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Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland

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ABSTRACT

Objectives: There are few published studies on the epidemiology of Langerhans cell histiocytosis (LCH). We undertook a survey to ascertain all newly diagnosed cases aged 0–16 years in the UK and Republic of Ireland.

Design: Three methods of ascertainment were used: the British Paediatric Surveillance Unit (BPSU) system, a survey by Newcastle University, and the Children's Cancer and Leukaemia Group (CCLG) registry. Deaths data were obtained from the UK Office for National Statistics and the Central Statistics Office in Ireland. Clinicians who reported cases were sent a questionnaire to obtain demographic and clinical details.

Results: Over the 2-year period, 94 cases were identified. The age-standardised incidence rate of LCH in children aged 0–14 years was 4.1 per million per year. The sex ratio (M:F) was 1.5:1 and the median age at diagnosis was 5.9 years. Single system disease (predominantly bony involvement) accounted for 73% of cases and 27% had multisystem disease of whom 7% had involvement of "risk organs" (liver, lung, spleen and bone marrow). Three children died, two of whom were diagnosed after death.

Conclusions: This is the first study of LCH to use an active surveillance method with additional sources of ascertainment. Our incidence is comparable with those in other national reports, although it is likely to be an underestimate as each method may have missed some cases, either diagnosed or undiagnosed.

Langerhans cell histiocytosis (LCH) is a disorder of regulation of antigen-presenting dendritic cells of the immune system resulting in a spectrum of single system or multisystem organ dysfunction. Skin involvement typically presents as "resistant" eczema, while affected bones develop granulomata which may resolve spontaneously or result in long-term deformity. On the other hand, isolated lymphadenopathy or diabetes insipidus may be the only manifestation of the disease. Multisystem disease involving any of the so-called risk organs, including bone marrow, lungs, liver and spleen, may be associated with a poor prognosis.

The aetiology of LCH is unknown and its epidemiology remains poorly documented. Reliable data on incidence are difficult to gather, but there have been a few international and regional studies of the disease and reports from cancer registries with geographically defined populations.^{1–9} However, none has used a prospective method of case ascertainment such as that used by the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH).¹⁰

What is already known on this topic

Langerhans cell histiocytosis can occur in children of any age with a peak in diagnosis between 1 and 3 years of age.

What this study adds

- ▶ The incidence of Langerhans cell histiocytosis (LCH) in children in the UK and Republic of Ireland aged 0–14 years is 4.1 per million per year.
- ▶ The incidence of LCH in children in the UK and Republic of Ireland in those aged under 1 year age is 9.9 per million per year.
- ▶ This is the first national study of LCH to use a prospective validated method of case ascertainment such as the British Paediatric Surveillance Unit.

A 2-year national survey of children newly diagnosed with LCH and resident in the UK or Republic of Ireland (RoI) began in June 2003. The aims were to ascertain all cases using multiple, complementary sources and to describe the incidence of LCH by age, sex, ethnic origin, season and region. Secondary aims were to identify any potentially relevant maternal history or associated illnesses, to describe presenting features, referral patterns, treatment, and outcome after 1 and 2 years, and to assess mortality.

METHODS

Cases were ascertained between June 2003 and May 2005 using three methods. The first was via the BPSU which undertakes active surveillance of uncommon childhood conditions using a network of over 2600 multispecialty paediatricians in the UK and RoI. Participants are sent a monthly case report card containing a "menu" of conditions under surveillance and are asked to report any new cases or "none seen". The overall response rate is over 90%.¹⁰ Positive returns are notified to the study team who then collect further information from clinicians.

Since cases may be seen by clinicians who are not paediatricians, two additional sources of ascertainment were used. A national mailing exercise to non-RCPCH clinicians was carried out in parallel with the BPSU survey by the authors from Newcastle University at 6-monthly intervals.

The list of over 1600 clinicians comprised relevant specialists including dermatologists, endocrinologists, pathologists, radiologists, neurologists and orthopaedic surgeons. Additionally, cases were cross-checked with the Children's Cancer and Leukaemia Group (CCLG) which registers in excess of 95% of all UK and RoI childhood cancers.¹¹

Reporting clinicians were sent a questionnaire to obtain demographic and clinical details. A combination of date of birth, hospital number, sex and the first part of the postcode was collected in order to exclude duplicate reporting. A follow-up form focusing on treatment and outcome was sent at 1 and 2 years after diagnosis, the information from which will be reported later.

