assessed by the Health Utility Index (Feeny et al 1995). Together, these measures give, on the one hand, an objective medical assessment and, on the other, a more subjective but personal perspective of the impact the disease has had on the patient, on his/ her ability to integrate into society and lead a 'normal' life.

Section 7.1. Morbidity Score

7.1.1. Introduction

The WHO defines 'impairment' as any loss or abnormality of psychological, physiological, or anatomical structure or function. A 'disability' is defined as any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal. A 'handicap' is defined as a disadvantage for an individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, gender, and social and cultural factors) for that individual. (World Health Organization 1980)

Several different measures of morbidity are used in disease-specific contexts (De Haan et al. 1993;Rankin 1957) including patients with cancer (Karnofsky & Burchenal 1949). However, none of these measures are particularly appropriate for the assessment of patients with LCH, as they do not deal with some of the specific problems known to be associated with this condition. We therefore felt it was necessary to develop a 'LCH-specific score' to assess the degree of impairment caused to each patient by sequelae of the disease and its treatment. Once validated, this score could be used to compare groups of patients treated in different institutions with different regimens. It would then be easier to assess the relative merits of the available treatment options, not just for immediate symptom control, but also for their impact on long term outcome.

This section describes the development of a simple and useful measure of morbidity and its application to these patients.

7.1.2. Methods

The various systemic sequelae of the disease were categorised and a scale devised to reflect the severity of impairment. The 6 categories considered to be relevant in long term follow up of LCH patients derived from this study were:

1. endocrine deficiencies including DI, GH insufficiency and other anterior pituitary hormone deficiency and hypothalamic dysfunction
2. motor neurological abnormalities including ataxia, incoordination and other motor dysfunction
3. learning deficit as measured by neuropsychometric assessment and psychological disturbance requiring specific management
4. hearing loss as measured by audiometry
5. pulmonary dysfunction with abnormal lung function and dyspnoea
6. cosmetic problems including facial asymmetry and other residual bony abnormalities and dental loss requiring correction.

Each category was then assigned 4 grades of severity, depending on the degree of impairment and the need for treatment or correction.

Severity of impairment in each category

GRADE	SEVERITY OF IMPAIRMENT
0	no abnormality
1	impairment which does not require any treatment
2	impairment which is correctable by appropriate replacement therapy or other specific treatment or the use of aids
3	disability/ handicap not completely correctable by therapy/ aids.

The sequelae in each patient were graded according to this classification and the grade in each category added to form a total score. The degree of disability was then graded according to the total score obtained.

Using this scale the highest score possible was 18.

Degree of impairment/ disability in each patient

SCORE	DEGREE OF IMPAIRMENT/ DISABILITY
0	no impairment
1 to 3	mild impairment
4 to 9	moderate impairment and disability
10 to 18	severe disability and handicap

Although this may seem to be to be a rather simplistic classification, it does cover all the major permanent consequences and is both easy to use and adaptable. The scoring system can be based on clinical findings without the need for special investigations, which might not be available at all centres. We recognise that not all sequelae cause the same degree of disability and have tried to grade the abnormalities according to the burden of impairment they cause. We also recognise that some handicaps are interrelated ie hearing loss and learning deficit.

7.1.3. Results

Each patient's problems were categorised according to this classification and graded. The number of patients with each grade of impairment are shown in **Table 7.1**. Physical and cosmetic problems were very common, and endocrine abnormalities, neurological damage and learning deficit were each present in nearly half the patients. Hearing loss requiring corrective aids and pulmonary damage occurred less often. Thus, 10 of the 40 patients (25%) had no impairment (Score 0), 11 (27.5%) had mild impairment (Score 1 to 3), 9 (22.5%) had moderate disability (Score 4 to 9), while 10 (25%) had severe disabilities (Score >10) that affected their ability to lead an independent life. The patients with the most severe handicap were those with ataxia, intellectual deficit and behavioural/ psychological problems which impaired their ability to learn, to care for themselves and to integrate normally into society. The single most important indicator of outcome was the presence of any CNS involvement (on clinical evidence and/ or neuroimaging), patients with CNS disease faring significantly worse than those without such involvement ($p<0.005$). This feature is depicted graphically in **Fig 7.1**.

We looked at the years of treatment received as a reflection of the duration of the 'active' phase of the illness, and related this to the outcome as measured by the scoring system. There was no difference in the duration of treatment in the patients with no sequelae (mean duration 1.2 years, range 0 to 3.84 years), mild disability (mean duration 1.45 years, range 0 to 7.3 years) or moderate disability (mean duration 2.0 years, range 0.34 to 3.66 years), However, the most severely affected patients did have a longer duration of treatment (mean 6.05 years, range 0.49 to 20 years). These results are depicted graphically in **Fig 7.2**. Although this difference in duration of treatment was statistically significant ($p=<0.05$), it needs to be remembered that a) these are small groups of patients so that the confidence intervals are wide and b) that chronic disease and prolonged treatment often go together. Some of these patients in this study had received prolonged courses of steroids with a mean duration of therapy of 4.3 years and a maximum of 10 years.

Vital organ involvement in the 'acute' phase of the disease did not appear to be a significant "risk factor" in determining outcome. Certainly there was no association between the presence of involvement of organs such as bone marrow, liver, spleen and lungs and the morbidity score.

Table 7.1. Morbidity Score

Abnormality	Score	No. of patients	%
Endocrine			
Panhypopituitarism +DI ± hypothalamic syndrome	**3**	4	10
Partial anterior pituitary deficiency and/ or DI	**2**	16	40
Partial DI, no anterior pituitary replacement required	**1**	0	0
No pituitary deficiency	**0**	**20**	**50**
Neurological (ataxia, motor deficit)			
Severe ataxia (Scale > 40) or other motor disability	**3**	6	15
Moderate ataxia (Scale 20 – 40)	**2**	3	7.5
Mild ataxia (Scale <20)	**1**	4	10
No ataxia	**0**	**27**	**67.5**
Education/ Employment/ Psychological			
Severe learning difficulty (IQ <70) and/or severe behavioural/ psychological problems impairing function	**3**	7	17.5
Moderate learning difficulty (IQ 71 to 79) /behavioural/ psychological problems correctable by therapy	**2**	5	12.5
Mild learning difficulty (IQ 80 to 89) / mild behavioural/ psychological problems not requiring psychotherapy	**1**	5	12.5
Normal IQ, no behavioural problems	**0**	**23**	**57.5**
Hearing deficit			
Severe bilateral hearing loss	**3**	3	7.5
Moderate bilateral hearing loss	**2**	4	10
Mild bilateral or moderate/ severe unilateral loss	**1**	5	12.5
No hearing loss or mild unilateral hearing loss	**0**	**28**	**70**
Pulmonary involvement			
Severe exertional dyspnoea	**3**	2	5
Moderate exertional dyspnoea	**2**	2	5
Mild exertional dyspnoea	**1**	4	10
No exertional dyspnoea	**0**	**32**	**80**
Physical features/ facial/ dental/ scarring etc			
Gross facial asymmetry/ orthodontic abnormality/ scarring requiring repeated or major surgery	**3**	5	12.5
Moderate facial asymmetry/ orthodontic abnormality/ scarring correctable with surgery /dental procedures	**2**	7	17.5
Mild facial asymmetry/ orthodontic abnormality/ scarring not requiring any procedures	**1**	10	25
No abnormality	**0**	**18**	**45**

Figure 7.1. Relationship between CNS involvement and morbidity score

This graph shows the difference in morbidity scores in 2 groups of patients - those with CNS involvement on clinical and/ or neuroimaging (n=10) and those without CNS involvement (n= 30). The mean value and error bars are depicted. The score in patients with CNS involvement is significantly higher (p= <0.005) than in those without CNS involvement and there is no overlap between the 2 groups.

