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Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000 - 2004: A study of 258 cases.

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Abstract

Introduction

Childhood Langerhans cell histiocytosis (LCH) is a rare and poorly-understood multisystemic disease. The French National Registry of Childhood Hematopoietic Malignancies (NRCH) has recorded LCH cases of all subtypes since 2000. The present study describes the data on LCH collected on a national scale over a 5-year period.

Materials and methods

The cases were children aged less than 15 years, diagnosed with LCH of any type between 2000 and 2004, and residing in mainland France at the time of diagnosis. Completeness was evaluated by capture-recapture after cross-checking against the database compiled by the French Langerhans Cell Histiocytosis Study Group.

Results

Two hundred and fifty-eight cases of LCH were registered. The completeness of the NRCH was estimated to be 97%. The annual incidence rate was $4.6/10^6$ children aged less than 15 years and the sex ratio was 1.2. Bone and skin were the most commonly involved organs at diagnosis. The incidence rate decreased with age from $15.3/10^6$ before 1 year to $2.0/10^6$ after 10 years. The disease was mainly unifocal ($2.6/10^6$) and rarely disseminated ($0.6/10^6$), but disseminated forms predominated in infants. The overall 2-year survival rate was 99% (95%CI: [97; 100]). About 30% of the LCH cases were enrolled in a clinical trial at first onset. No case was treated by radiotherapy.

Conclusion

This study evidenced the main features of LCH incidence in the overall population and was consistent with previous studies. The NRCH thus appears to be a very promising tool for further elucidation of LCH.

Introduction

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is a rare and poorly known childhood disease. LCH is an oligoclonal accumulation of Langerhans cells (1). The clinical spectrum of LCH is highly heterogeneous. Langerhans cell histiocytosis may involve several organs (bone, skin, central nervous system, spleen, lungs, liver or gastrointestinal tract), or may result in hematologic dysfunction. Some entities, such as isolated bone lesions, have a good prognosis. In contrast, disseminated LCH with hematologic dysfunction, formerly known as Letterer-Siwe disease, may be fatal (2). The descriptive epidemiology of LCH remains poorly documented. To date, no more than 4 published studies, conducted on at most about a hundred cases, have reported incidence rates. Moreover, few studies refer to the etiology of LCH (3, 4).

The third version of the International Classification of Diseases for Oncology (ICDO-3) (5) provides for coding the 3 main clinical subtypes of LCH: the unifocal (9752/1) and multifocal (9753/1) variants, which are considered non-neoplastic borderline diseases, and disseminated LCH (9754/3), considered a malignant disease. The French National Registry of Childhood Hematopoietic Malignancies (NRCH) has recorded all subtypes of LCH since 2000. This article describes the data generated by the first 5 years of national registration of LCH, in association with the French LCH study group.

Patients and methods

Case registration

The present study includes the cases of LCH registered by the NRCH from 2000 to 2004. The NRCH includes all children diagnosed with LCH of any type before the age of 15 years and residing in mainland France at the time of diagnosis. The cases were actively sought in all French pediatric hematology and oncology departments. They were also retrieved from the

admission lists of all the French teaching hospitals and cancer treatment centers. The database was also crosschecked against the clinical trial database and the Inserm department responsible for collecting information on the medical causes of death (Cépi-dc). The completeness of the NRCH with regard to registration of hematopoietic malignancies has been estimated to be very close to 100% (6). Cases of LCH are also recorded by the French Langerhans Cell Histiocytosis Study Group (F-LCH-SG), which consists in a variety of specialists responsible for LCH care and has lead several studies (7, 8) and treatment protocols worked out by the Histiocyte Society.

The NRCH registration form includes identification data (first and last names, gender, date and place of birth, address at diagnosis), diagnostic data (date of diagnosis, ICDO-3 morphology code, primary sites, and radiologic, histologic and laboratory test results), treatment and enrolment in a clinical trial, organs involved in relapses, vital status and last contact date. The F-LCH-SG collects more precise clinical data and is constituting a blood and tissue bank. F-LCH-SG pathologists review all histologic reports on biopsy specimens. In line with the recommendations for cancer registration, the date of diagnosis is considered to be the date of first histological diagnosis defined as per the criteria of the Histiocyte Society (9, 10). In the absence of a biopsy, the diagnosis of LCH may be based on clinical criteria and radiological, scintigraphic or MRI images.

Case classification

Disseminated LCH was defined by the involvement of risk organs: liver, spleen, lungs or hematopoietic system in line with the criteria of the Histiocyte Society. Multifocal LCH was defined by the involvement of at least 2 organs other than risk organs. The ICDO-3 code was allocated in the light of the clinical and radiologic investigations and laboratory tests needed for staging: pulmonary lesions, marked hematologic dysfunction (hemoglobin < 7g/dL or platelet count < $100/mm^3$), hepatic or splenic involvement evidenced by imaging or clinical

manifestations, skin involvement or central nervous system involvement (including pituitary involvement).