For completeness, deaths data were obtained from the UK Office for National Statistics (ONS) and the Central Statistics Office (CSO) in the RoI for those who died between 1996 and 2005 and had LCH mentioned anywhere on their death certificate.

Cases were defined as children of any age resident in the UK and RoI at diagnosis and newly diagnosed with either biopsy-proven LCH or pituitary/hypothalamic abnormality, or lytic bone lesion with the characteristics of LCH (but not biopsied because of the risk of the procedure or because features suggested spontaneous resolution). Cases were categorised as having multisystem disease, with or without risk organ involvement (RO⁺ or RO⁻), or single system disease, distinguishing between unifocal and multifocal bony involvement.

ONS annual mid-year population estimates for the study period and census data for 2002 and 2006 for the RoI were used in calculating age-standardised (to European Standard Population) and age-specific incidence rates with corresponding 95% confidence intervals. Capture-recapture analysis was used to estimate the number of cases missed by reporting sources.¹² The mailing lists for the Newcastle University and BPSU surveys were cross-checked and no clinician appeared on both lists. CCLG cases may have been notified by clinicians already surveyed by the BPSU or Newcastle University and were not included in capture-recapture analysis. The use of two independent sources, the BPSU and Newcastle University surveys, allowed for an estimate of the overall population by capture-recapture analysis. Potential seasonality of birth, symptom onset and diagnosis were assessed using Edwards' test with correction for differing month lengths.¹³ Statistical analyses were performed using the statistical software package Stata v 9 (StataCorp, College Station, TX). The study was given appropriate ethics approval by UK and RoI ethics bodies.

RESULTS

Case ascertainment

On average, 92% of the report cards were returned to the BPSU each month by paediatricians and an average of 53% of clinicians responded to each mailing from the Newcastle University survey.

Over 350 case notifications were received but, after removing adult cases (over 16 years of age), cases diagnosed outside the study period, misdiagnoses and duplicate reports, 94 cases were confirmed. The reporting rates were CCLG 75/94 (80%), BPSU 69/94 (73%) and Newcastle University 58/94 (62%) (fig 1). No additional cases were identified from the deaths data. Using capture-recapture analysis the estimated total number of cases was 102 (95% CI 89 to 126.2) rather than the 88 cases reported by the BPSU and Newcastle sources. Case ascertainment for each was estimated to be 69% and 58%, respectively, and overall ascertainment by these two sources was 86%. However, a

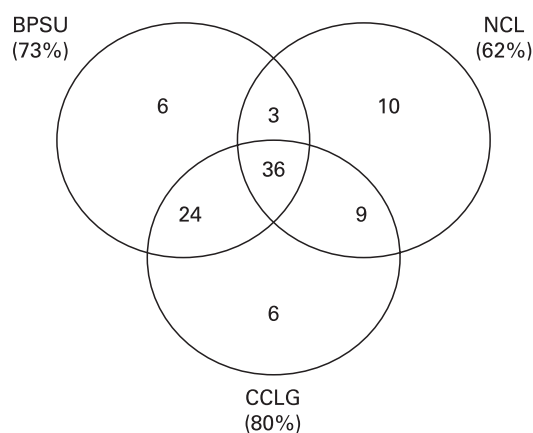


Figure 1 Number of cases identified by source. BPSU, British Paediatric Surveillance Unit; CCLG, Children's Cancer and Leukaemia Group; NCL, Newcastle University.

further six cases were identified via the CCLG, all of whom were treated by clinicians who had responded to the BPSU or Newcastle surveys.

The surveys asked for "children of any age" to be reported, whereas the CCLG registry includes those up to their 15th birthday. However, at the upper age range there was a single 15-year-old with unifocal bone disease reported to all three groups and no 16-year-olds (fig 2).

Incidence

From our study population the age-standardised incidence (ASR) of LCH in 0–14-year-olds is 4.12 per million per year (95% CI 4.11 to 4.13). For those aged <1 year the incidence is 9.9 per million per year (95% CI 5.5 to 16.3). ASRs and age-specific incidence rates are shown in table 1. The population studied covers 13 geographical health care regions. The regional incidence varied from 2.6 to 6.0 per million per year, but analysis of heterogeneity (using Cochran's Q test) found no statistically significant differences between health regions.