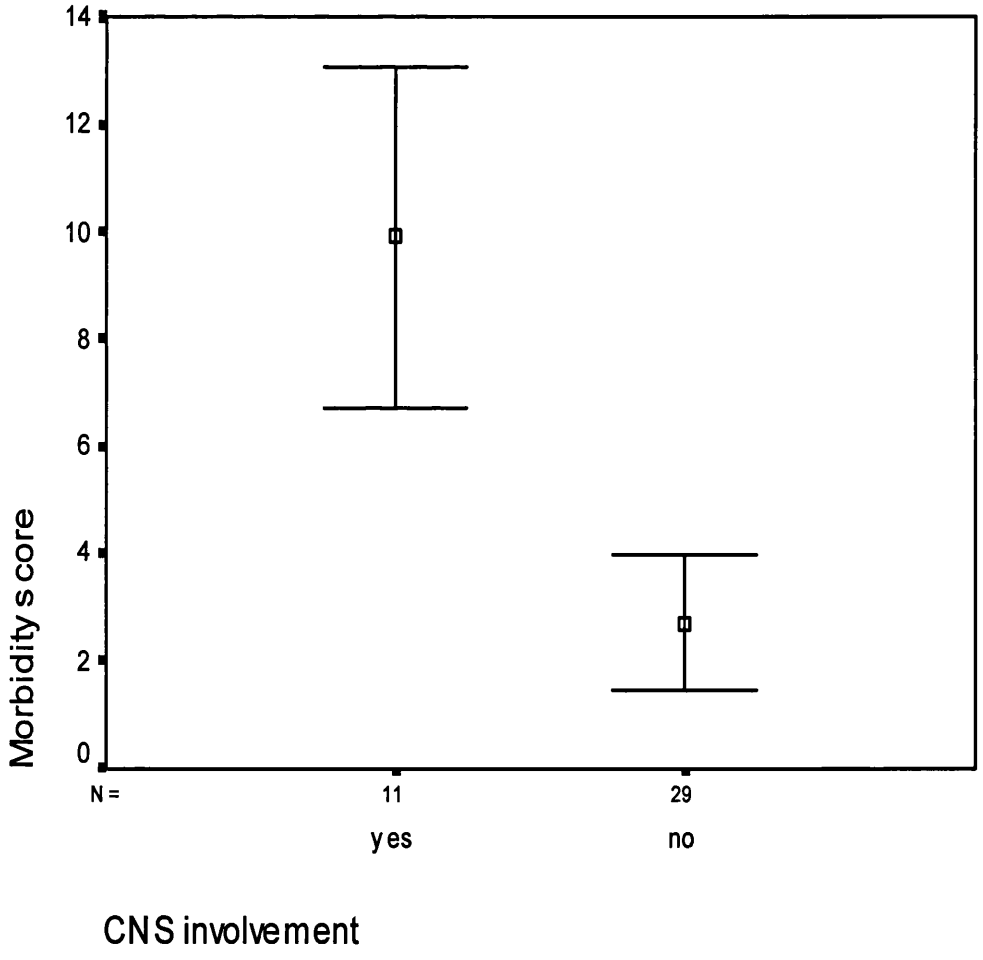
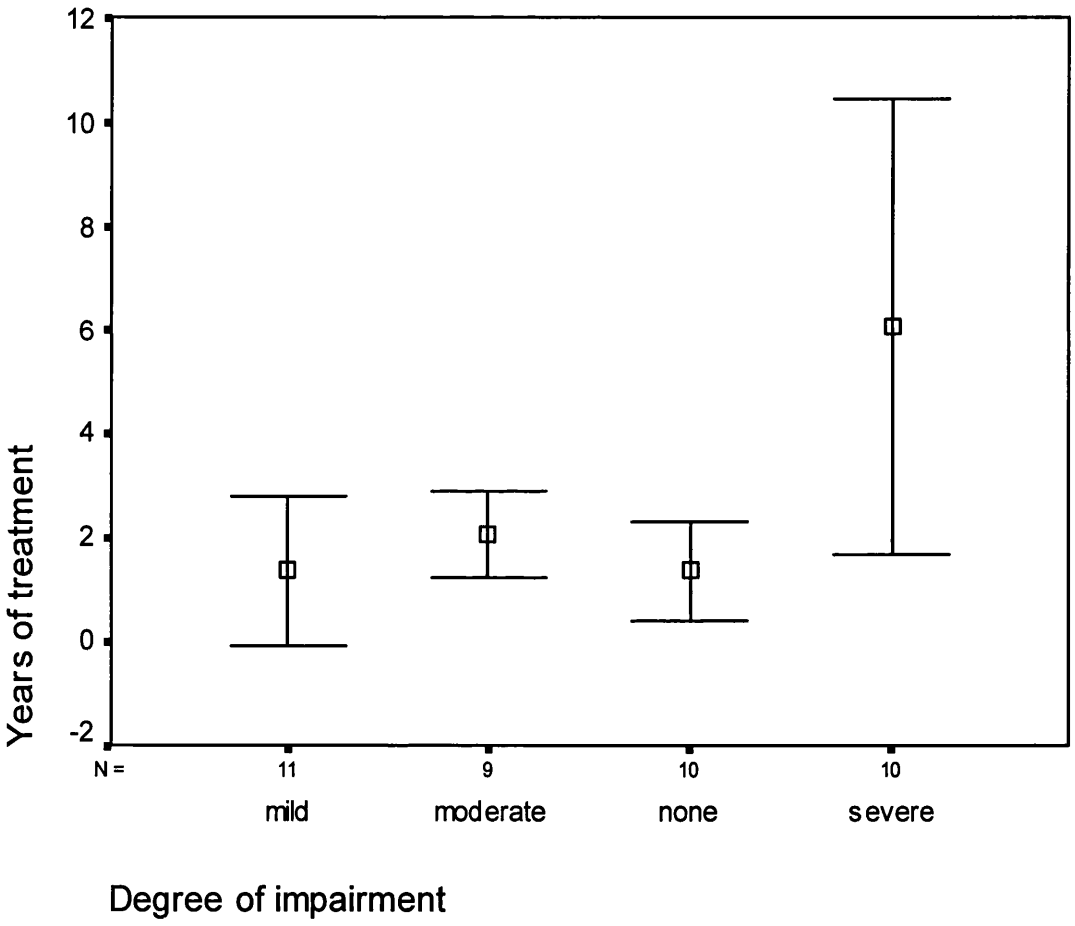


Figure 7.2. Relationship of duration of treatment to the outcome

This graph depicts the outcome of patients in relation to the duration of active disease as reflected in the years of treatment received. The average values and 95% confidence intervals are depicted. There is no difference in duration of treatment required in those patients with no sequelae, or mild or moderate disability. Although, the patients with more severe problems appear to have been on treatment for a longer time and this difference was statistically significant 9p=<0.005) the numbers of patients are small and confidence intervals wide.