Vital status

The vital status of each case was checked in the records of the Records Office of his/her place of birth, using a national electronic procedure. Otherwise, the last follow-up date was the date of the last consultation reported in the hospital files. The date of point was July 1, 2006.

Statistical analysis

The completeness of the NRCH was tested by two-sample capture-recapture method (11) using the F-LCH-SG as the other source, which was made possible because NRCH and F-LCH-SG comply with independent registration procedures. Age-specific incidence rates (<1 year, 1-4 years, 5-9 years, 10-14 years) were estimated by gender for each LCH subtype. Person-years for each age and gender class were provided by the French Institute of Statistic and Economic Studies (INSEE). The incidence rates were age-standardized taking the world population age structure as a reference. The survival time was defined as the difference between the date of diagnosis and either the date of death or the last contact date for censored observations. The 1- and 2-year survival rates were estimated by the Kaplan-Meier method.

Results

Completeness and quality of data

Between 2000 and 2004, the NRCH recorded 251 cases of LCH, 36 of which were missing from the F-LCH-SG database, and the F-LCH-SG recorded 222 cases of LCH, 7 of which were missing from the NRCH database. The completeness of the NRCH for childhood LCH registration was thus estimated to be 97%. by capture-recapture. The NRCH was updated with the 7 missing cases that had been detected by the F-LCH-SG. The present study thus included 258 cases of childhood LCH diagnosed in France over the 2000-2004 period.

The diagnosis of LCH was documented by histology in 230 cases (89%) and on radiologic images of lytic lesions typical of LCH in 23 cases (9%) for which no biopsy was available. The histology reports were missing for the 5 remaining cases. For 99% of the cases, the information was sufficient to code the LCH as unifocal, multifocal or disseminated as per the ICDO-3. For the other 3 cases, code 9751/1 (LCH, not otherwise specified) was used.

Estimation of incidence rates

Table I shows the distribution of the cases by age, gender and subtype. Age at diagnosis ranged from 1 day to 14.6 years, with a median of 3.5 years. The overall LCH incidence rate was 4.6 cases per million per year. The sex ratio (M/F) was 1.2. The incidence rate was highest before age one year (15.3 cases per million per year), then decreased steeply with age. Male predominance was not observed in the age group < 1 year. Overall, LCH was most often unifocal (57%; IR = 2.6 cases per million per year), while disseminated forms accounted for 14% of the cases (IR = 0.6 cases per million per year). However, disseminated LCH was far more frequent before age one year (31%). Half of the cases of disseminated LCH were less than 1 year old and almost all of them (32/35) were diagnosed before the age of 5 years.

Primary sites

The distribution of the cases by primary LCH site is given in table II. Overall, LCH mainly affected bones (75%) and, to a lesser extent, skin (34%). Bone lesions were present in 70% of the unifocal forms and 93% of the multifocal forms. However, skin sites predominated before age 1 year in all LCH subtypes (77, 89 and 78% of unifocal, multifocal and disseminated LCH, respectively). Five of the 147 unifocal LCH cases, all aged over 5 years, presented with central nervous system disease sites: 4 cases with a pituitary site and diabetes insipidus and 1 case with a cerebellar site. Among the 73 cases with multifocal LCH, 14 had lesions of the central nervous system, of which 12 with a pituitary site and diabetes insipidus and 2 with a cerebellar or meningeal site. Four cases with disseminated LCH at diagnosis had neurologic

lesions: 2 with a pituitary site and diabetes insipidus, 1 with pituitary and cerebellar sites, and 1 with a meningeal site. The risk organs affected in disseminated LCH were the lungs in 20 cases and liver or spleen in 11 cases. Hematologic dysfunction was diagnosed in 13 cases. Gender did not influence the distribution of the primary sites in any type of LCH.

LCH presenting in the neonatal period

Five cases of LCH were diagnosed within the first 4 weeks of extrauterine life. Two of the cases presented with disseminated LCH: one male had cutaneous, gastrointestinal and splenic involvement with thrombocytopenia and one female, who died shortly after diagnosis, had cutaneous, gastrointestinal, neurologic, hepatic, splenic and pulmonary involvement with hematologic dysfunction at age 8 days. In the other 3 cases, LCH was unifocal and affected the skin.