Reporting patterns

The pattern of reporting according to disease extent is shown in table 2. The 10 cases identified uniquely by the Newcastle University survey were all unifocal bone disease, eight of whom were diagnosed and treated at a single national orthopaedic centre. The two cases of multisystem, RO⁺ disease uniquely

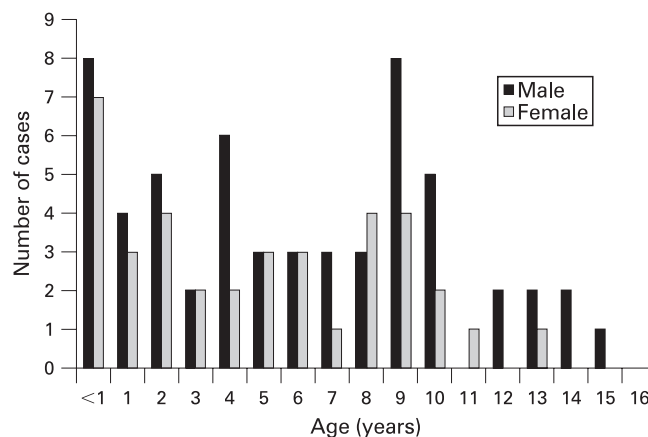


Figure 2 Number of cases by age at diagnosis.

Table 1 Estimation of incidence rates

	Age (years)					ASR
	<1	1–4	5–9	10–14	0–14	
IRs						
Boys	10.3	5.7	5.0	2.6	4.7	4.8
Girls	9.5	3.8	3.9	1.0	3.2	3.4
Both	9.9	4.8	4.5	1.8	3.9	4.1
Sex ratio	1.1	1.5	1.3	2.7	1.5	

ASR, age-standardised incidence; IR, incidence rates.

reported to the BPSU were diagnosed after death. Of the 25 cases not identified by the BPSU, 20 had unifocal bone disease, but two cases of multisystem, RO⁻ disease were not reported. Similarly, 16/19 of cases not reported to the CCLG were unifocal bone disease. The CCLG were notified of all cases with multifocal bone involvement and of multisystem disease, apart from the two cases diagnosed at autopsy.

Diagnosis

Data were received on all of the confirmed 94 cases, although questionnaires varied in their completeness. The number and sex of cases, systems involved and age at diagnosis are shown in table 3. There were 57 boys and 37 girls with an age range of 0.09–15.1 years. The M:F sex ratio was 1.5:1 increasing to 2.7:1 in children aged 10–14 years. Diagnostic biopsies were reported in 78 cases. Typical radiological appearance was the basis of the diagnosis in 11 bony lesions and two cases with isolated diabetes insipidus. For one case of bone disease the basis of the diagnosis was not stated and two cases were diagnosed at autopsy.

Spectrum of disease

Overall, 69/94 (73%) cases had single system disease. Among these were 53 cases of unifocal (15 skull vault; 8 pelvis; 7 vertebrae; 5 femur; 4 mandible; 3 humerus; 2 each orbit, facial, scapula and clavicle; 1 each fibula, radius and rib) and 10 of multifocal bone disease. The remainder comprised two cases each with skin, pituitary and lymph node involvement. The unifocal bone cases were diagnosed at a median age of 7.3 years compared to 4.8 years for multifocal bone and 0.54 years for skin disease.

Of the 25 multisystem cases, 18 were RO⁻ (14 bone, 8 skin, 5 diabetes insipidus and ear) and 7 RO⁺ (6 liver/spleen, 5 lung, 3 gut, 3 bone marrow). Whereas all RO⁺ cases had skin disease, only one had bony involvement. The M:F ratio in this group

was 2.1:1 with the RO⁺ cases being diagnosed at the younger median age of 0.7 years compared to 3.2 years in the RO⁻ patients. Three children died during the study period, all of whom had multisystem, RO⁺ disease. However, LCH was not the primary cause of death in one case.

Time to diagnosis

The time from first symptom to diagnosis is detailed in table 4. There is wide variation with the longest median time to diagnosis in patients with non-bony single system disease and the shortest in patients with multisystem, RO⁺ disease. The longest time to diagnosis, 170 weeks, was in a patient with a single bony lesion.

Ethnicity and seasonality

Overall, 80% of children were of white Caucasian (95% CI 70 to 87%) and 13% (95% CI 7.6 to 22%) were of mixed or other ethnicity. In 6% (95% CI 2.4 to 13%) of cases ethnicity was unknown.