Section 7.2. Quality of Life

7.2.1. Introduction

Over the last decade, there has been increased interest in the measurement of the "Quality of Life" of sick children and adults. It has now been acknowledged that it is important to try to assess the patient's perception of the burden of their disease and its treatment on his/her life. Measures of outcome are incorporated into treatment trials and are taken into account in the allocation of funding for new research studies and clinical trials. Despite all this interest, it is still very difficult to define "Quality of Life" and even more difficult to measure it and assess its implications for individual patients. A useful definition of Quality of Life has been devised for children and adolescents with cancer. (Bradlyn et al. 1996) as follows: 'Quality of Life in paediatric oncology is multidimensional. It includes, but is not limited to, the social, physical and emotional functioning of the child and adolescent and when indicated, his/her family, and it must be sensitive to the changes that occur throughout development'.

Several groups have suggested measures of 'Quality of Life' but as yet no single measure can be considered "standard". There is also controversy over whether disease-specific measures should be used or whether generic methods, which can be used in both ill and healthy subjects, are better. There is also concern over the reliability, validity and reproducibility of the various tests available. True 'Quality of Life' is multidimensional, intrinsically subjective, and therefore very difficult to measure. In children/ adults with an illness it is perhaps more appropriate to use a measure such as the "Heath-related Quality of Life" (HRQOL) or 'Health Status' in which the impact of both the disease and treatment are assessed. We have used the Health Utilities Index (Feeny et. al. 1995) to assess the Heath-related Quality of Life.

7.2.2. Methods

Of the 40 patients in this cohort, 8 were excluded from this section of the study
7 were < 12 years at assessment and 1 patient had moved out of the country. The remaining 32 patients were entered.

Questionnaires

A modified version of the 15-item self-administered Health Utility Index (HUI) questionnaire (Feeny, Torrance, & Furlong 1996) was mailed out, with stamped, addressed return envelopes, to the 32 patients, as were questionnaires on educational attainment in patients <16 years and employment in those >16 years.

Information from the questionnaires was converted by an established logarithm to health status classification system attribute levels of the HUI mark 2 (HUI2) (Feeny, Furlong, & Boyle 1995). The 7 'attributes' in the HUI2 system are sensation, mobility, emotion, cognition, self-care, pain and fertility with 3 to 5 levels of function per attribute. We assessed the first 6 of these attributes - fertility was not tested in this study. A single-attribute utility score and global health status utility score were then calculated from the multi-attribute "HUI" system (Torrance, Furlong, & Feeny 1995). The utility scale for a single attribute ranges from 1.00 (= normal) to 0.00 (= most highly impaired). The global health status utility scale ranges from 1.00 (= perfect health) to 0.00 (= death).

7.2.3. Results

A total of 28 patients (87.5% of 32) questionnaires were completed. Twenty of the 32 patients returned the completed questionnaires within 4 weeks. The other 8 patients returned their questionnaires after a telephone call to remind them. There were 12 females and 16 males. The age at the time of this assessment ranged from 12.5 to 33 years (mean 19.9, median 19.0 years). Twenty one of the 28 patients were ≥ 16 years at the time of assessment.

HUI Results

The utility scale for each attribute was assessed for each patient and for the whole cohort. The results obtained for each of the 6 attributes assessed in individual patients are tabulated in the Appendix. Overall results for the cohort are as follows:

ATTRIBUTE	RANGE	MEDIAN	MEAN
Sensation	0.86 to 1	0.97	0.86
Mobility	0.73 to 1	1	0.98
Emotion	0.53 to 1	0.93	0.95
Cognition	0.88 to 1	0.97	0.97
Self care	0.97 to 1	1	0.99
Pain	0.85 to 1	1	0.98

Although the average result was near normal, there was a wide range with some individuals being more severely affected than others. Emotion was affected most, while self-care was not perceived by most as being a problem.

Eight patients had no attributes affected (i.e. scores of 1). Four patients had 1 attribute affected (3 had scores of 0.95 each for sensation, while 1 scored 0.93 for emotion). Seven patients reported 2 of the following attributes affected (sensation, cognition, emotion, self care and pain), with scores ranging from 0.53 to 0.97. Two had 3 attributes affected, while 4 reported 4 attributes affected. Two patients had 5/ 6 attributes affected, while the patient with the worst perceived "Quality of life" reported all 6 attributes as being affected (scores 0.73 to 0.97).

The global health status utility score ranged from 0.48 to 1 (median 0.86, mean 0.88).

As with the morbidity score, the utility scale was significantly lower ($p<0.05$) in patients with CNS involvement adjudged from clinical examination and / or MRI – mean 0.73 (SD 0.16) than in those without CNS involvement – mean 0.91 (SD 0.11) (**Fig. 7.3**). Patients with CNS involvement had significantly lower ($p<0.05$) attribute scores for sensation, cognition and emotion than those without CNS involvement. There was a close correlation between FSIQ and global health status, with patients with lower IQ usually having a lower utility scale.

Severe pulmonary involvement was also significantly associated with a low utility score with the 2 most severely affected patients scoring 0.63 and 0.71.

No other factor, such as duration of illness, treatment received or involvement of vital organs in the 'active' phase, correlated with the health status or the morbidity score. Children who were unwell for over 1 year or received treatment for > 1year did no worse than those who were treated for <1year ($t=1.76$, $p=0.089$). Children who survived vital organ involvement in the 'active' phase had an outcome similar to those without vital organ involvement ($t=-0.87$, $p=0.39$).

There was a close inverse correlation between the morbidity score and utility scale ($r= -0.73$, $p<0.001$). This is to be expected given that a higher Utility score indicates well being, while a higher morbidity score indicates increasing disability (**Fig 7.4**).

Figure 7.3. CNS involvement and Heath-related Quality of Life

This graph shows the relationship between CNS involvement and Health-related QOL as measured by the Utility scale. It depicts the difference in utility scales in 2 groups of patients - those with CNS involvement on clinical and/ or neuroimaging (n=10) and those without CNS involvement (n= 30). The mean value and error bars are depicted. There is a significant difference (p=<0.005) between the patients with and without CNS involvement and there is no overlap between the 2 groups.

