

Langerhans cell histiocytosis

Principal investigator

Bruce Crooks, MB, ChB, Paediatric Haematology/Oncology, Dalhousie University, IWK Health Centre, 5850-5980 University Ave., Halifax, NS B3K 6R8; tel: 902-470-6404; fax: 902-470-7208; e-mail: bruce.crooks@iwk.nshealth.ca

Co-investigators

David Dix, MD, University of British Columbia Louise Parke, PhD, Dalhousie University Sheila Weitzman, MD, University of Toronto

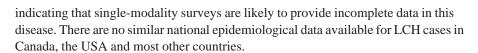
Background

Langerhans cell histiocytosis (LCH) is a rare disease of unknown cause, characterized by the proliferation of pathogenic Langerhans cells and cytokine overproduction causing inflammation, infiltration and destruction of many tissues of the body. LCH is a heterogeneous condition and may present with simple painful bony lesions, often affecting the skull or long bones, chronic otitis, proptosis or skin rash resembling seborrhoeic or napkin dermatitis. Diabetes insipidus due to hypothalamic-pituitary involvement is also well recognized. Many tissues, including lungs, CNS, liver and bone marrow may be involved in fulminant, multisystem disease (usually seen in infants, where mortality may approach 20%). Treatments may range from observation (spontaneous regression may occur), surgical curettage, steroid injection or chemotherapy. Haemopoietic stem cell transplant may be indicated in fulminant disease. International collaborative clinical trials are conducted to develop treatments of all groups. Some patients may develop chronic or relapsing disease. Survivors may have significant long-term sequelae, both from the disease or its treatment, including relapsing disease, malignancy and neurodegenerative disease of unknown origin.^{1,2}

LCH appears commoner in children than adults, but exact epidemiological data are scarce. Reported incidences from European studies range from 2.24 to 8.9 per million children. 3,4,5,6,7 Most studies derive from either institutional data or registry data only. The majority of patients are managed by paediatric haematologists/oncologists. However, as LCH is heterogeneous, and diagnosis difficult, patients may present to services such as orthopaedics, neurosurgery, ENT, dermatology and endocrinology for treatment and not referred on to paediatrics. Two recent national epidemiological studies from the UK and France used multiple parallel methods of case collection. The British Paediatric Surveillance Unit (BPSU) survey reported an overall incidence of 4.12/million children aged 0-14.3 Researchers accessed the UK Children's Cancer and Leukaemia Group Registry and the BPSU survey mechanism, as well as contacted non-BPSU specialists who may see LCH cases. Even though there was duplication of case reporting using parallel mechanisms, 17% of cases were not identified through the BPSU survey, but were obtained via other collection methods. The French survey, reporting incidence at 4.6/million children, accessed several different registries, death statistics and separate institutional databases and admissions data. Again, there were cases identified uniquely within each mechanism,

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It is unclear whether the incidence of LCH differs among ethnic groups. The Canadian population is growing and diversifying steadily through immigration, allowing the study to capture data on ethnicity. Other postulated links include neonatal infection, thyroid disease and low usage of infant vaccination. Around 1% of cases have another affected family member, suggesting a genetic predisposition may exist for this condition. Also, increasing population mobility can significantly affect continuity of long-term care and follow-up.

There is a need for clear information regarding the epidemiology of this disease in order to optimize diagnosis, management, future research and resource allocation for these patients. The research team hopes that study results will form a platform to develop a Canadian LCH registry to optimize care and research for these patients.

Methods

To maximize case capture, national surveillance of LCH will be conducted using three parallel methods:

- Clinically active paediatricians and paediatric subspecialists will be questioned monthly through the CPSP regarding LCH. Respondents who identify a case will be asked to complete a detailed questionnaire for each case.
- 2. Haematologists/oncologists in the 17 paediatric haematology/oncology centres in Canada will be contacted monthly by the research team regarding LCH. Respondents who identify a case will be asked to complete identical detailed questionnaires by mail or by web-based reporting. If respondents are members of the CPSP, they will be asked to report via the CPSP program.
- 3. Other allied specialty physicians (orthopaedics, neurosurgery, otorhinolaryngology, dermatology, ophthalmology, endocrinology and pathology) will be contacted quarterly by the research team regarding LCH and will proceed as described under #2.

Objectives

Primary objective

To identify the epidemiological features of LCH in Canada.

Secondary objectives

- 1. To describe the patterns of presentation, clinical and pathological features of newly diagnosed LCH cases.
- 2. To examine the pathways of referral and diagnosis of LCH cases.
- 3. To identify the time delays from symptom onset to definitive diagnosis.
- 4. To describe the initial treatment of LCH cases, including access to, and participation in, clinical trials.
- 5. To compare Canadian data with other published epidemiological surveys to improve global knowledge of this condition.



Langerhans cell histiocytosis (continued)

Case definition

Report any new patient presenting from birth to 18th birthday with:

Clinical LCH features that may include unexplained bone pain and soft tissue swelling, diabetes insipidus and hypothalamic-pituitary dysfunction, proptosis, recurrent otitis or otorrhoea, maculopapular rash or seborrhoeic dermatitis or napkin dermatitis resistant to treatment, interstitial pneumonitis or sclerosing cholangitis.

AND

- Biopsy proven LCH with lesional cells containing:
 - Birbeck granules demonstrated on electron microscopy and/or
 - CD1a positive cells on immunohistochemistry and/or
 - Langerin-positive cells and/or
 - S100 positive cells with characteristic histopathology
- Lytic bone lesions or pituitary/ hypothalamic lesions characteristic of LCH without biopsy where:
 - Risks of biopsy are considered too hazardous due to site of lesion
 - Lesion has shown characteristic spontaneous regression

or

Duration

July 2009 to June 2011

Expected number of cases

The expected number of new LCH cases per year is approximately 30-40, given reported incidences from BPSU and other studies and Canadian Census data.⁸

Ethical approval

Research Ethics Board, IWK Health Centre, Halifax

REB approval will also be sought from the 17 Canadian paediatric haematology/oncology centres for institutional participation.

Analysis and publication

All data will be collected in a central database located at the IWK Health Centre. Results will be reported using descriptive statistics in appropriate peer-reviewed journals (e.g., *Pediatric Blood and Cancer, Paediatrics & Child Health*), presented to the Histiocyte Society, ¹¹ the Canadian Paediatric Society, the Histiocytosis Association of Canada, ¹² and published in the annual *CPSP Results*. Study results will also be compared with the British Paediatric Surveillance Unit results and made available for comparison with future INoPSU¹³ studies of LCH.

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