While there was no evidence of seasonality of birth ($p = 0.93$) or of first symptom ($p = 0.81$), there was an association with month of diagnosis ($p = 0.04$, amplitude 0.37); a higher number of cases than expected (under an assumption of no seasonal effect) were diagnosed from March to June.

Birth-associated factors

There were three sets of twins with one of each pair affected. One was born prematurely and after many neonatal complications developed unifocal skull vault disease aged 1 year. The two other cases (2%: 95% CI 0.2 to 7%) were reported to have been conceived by IVF. One developed unifocal vertebral bone disease at age 11 years and the other had congenital self-healing histiocytosis (Hashimoto-Pritzker disease). There were three other congenital cases; one boy with proptosis and two boys with multisystem disease, one of whom was RO⁺ and died. Birth weights and gestational age were similar to national averages, the medians being 3.3 kg and 39 weeks, respectively.

Associated diagnoses

Two children had medulloblastoma. In one case the tumour preceded the diagnosis of single system, unifocal bone disease. The second was diagnosed 6 months after single system, unifocal bone disease which had not required treatment. One child had partial trisomy 3. Other conditions preceding diagnosis of LCH included seizure disorder and developmental

Table 2 Pattern of case reporting showing types of cases uniquely identified and not identified by each source

Source	Total cases	Single system disease			Multisystem disease	
		Bony			RO ⁺	RO ⁻
		Unifocal	Multifocal	Other		
Total	94	53	10	6	7	18
Uniquely identified by						
BPSU	6	3		1	2	
Newcastle University	10	10				
CCLG	6	4	1			1
Not identified by						
BPSU	25	20	2	1		2
Newcastle University	36	19	3	3	5	6
CCLG	19	16		1	2	

BPSU, British Paediatric Surveillance Unit; CCLG, Children's Cancer and Leukaemia Group; RO⁺, with risk organ involvement; RO⁻, without risk organ involvement.

Table 3 Cases of Langerhans cell histiocytosis by type of disease, sex and age at diagnosis

LCH system	Number	Sex		Median age at diagnosis	Age range (years)
		Male	Female		
Single system	69	40	29	6.7	0.12–15.1
Bone	63	36	27	6.7	0.38–15.1
Unifocal	53	31	22	7.3	0.38–15.1
Multifocal	10	5	5	4.8	1.58–13.63
Skin	2	1	1	0.54	0.12–0.96
Other	4	3	1	9.8	8.8–10.0
Multisystem	25	17	8	1.2	0.09–14.8
RO ⁺	7	5	2	0.7	0.09–0.9
RO ⁻	18	12	6	3.2	0.32–14.8

LCH, Langerhans cell histiocytosis; RO⁺, with risk organ involvement; RO⁻, without risk organ involvement.

delay in one child and pneumothorax and necrotising enterocolitis in the preterm twin.

One of each of the following conditions were reported in the maternal histories of pregnancy: Darier's disease (affected child had multisystem, RO⁺ disease, diagnosed at autopsy), hypothyroidism, epilepsy, melanoma, thalassaemia, asthma/psoriasis, diabetes/epilepsy and cholestasis.

DISCUSSION

Our age-specific incidence rate for 0–15-year-olds was 3.7 per million per year (95% CI 3.0 to 4.6) with over 86% of cases estimated to have been ascertained. In comparison with other studies, our ASR of 4.1 per million per year in children aged 0–14 years is higher than the 2.5 per million per year (42 cases from 1968–1995) and the 2.6 per million per year (101 cases from 1954–1998) reported by children's cancer registries in the northeast and northwest of England.^{7,9} Interestingly, our incidence rates for these regions were 3.1 and 4.4 per million per year, respectively, which taken with our overall rate may suggest a degree of under-reporting or under-diagnosis in these previous studies. An increase in incidence of LCH may also be a possibility for the variation, although Alston *et al* found no evidence of this in their study of cases diagnosed over a 40-year period.⁷

Other national studies have reported comparable incidence rates (2.2–6.0 per million per year).^{1,3,4,8} The different rates may simply reflect the different methods of ascertainment, especially as discussed below for unifocal bone disease, or may reflect the small number of cases. However, in all these studies where data are available, the incidence rate drops markedly beyond the age of 10 years, suggesting the possibility that small variations beyond this age may be contributing to the reported differences.