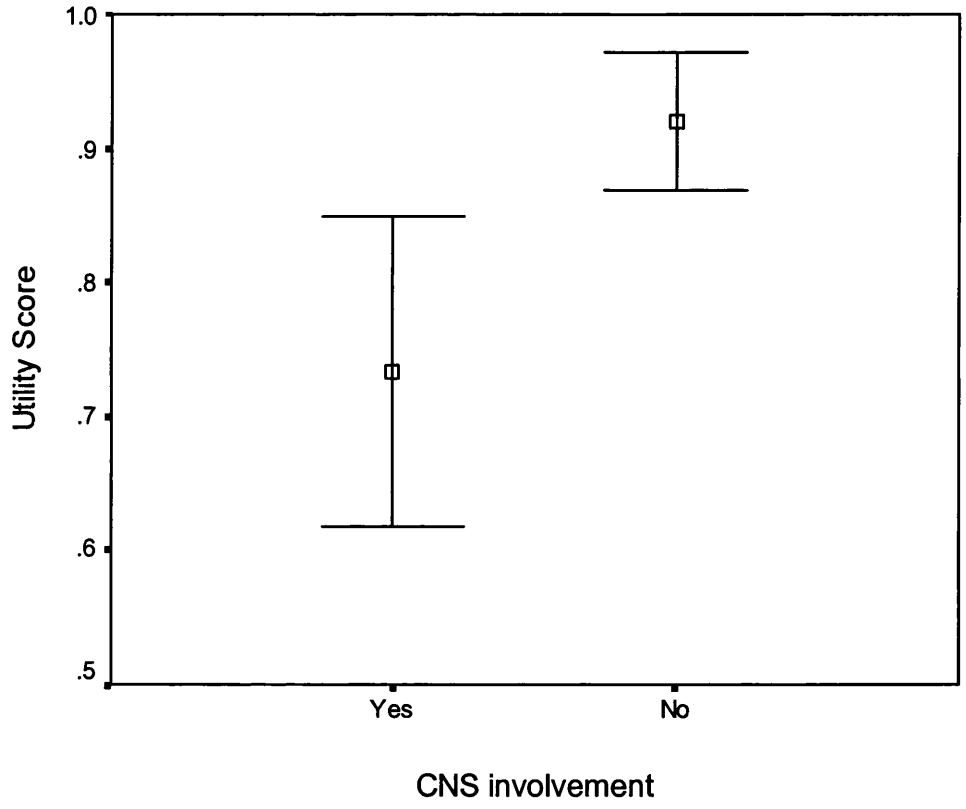


Figure 7.4. Correlation between Utility Scale and Full scale IQ

This scatter graph shows the correlation between full scale IQ and the global health status utility scale in the 20 patients who had both assessments. Patients with CNS involvement on clinical examination and / or MRI are identified by the × symbols, while those without CNS involvement are shown by the □ symbol. Patients with CNS involvement are the worse off for both parameters.

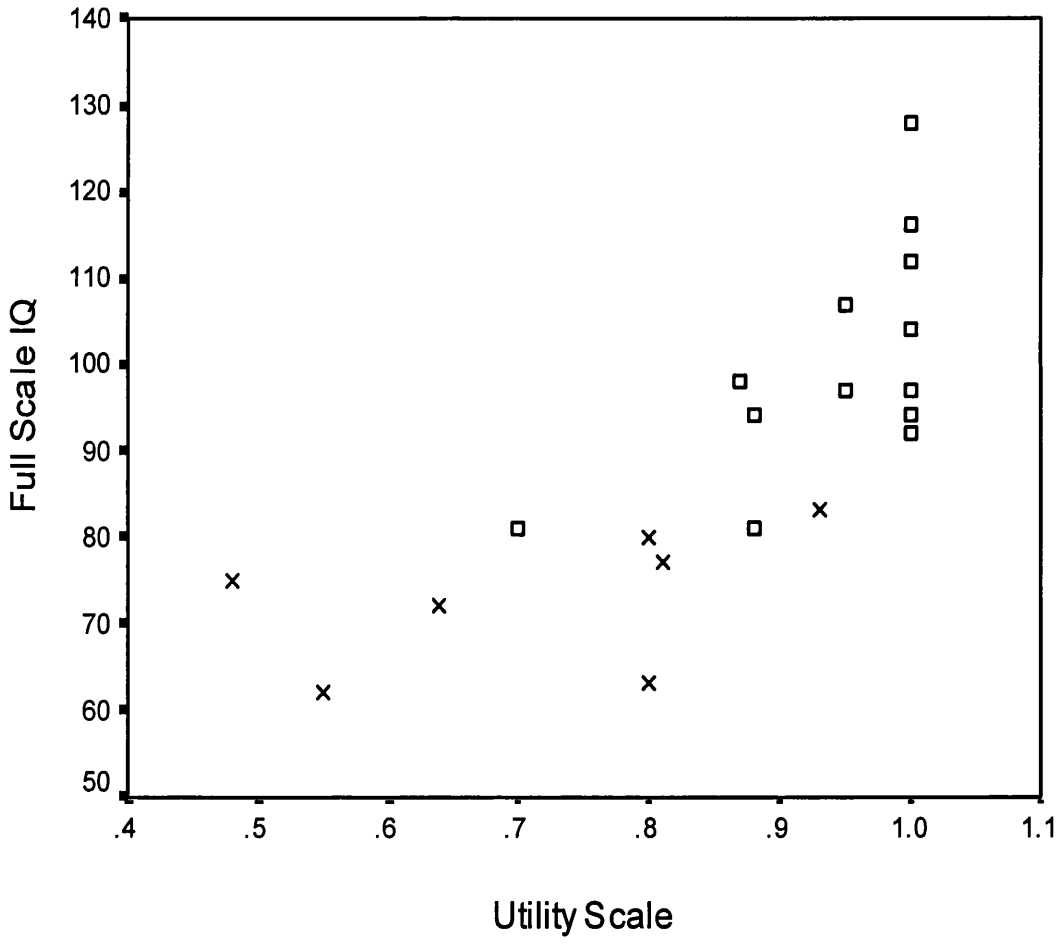
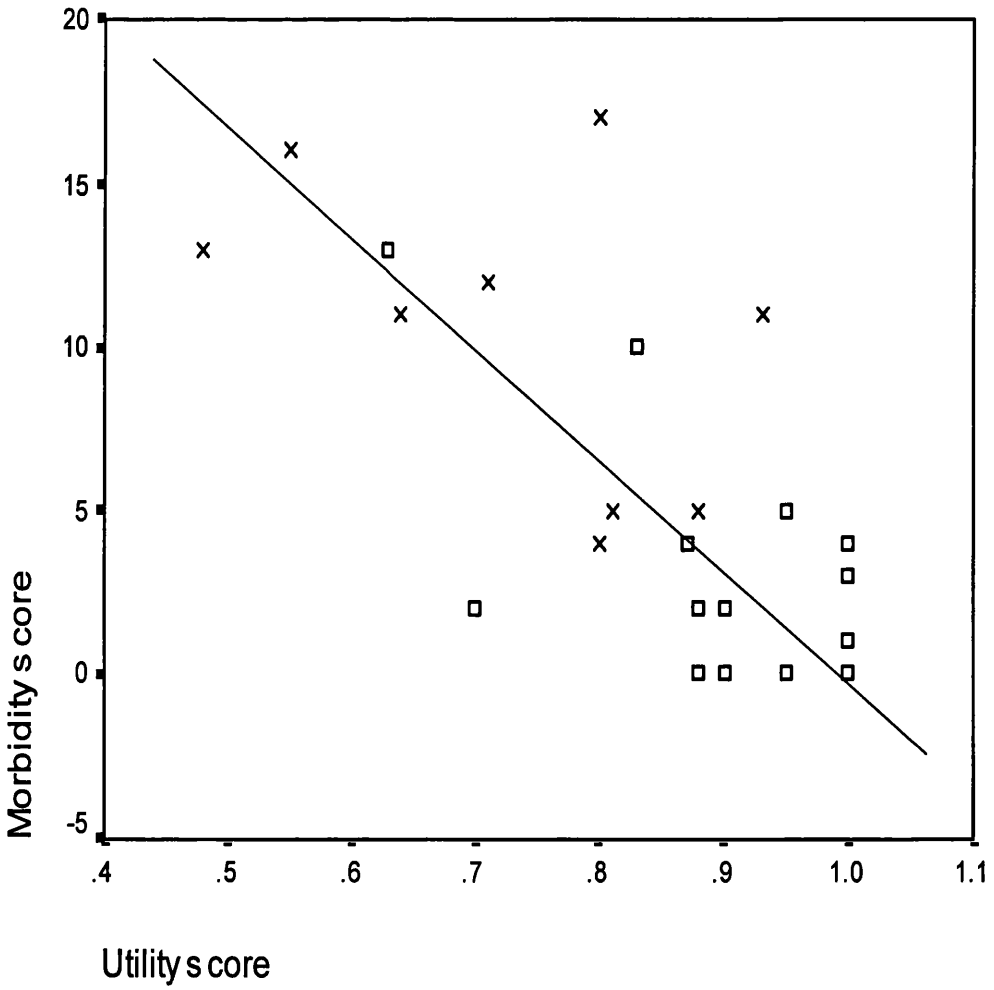


Figure 7.5. Morbidity score and Utility Scale

There was a close inverse correlation between the objective clinician's assessment of function using the morbidity scale and the patient's perception using the utility scale. ($r = -0.73$, $p<0.001$). Patients with CNS involvement on clinical examination and / or MRI are identified by the × symbols, and those without CNS involvement by the □ symbols.



Education/ Employment

Patients aged 12 to 16 years

All patients under the age of 16 years are currently in full time education. Two of them go to a special school and 1 other child, though attending a mainstream school, receives extra help.

Patients over 16 years of age

Seven of the 20 patients are in full time education. Five of them have recognised learning difficulty and are attending courses where they are taught skills required for independent living. Six patients are in full time employment and 4 are in part time employment as they continue with their studies. Three patients are currently unemployed, 1 due to psychological problems preventing him from working and the other 2 due to physical disability.

Educational attainments in patients aged over 16 years

Fifteen of the 20 patients have completed their GCSEs.

Twelve of the 15 patients aged ≥ 18 years have completed A levels.

Four of the 8 aged ≥ 21years have attained undergraduate degrees.

Two have postgraduate degrees

Financial Support

Six of the 20 patients (30%) above the age of 16 years receive benefits. Three receive disability living allowance, 1 each receive income support and mobility allowance and the 6th patient receives disability living allowance, income support and incapacity allowance.

Social Situation

Only 6 of the 20 are in stable relationships with a partner.

Sixteen of 20 (80%) patients aged > 16 years still live with their parents/ family.

Of the 4 who live independently, 1 lives in supervised accommodation with a warden on site because of 'dependence' on others due to severe lung damage and psychological problems.

Section 7.3. Discussion

Langerhans' cell histiocytosis is known to result in functionally significant long term sequelae in up to half of patients (Komp 1981), but the morbidity has never previously been fully quantified, nor has the overall impact on patients ever been studied. This is the first time that the whole spectrum of sequelae, including orthopaedic disabilities, abnormal lung function, diabetes insipidus and growth hormone deficiency and neurological abnormalities have been quantified in a sizeable group of LCH patients, and their impact on the individual's life assessed. Our study shows that survivors of multisystem LCH have clearcut long term morbidity as a result of these sequelae. So far as morbidity is concerned, only a quarter of the patients were well with no sequelae and nearly one half had moderate to severe disability as a result of permanent tissue or organ damage. This finding emphasises the importance of long term follow up to detect abnormalities and provide appropriate interventions to improve outcome.

The morbidity score we have devised seems to have potential as a useful quantitative measure of the overall burden of disease sequelae and can easily be used as a measure of outcome in clinical trials and long term follow up studies. Experience shows that complex scoring systems are often not used because they are time- and paper-consuming. Our morbidity score therefore uses straightforward language that will be internationally understood. This scoring system does need to be validated and this will be the next step before it can be put forward for wider use.

There appears to be a close correlation between the Morbidity Score, which represents the clinician's view of functional outcome, and the Utility Scale, which measures the impact from the patient's perspective.

Overall results indicate that the disease and its sequelae have a significant impact on the patient's Health Status and Heath-related Quality of Life. The domains most affected seemed to be emotion and cognition, while patients did not feel that self-care was a problem. This finding was surprising in view of the fact that several young adults were in special college where they were being taught basic skills to enable them to lead an independent life. Perhaps, 'insight' is affected as a result of the disease of the brain.

The Health Utility Index, it must be stressed, is a measure of 'Heath-related Quality of Life' or 'Health Status' and not of 'Quality of Life' which has a much wider perspective and incorporates the impact of the condition on not just the patient's health, but also on his/ her psychological, social, financial and spiritual well being. This study represents an important developmental step and further work on the measurement of 'Quality of Life' in survivors of LCH is needed.

Using either measure, involvement of the brain appears to be the single most important factor in determining outcome. The Heath-related Quality of Life has been studied in survivors of childhood brain tumours and found to be affected (Barr et al. 1999;Glaser et al. 1999). It would be useful to compare the impact on Health Status of LCH involvement in the brain to that of brain tumours. Severe lung disease also leads to significant morbidity, but mild abnormalities of lung function do not seem to impair health. It is much more difficult to assess the impact of facial dysmorphic features on the Quality of Life of these patients. All future national and international co-operative studies of treatment in LCH should incorporate measures of functional status and Quality of Life in clinical follow up and in comparing the influence of different treatments on long term outcome. Some groups involved in the study and follow up of patients with LCH (e.g. The Histiocyte Society) are already well into the planning stages of incorporating outcome measures including "Quality of Life" into their follow up assessment. Our scoring system will be offered, after validation, as the basis of a possible internationally acceptable starting point.

Chapter 8. Summary and Conclusions

This is the first cross-sectional, systematic, detailed long term follow up study to be performed on survivors of multisystem Langerhans' cell histiocytosis. This chapter summarises the findings of this study and discusses their impact on the management and follow up of these patients.

We studied 40 patients who were more than 5 years from the end of treatment for multisystem LCH and characterised the findings from clinical examination and specific investigations. Detectable long term sequelae were found in 30 of the 40 patients (75%), of whom 19 had moderate to severe problems requiring life long treatment and support. In a quarter of the cohort, physical disability, learning deficit and/or severe psychological abnormalities constrained their ability to lead an independent life. These deficits have led to considerable impairment of their 'Quality of life' and overall long term outcome.

Bony defects were the most common sequelae, and occurred in 60% of patients. The most common abnormality was asymmetry of the skull and face, with deformity requiring surgical correction in the most severely affected patients. Many of those with less prominent changes, however, felt that their facial appearance was unsatisfactory and that they might consider plastic surgery in the future. These sequelae have an impact both on the perception of 'body image' and on 'self- confidence'. The facial appearances seem to be rather characteristic of survivors of LCH and include features such as residual proptosis, small chins, short necks and underdeveloped facial bones. We feel that there is a facial resemblance between these patients and further studies into facial structure and facial growth are planned. Scarring of the skin and other skin lesions were seen in over a third of patients and were of considerable cosmetic concern in the worst affected.