Our findings are comparable with other national studies in that the peak incidence was in children aged 0–4 years, there

was a predominance of boys and the majority of cases were bone disease.^{1,2,6}

LCH cases are not included in national cancer statistics in the UK and cases treated without chemotherapy may not be registered with the CCLG. The use of the BPSU survey system was therefore attractive. However, LCH is diagnosed by a wide spectrum of clinicians and it has always been appreciated that uncomplicated bone disease (eosinophilic granuloma) in older children may be treated without paediatric input. For these reasons our study was designed to use three complementary methods of ascertainment. In general the pattern of reporting confirmed the limitations of each method. Significantly, only three cases of non-bony single system, multifocal bone or multisystem disease were uniquely identified, suggesting that these cases have been appropriately collected. The majority of cases not reported by the CCLG or BPSU were of unifocal bone disease, the cases missed by the CCLG requiring little or no treatment. Nineteen cases were not identified by the Newcastle University survey, which extended outside general paediatrics. However, all ten cases uniquely reported, were, as expected, unifocal bone, which may indicate under-reporting in this area.

During the study period the Histiocyte Society trial LCH III commenced with randomised chemotherapy protocols for patients with multisystem RO⁺ or RO⁻ disease. The trial, which additionally recommended chemotherapy for, and collected data on, patients with multifocal or special site unifocal bony disease, undoubtedly contributed to the apparent 100% registration of these patients with the CCLG.

As expected for any rare disease, the time from first symptom to diagnosis was very varied, ranging from a few days to over 3 years for one patient with unifocal bone disease. The shortest median time of 9.2 weeks (range 3.1–26.7) was for patients with multisystem RO⁺ disease. The longest median interval, 29 weeks (range 6.7–37), was reported for the six children with "other" disease (two each of single system lymph node, skin and diabetes insipidus).

LCH has been predominantly reported in white children, although this may be due to a reporting bias. The proportion of non-white cases in our study (13%) was not significantly different from that among the total UK population (7.9%) reported in the 2001 census, and was the same as that reported in a UK hospital series between 1980 and 1987 (8/58 cases).^{14,15}

Two cases were born after IVF treatment which is similar to the proportion of artificial reproductive technology (ART) births in the UK population (1.3%), although it is not known if any other cases were conceived by IVF or other forms of ART.¹⁶

An association was found with month of diagnosis, with more cases being reported in the spring (March–June), although

Table 4 Number of weeks from first symptom to diagnosis

LCH system	Median	Range
Single system	10	0.5–170
Bone	10	0.5–170
Unifocal	10	0.5–170
Multifocal	13	0.5–65
Other	29	6.7–37
Multisystem	16	2.5–149
RO ⁺	9	3.1–26.7
RO ⁻	17	2.5–149

LCH, Langerhans cell histiocytosis; RO⁺, with risk organ involvement; RO⁻, without risk organ involvement.

it is recognised that Edwards' test is unreliable with small samples of data. However, no evidence of seasonality by month of birth, month of first symptom or month of diagnosis was found in a study in the northwest of England over four decades.⁷ In the study in Stockholm county, 75% of cases were diagnosed during the autumn and winter months.⁶ Other studies have reported a higher incidence in summer months in wet regions or during periods of high rainfall.^{5 17} Variation in seasonal infection rates and school holidays may contribute to this apparent association.

In two US studies of risk factors, LCH was associated with maternal urinary tract infections, feeding problems and medication in infancy, a family history of thyroid disease and infections in the postnatal period.^{18 19} Our questionnaire included questions on family history, pregnancy and neonatal history, but only one mother with a thyroid condition and only single cases of infections or other conditions were reported. Further large studies are needed to look for possible aetiological factors.

This is the first national study of LCH to use a well-established active surveillance method with additional sources of case ascertainment. The study had the advantage of using an established (and enhanced) large network inclusive of multi-specialty clinicians rather than ascertainment via a cancer registry. However, with only 2 years of case ascertainment the number of cases is too low to form different groups within the study.

Our incidence rate is likely to be an underestimate given our estimate of the total number of cases by capture-recapture analysis. Each method may have missed recognised cases and mild cases that may never have been diagnosed. Our findings suggest that cancer registries and specialty groups alone may be insufficient to ascertain all cases of LCH and that future studies should cast a wide net. However, by using several sources to maximise ascertainment, sufficient data have been collected to assess presentation, management and outcome which we aim to present in a future publication.

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Competing interests: None.

Ethics approval: The study received appropriate ethics approval by UK and Republic of Ireland ethics bodies.

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