Endocrine deficiencies were present in half the patients, the most common being diabetes insipidus (48%). Anterior pituitary hormone deficiencies including growth hormone insufficiency were more common (32%) than have previously been reported, possibly partly due to a selection bias, but also due to closer monitoring of growth and early investigation. Panhypopituitarism with its attendant risk of morbidity and possible mortality was present in 3 of the patients. Growth was affected in most patients with LCH, not only in those with GH insufficiency, but also in those without pituitary

deficiency, indicating that the disease itself and possibly its treatment, including long term steroids in many cases, had a detrimental effect on growth.

The high incidence (25%) of central nervous system involvement identified in this cohort of patients was a worrying finding. A quarter of the patients had clinical and /or MRI evidence of brain involvement. The clinical signs included ataxia and incoordination, learning difficulty and psychological and behavioural abnormality. These problems were usually not identified during the acute phase of the illness but manifested several years later. There were no obvious risk factors to indicate the likelihood of developing CNS damage, apart from an association with the presence of DI and with skull lesions. It has been suggested that patients who have chronic or relapsing LCH are more likely to develop CNS complications. We could not confirm this finding in our study. Neither the duration of treatment for active disease nor the cumulative dose and duration of steroids appeared to be related to the development of CNS disease. We are therefore unable to predict the long term outcome of patients with LCH based on features of their initial illness and presentation.

Nearly a quarter of the patients suffered learning difficulty with intelligence quotients below the lower limit of the normal range. This has implications for the long term management of these patients, on the requirement for extra help in school, on their chances of being gainfully employed and, very importantly, their ability to care for themselves. Several are in schools or colleges for children with special educational needs and require training in basic life skills. In some children, the difficulties in social adjustment are compounded by behavioural and psychological disturbance. Several of the more severely affected individuals are unable to work or even to move away from their home.

Hearing deficit was permanent in 15 patients, of whom 4 had severe, bilateral hearing loss requiring aids. This causes an additional handicap on on learning.

We identified acquired basilar invagination, on MRI scans, in 17.5% of our patients. The long term prognosis and implications of this new finding in patients with LCH are not known, but this cranio- cervical abnormality can have serious consequences in other conditions. It has been recognised that basilar invagination can result in sudden syncope (Corbett et al 1976) or even death (Williams, 1977, McAllion and Patterson, 1996). There is therefore a need for patients and their parents to be given appropriate

precautionary advice regarding 'dangerous' sporting activities (eg. rugby, trampolining, gymnastics) and also the potential 'anaesthetic risk' during intubation.

Two patients have pulmonary fibrosis resulting in severe restriction of activity and may require lung or heart- lung transplantation in the future. None of our cohort had evidence of liver fibrosis / cirrhosis, and this could be because the patients with liver disease in the 'acute' phase did not survive and / or because this complication is very rare (1%) and therefore may not have occurred in our cohort of 40 patients.

We were able to devise a morbidity score for the objective assessment of survivors of multisystem LCH. The system assesses each individual sequela and its severity and then calculates a composite score for each patient. Using this morbidity score 10 of the 40 patients (25%) had no impairment, 9 (22.5%) had moderate disability and 10 (25%) had severe disabilities. The single most important risk factor for severe disability, associated with a significantly worse outcome, was the presence of CNS involvement. This morbidity score is the first of its kind devised specifically for patients with LCH and can be used to compare patients treated in different centres and on different regimens. It is simple and easy to apply without the need for special/ additional investigations so it is universally applicable. We hope that it will be widely used and ultimately be incorporated into the 'late effects' studies of the Histiocyte Society. We were also able to assess the patients' "Heath-related Quality of Life" using the Health Utility Index. Thus both the objective morbidity score and the more subjective Health Utility Index have been used to assess the outcome. We have shown a gratifying direct correlation between the 2 measures.

There are few long term follow up studies of LCH reported in the literature (Donadieu & French LCH Study group. 1996;Komp, El Mahdi, Starling, Easley, Vietti, Berry, & George 1980;Komp 1981;Willis, Ablin, Weinberg, Zoger, Wara, & Matthay 1996). Most studies have looked at all patients with LCH, both single system (recognised as having minimal sequelae) and multisystem, and have often been questionnaire – based discussing only those problems reported by patients. No group, except ours, has studied a cohort of patients with multisystem LCH systematically, with a detailed assessment of sequelae. It is difficult to directly compare our findings with those from other studies as the denominators vary so widely between the studiy cohorts. However, there do appear to be a significant number of patients with sequelae in our study, probably more so than previously reported.

We do recognise that our interpretation of data based on this study needs to take several factors into account. We present an analysis of retrospective data rather than a prospective case-control investigation, but the study incorporates additional cross-sectional assessment and investigations that strengthen it. As our Institution is a recognised tertiary/quarternary referral centre, there is an inherent selection bias and this cohort of patients might well have had more severe illness. However, we feel that the relatively high prevalence of sequelae in these patients is an important observation and might represent an under-recognition of the problems in other cohorts, rather than a specific increase in problems in our patients. Further multi-centre studies into the late sequelae in LCH are necessary before this suggestion can be confirmed or refuted. Early recognition of these problems, and perhaps others yet to be identified, can result in the design and application of appropriate interventions that may reduce handicap and improve quality of life of the patient.

Our study did not enable us to determine risk factors during the initial illness that could predict a worse outcome. This was probably because of the relatively small total numbers of patients available and the wide range of presenting features and treatments used over the long study period. However, comparing our data with those from other centres, and formulating hypotheses for testing in future trials should help to elucidate the 'risk factors' involved. Resultant changes of management tested in appropriately designed trials, will hopefully lead to improvements in the outcome for patients affected by this rare, but fascinating disease.

The high frequency of abnormalities detected in this cohort of patients stresses the need for comprehensive long term folow up for all patients who survive LCH, especially as sequleae may not appear for several years after the disease has been "cured". This study forms the basis for future work into the long term outcome of Langerhans' cell histiocytosis and further international collaborative studies are being planned which will improve our understanding of this disease and its sequelae.

Appendices

Appendix 1. Long Term Sequelae

Pt No.	Age at Assessment (years)	Long term Sequelae	Severity of Dysfunction
1	9.6	None	None
2	12.5	None	None
3	9.7	Scars, diabetes insipidus, loss of teeth	Moderate
4	23.1	Panhypopituitarism, diabetes insipidus, obesity, hypothalamic damage, learning difficulty, psychological/ behavioural abnormalities	Severe
5	16.2	Scars, facial asymmetry	Mild
6	10.3	Loss of teeth	Mild
7	21.5	Diabetes insipidus	Moderate
8	20.1	Diabetes insipidus	Moderate
9	9.0	Faint scars, loss of teeth, short stature	Mild
10	18.8	Scars	Mild
11	18.6	Growth hormone insufficiency, cerebellar ataxia, learning difficulty	Severe
12	19.2	Scars, loss of teeth	Mild
13	24.5	None	None
14	15.9	None	None
15	30.4	Hemiparesis, abnormal lung function, loss of teeth, basilar invagination	Severe
16	21.0	None	None
17	12.9	None	None
18	13.9	Diabetes insipidus, loss of teeth	Moderate
19	14.4	Short stature, loss of teeth, basilar invagination	Moderate
20	15.0	Diabetes insipidus, growth hormone insufficiency, unilateral visual loss, residual proptosis	Moderate

Pt. No.	Age at Assessment	Long term Sequelae	Severity of Dysfunction
21	17.6	Scars, facial asymmetry, loss of teeth, diabetes insipidus, growth hormone deficiency, gonadotrophin deficiency, learning difficulty, psychological problems	Severe
22	7.0	Resolving ataxia, mild learning difficulty	Mild
23	16.8	Residual proptosis, short stature, diabetes insipidus, growth hormone deficiency	Moderate
24	23.8	Diabetes insipidus, ataxia	Moderate
25	19.7	Short stature, diabetes insipidus, growth hormone deficiency, gonadotrophin deficiency	Moderate
26	15.7	Short stature, facial asymmetry, loss of teeth, prognathism, partial diabetes insipidus, growth hormone deficiency, cerebellar ataxia, hydrocephalus, hypothalamic damage, learning difficulty, psychological/ behavioural problems	Severe
27	13.8	Diabetes insipidus, growth hormone deficiency, delayed puberty, hypothalamic damage, behavioural problems (resolving)	Moderate
28	12.8	None	None
29	30.0	Loss of teeth, diabetes insipidus, panhypopituitarism, hypothalamic damage, psychological problems	Moderate
30	11.7	Scars, loss of teeth, minimal ataxia	Mild
31	14.6	Short stature, scars, facial asymmetry, residual proptosis, hearing loss, growth hormone deficiency, hydrocephalus, basilar invagination, cerebellar tonsillar herniation, learning difficulty, psychological/ behavioural problems	Severe
32	18.0	Short stature, DI, panhypopituitarism, psychological/ behavioural problems	Severe
33	17.8	DI,GHI, secondary hypothyroidism	Moderate
34	17.7	Basilar invagination	Mild
35		DI	
36	12.5	Loss of dentition	Mild
37	17.8	Scars, facial asymmetry, residual proptosis, mild hearing loss	Moderate
38	8.6	None	None
39	26.0	None	None
40	16.5	Bony defect, facial asymmetry, hearing loss, diabetes insipidus, growth hormone deficiency, learning difficulty, basilar invagination, behavioural problems	Severe

Appendix 2. Proforma for Study

LCH LONG TERM FOLLOW UP STUDY

Name: Sex: Hosp no:

DoB: Age at Diagnosis: Current Age:

Occupation: Date of Examination:

Current Problems:

SYSTEMS	Y/N	DATES OF INVOLVEMENT
Bone		
Skin		
B M / Haematological		
Diabetes Insipidus		
Other Endocrinopathies		
Ears		
Lungs		
Oral Mucosa/ Dentition		
Gastro Intestinal		
Liver		
Spleen		
Lymph nodes		
Eyes		
Nervous System		
Genital Mucosa		

HISTOLOGY

DETAILS OF TREATMENT

TREATMENT	Y/N	DATES AND DETAILS
Curettage		
Oral Steroids		
IV Steroids		
Intralesional Steroids		
Vinblastine		
Etoposide		
DXT		
Mustine (Topical)		
Mustine Ear Drops		
Other		

Summary of Treatment:

INVOLVEMENT OF SPECIFIC ORGAN SYSTEMS

BONE:

SKIN

LYMPH NODES

EARS

LUNGS

BONE MARROW

ORAL SOFT TISSUE/ DENTITION

GASTROINTESTINAL

LIVER/SPLEEN

EYES

CENTRAL NERVOUS SYSTEM

DIABETES INSIPIDUS

Date of onset of symptoms:

Investigations:

Current Treatment:

OTHER ENDOCRINOPATHIES

Growth hormone deficiency:

Anterior Pituitary Investigations:

Puberty:

Current replacement:

PHYSICAL EXAMINATION

Ht: cms Wt: kgs Parental Hts: Mother:
Father:
Centile Centile Mid-parental centile:

Pubertal Staging:

Appearance:

Skin:

Scalp:

Mouth and Gums:

Dentition:

Ears:

CVS:

Respiratory:

Abdominal:

CNS

Cranial nerve involvement:

Cerebellar involvement: Score:

Hypothalamic involvement:

MRI:

Neuropsychometry:

SUMMARY

INVESTIGATIONS

	DATE BOOKED	DONE
QUESTIONNAIRE		
NEUROPSYCHOMETRY		
ENDOCRINOLOGY		
DENTAL		
AUDIOLOGY		
LUNG FUNCTION		
OPTHALMOLOGY		
MRI		
BLOODS		
OTHERS		

Appendix 3. Ataxia Scale

International Cooperative Ataxia Rating Scale for assessment of cerebellar function

(Trouillas, Takayanagi, et.al. 1997)

i. Posture and gait disturbances

1. Walking capacities Score: .....
2. Gait speed Score: .....
3. Standing capacities, eyes open Score: .....
4. Spread of feet in natural position eyes open Score: .....
5. Body sway with feet together, eyes open Score: .....
6. Body sway with feet together, eyes closed Score: .....
7. Quality of sitting position Score: .....

Posture and gait score (static score) ...../34

ii. Kinetic functions

8. Knee-tibia test Score right: ... Score left: .....
9. Action tremor in the heel-to-knee test Score right: .... Score left: .....
10. Finger-to-nose test, dysmetria Score right: ...Score left: .....
11. Finger-to-nose test: intentional tremor Score right: ...Score left: .....
12. Finger- finger test: Score right: ...Score left: .....
13. Pronation-supination movements Score right: ...Score left: .....
14. Drawing of Archimedes' spiral Score: .....

Kinetic score (limb coordination) ..... /52

III. Speech disorders

15. Dysarthria: fluency of speech Score: .....
16. Dysarthria: clarity of speech Score: .....

Dysarthria score = .../8

IV. Oculomotor disorders

17. Gaze-evoked nystagmus Score: .....
18. Abnormalities of the ocular pursuit Score: .....
19. Dysmetria of the saccade

Oculo- motor score ...../6

TOTAL ATAXIA SCORE: ...../100

Appendix 4. Results of Individual Neuropsychological tests

Patient No.	1	3	5	6	8	9	10	11	12	16
intelligence (Standard Scores)										
Verbal IQ	92.00	122.00	103.00	84.00	96.00	113.00	126.00	76.00	80.00	87.00
Non Verbal IQ	86.00	86.00	104.00	82.00	97.00	99.00	134.00	70.00	86.00	106.00
Full Scale IQ	88.00	122.00	104.00	81.00	97.00	107.00	134.00	72.00	81.00	94.00
Memory (Percent Correct)										
Immediate Verbal Memory	97.92	95.83	87.50	75.00	83.33	88.54	97.92	44.79	52.08	61.46
Delayed Verbal Memory	81.25	88.54	78.13	72.92	71.88	79.17	89.58	30.71	43.75	41.67
Immediate Non Verbal Memory	67.86	78.57	92.86	64.29	82.14	89.29	92.86	49.72	82.14	100.00
Delayed Non Verbal Memory	42.86	78.57	100.00	57.14	82.14	85.71	92.86	-	82.14	100.00
List Learning (Standard Scores)										
Immediate Memory Span	124.00	115.00	109.00	106.00	109.00	140.00	128.00	87.00	104.00	98.00
Level of Learning	111.00	105.00	116.00	121.00	116.00	137.00	109.00	63.74	88.00	83.00
Interference in Learning	114.00	103.00	119.00	104.00	111.00	140.00	125.00	76.00	111.00	111.00
Immediate Recall in Learning	103.00	106.00	93.00	60.00	99.00	136.00	93.00	67.00	67.00	87.00
Delayed Recall in Learning	108.00	82.00	94.00	102.00	100.00	134.18	94.00	62.02	76.00	94.00
Language (Standard Scores)										
Receptive Vocabulary	74.00	104.00	133.00	92.00	94.00	122.00	127.00	61.48	-	127.00
Listening Comprehension	-	112.00	109.00	88.00	105.00	-	130.16	83.00	-	-
Oral Expression	-	110.00	104.00	106.00	97.00	-	106.00	86.00	-	-
Academic Attainments (Standard Scores)										
Word Reading	85.00	113.00	108.00	102.00	108.00	110.00	102.00	78.00	76.00	90.00
Word Spelling	96.00	123.00	114.00	106.00	117.00	105.00	99.00	71.00	67.00	71.00
Reading Comprehension	97.00	94.00	97.00	82.00	107.00	115.00	109.00	68.00	86.00	86.00
Mathematical Reasoning	86.00	120.00	86.00	95.00	97.00	113.00	121.00	70.00	82.00	91.00
Numerical Operations	93.00	108.00	81.00	105.00	102.00	103.00	123.00	74.00	81.00	84.00

Patient No.	17	19	20	21	22	23	26	27	28	30
intelligence (Standard Scores)										
Verbal IQ	110.00	79.00	111.00	81.00	83.00	99.00	76.00	91.00	110.00	109.00
Non Verbal IQ	136.00	80.00	110.00	87.00	74.00	98.00	75.00	73.00	101.00	78.00
Full Scale IQ	128.00	77.00	112.00	83.00	77.00	98.00	75.00	80.00	107.00	94.00
Memory (Percent Correct)										
Immediate Verbal Memory	57.29	67.71	71.88	59.38	56.25	66.67	42.88	-	66.67	58.33
Delayed Verbal Memory	56.25	62.50	72.92	50.00	30.71	60.42	30.71	-	64.58	60.42
Immediate Non Verbal Memory	96.43	64.29	92.86	49.72	-	96.43	50.00	-	89.29	-
Delayed Non Verbal Memory	96.43	64.86	85.71	39.29	-	75.00	35.71	-	60.71	-
List Learning (Standard Scores)										
Immediate Memory Span	90.00	82.00	111.00	62.07	-	114.00	70.00	-	-	95.00
Level of Learning	101.00	104.00	81.00	97.00	-	109.00	63.74	-	-	104.00
Interference in Learning	108.00	87.00	97.00	69.23	-	125.00	85.00	-	-	104.00
Immediate Recall in Learning	116.00	114.00	95.00	80.00	-	106.00	60.00	-	-	115.00
Delayed Recall In Learning	116.00	107.00	101.00	94.00	-	100.00	62.02	-	-	111.00
Language (Standard Scores)										
Receptive Vocabulary	102.00	72.00	94.00	68.00	-	133.00	71.00	-	-	-
Listening Comprehension	89.00	95.00	109.00	77.00	-	93.00	-	-	-	-
Oral Expression	108.00	88.00	106.00	74.00	-	104.00	-	-	-	-
Academic Attainments (Standard Scores)										
Word Reading	102.00	69.00	109.00	96.00	-	114.00	102.00	97.00	-	97.00
Word Spelling	95.00	64.00	113.00	102.00	-	102.00	93.00	110.00	-	96.00
Reading Comprehension	76.00	76.00	99.00	72.00	-	97.00	62.00	82.00	-	90.00
Mathematical Reasoning	96.00	73.00	102.00	80.00	-	82.00	66.00	-	-	129.00
Numerical Operations	88.00	75.00	112.00	76.00	-	78.00	87.00	-	-	114.00

Patient No.	31	34	35	36	37	38	39	40
Intelligence (Standard Scores)								
Verbal IQ	64.19	69.00	95.00	111.00	95.00	103.00	95.00	64.19
Non Verbal IQ	46.00	105.00	96.00	116.00	98.00	103.00	89.00	66.00
Full Scale IQ	61.68	83.00	94.00	116.00	97.00	103.00	92.00	63.00
Memory (Percent Correct)								
Immediate Verbal Memory	-	72.92	75.00	91.67	72.92	55.21	60.42	56.25
Delayed Verbal Memory	-	70.83	61.46	83.33	60.42	60.42	36.46	45.83
Immediate Non Verbal Memory	50.00	67.86	89.29	85.71	85.71	67.86	96.43	71.43
Delayed Non Verbal Memory	27.45	50.00	64.29	85.71	85.71	57.14	82.14	42.86
List Learning (Standard Scores)								
Immediate Memory Span	-	-	-	128.00	119.00	89.00	81.00	-
Level of Learning	-	-	-	122.00	116.00	113.00	97.00	-
Interference in Learning	-	-	-	125.00	119.00	95.00	85.00	-
Immediate Recall in Learning	-	-	-	116.00	106.00	106.00	87.00	-
Delayed Recall in Learning	-	-	-	122.00	100.00	110.00	94.00	-
Language (Standard Scores)								
Receptive Vocabulary	-	-	-	99.00	91.00	-	84.00	-
Listening Comprehension	-	-	-	122.00	86.00	92.00	-	86.00
Oral Expression	-	-	-	97.00	100.00	107.00	-	73.23
Academic Attainments (Standard Scores)								
Word Reading	-	-	72.00	98.00	111.00	109.00	-	66.78
Word Spelling	-	-	65.00	85.00	114.00	97.00	-	59.61
Reading Comprehension	-	-	93.00	93.00	88.00	114.00	-	60.89
Mathematical Reasoning	-	-	94.00	111.00	100.00	101.00	-	64.02
Numerical Operations	-	-	99.00	100.00	84.00	113.00	-	71.00

Appendix 5. Recommendations for Long Term Follow up

Reguiar (6 months or 1 year) ciinic appointments

1. Detailed clinical examination
2. Accurate measurement of height, weight and pubertal assessment at each appointment
3. Children with poor growth, delayed puberty and/ or diabetes insipidus (DI) to have growth hormone (GH) stimulation test with stimulation of other anterior pituitary hormones in addition.
4. Ideally, all children should have baseline neuropsychometric assessment at long term follow up, with repeated assessments at 1-2 years in those children with CNS involvement or abnormal cognitive function.
5. MRI scan of the brain and pituitary in all children with DI, GH deficiency or other hormone deficiency.
6. All children should have regular assessment of cerebellar function using a standardised scale to enable early recognition of abnormality.
7. MRI scan of the brain every 1-2 years in all children with CNS involvement.
8. All children to have baseline audiometry, with repeated assessments at regular intervals if initial test abnormal or any symptoms of hearing loss.
9. Children with abnormal hearing should ideally have CT scans of the petrous temporal bone to assess structure of the middle and inner ear and aeration of the mastoids.
10. All children should have baseline lung function tests with further tests if they develop cough or symptoms of respiratory distress. All patients should have the dangers of smoking explained and cigarettes avoided if at all possible. In those patients who smoke, more frequent lung function tests would be helpful in recognising damage early.
11. CT scan of the chest is useful in assessing pulmonary fibrosis.
12. Ideally, measurement of "Quality of Life" and Morbidity scores should be a routine part of the assessment of the patients who survive LCH.

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