Treatment

Treatment was documented for 231 cases (90%). The decision to keep the child under medical surveillance without any treatment was taken for 106 cases. Seventy-four cases were enrolled in the protocol of clinical trial LCH-II (n = 6) or LCH-III (n = 68). The cases consisted in 15% unifocal, 40% multifocal and 80% disseminated LCH (table III). In particular, the clinical trial LCH was observed for 7 cases and 15 cases of the infants with multifocal or disseminated LCH respectively. The cases of unifocal LCH who were enrolled in clinical trial LCH had bone (13 cases), skin (5 case) or central nervous system (1 case) disease sites. Even cases not enrolled in clinical trial were treated by chemotherapy (VLB+steroid) except for one case born with LCH and died before treatment. No case was treated by radiotherapy.

Survival

Vital status was ascertained for 212 (82%) of the 258 cases. For the 46 remaining cases, the last contact date was the date of the last consultation. For 16 of them, the last contact took

place less than one year after the diagnosis. Two deaths had been registered, both within 1 year of diagnosis. The 1-year and 2-year survival rates were both 99% (95%CI [97-100]), all LCH taken together. The 2 fatal cases consisted in disseminated LCH. Thus the 2-year survival rates were 94% [79-98] for disseminated LCH and 100% for the other subtypes. The first death occurred at age 24 days. The case consisted of a female who presented a disseminated LCH at 8 days of age. The other one occurred 9 months after diagnosis, and this case consisted in a young female diagnosed at age 5 months and presenting with skin, hepatic, splenic and gastrointestinal involvement and hematologic dysfunction.

Discussion

This study describes data from a national population-based registration of LCH. A substantial strength of this study is the completeness of the data throughout the period 2000-2004. The data were obtained using well-established and reliable methods of cancer registration. Only 3 cases had not been precisely coded. Cross-checking the NRCH database against that of the F-LCH-SG enabled the completeness and precision of the data to be enhanced. Despite the fact that LCH is treated in a large number of departments with differing fields of specialization, the completeness of the NRCH was high (97%) and close to that for leukemia and lymphoma (6). However, the completeness of unifocal LCH may have been overestimated (and hence the incidence underestimated), particularly with respect to undiagnosed cases with spontaneous regression and cases treated outside of hospital. Such cases could have been overlooked by both the NRCH and the F-LCH-SG databases.

The age-adjusted incidence rate estimated for all LCH taken together (5.0 cases per million per year) is similar to that found by a Danish study of the period 1975-89 (5.4 cases per million per year) published in an abstract (12) (table IV) and that reported by the German Childhood Cancer Registry for the period 2000-2004 (6.0 cases per million per year) (13).

The incidence rate was higher (8.9 cases per million per year) in a series of 29 cases admitted to a single medical department in the Stockholm area from 1992 to 2001 (14). The proportions of unifocal (57%) and disseminated (14%) LCH in the present study were close to those reported in Denmark (12) and Sweden (14). The Manchester Children's Tumour Registry (15) reported lower incidence rates (2.6 cases per million per year) over the 1954-1998 period with a particularly low incidence of unifocal subtypes, which are less traceable through the health care system. The primary disease sites were similar in all the studies, with bone and skin sites predominating, as they did in our study (2, 14-16). In the present study, 64% of the cases were aged less than 5 years (median age: 3.5 years), and the incidence rates decreased with age, as had been previously reported in England, Sweden and Germany (12, 13, 15). The Austrian/German/Swiss/Netherlands LCH Study Group (GPOH) reported that 2% of the LCH cases enrolled in clinical trials were diagnosed in the neonatal period, before the age of 28 days (17). That was also the case in the present study. This GPOH Study Group also showed that, in 6% of the cases, LCH actually began in the first 28 days of extrauterine life. In this study, LCH was unifocal in 41% of the neonatal cases and disseminated in 44%, which is compatible with the distribution of the 5 neonatal cases: 3 unifocal and 2 disseminated LCH. The skin was the primary disease site in 89% of the cases and it was involved in all 5 neonatal cases and in 79% of the infants.

About 75% of the unifocal LCH cases did not receive treatment, which is in line with current international practice (16). However, 19 cases that presented with substantial pain or functional disorders were enrolled in clinical trial LCH-III. No case was treated by radiotherapy, as is recommended in France in order to prevent second tumors (18).

Because of the short duration of follow-up, survival rates were estimated for 1 and 2 years post-diagnosis. The two deaths observed were due to disseminated LCH and occurred within one year of diagnosis. As was observed in three previous studies, age less than 1 year (19,

20) or less than 2 years (21) and pulmonary, hepatic or splenic involvement or hematologic dysfunction (19-21) were adverse prognostic factors. However, the 2 prognostic factors are difficult to isolate in terms of their individual impact, since risk organ involvement is more common in infants.

The NRCH was shown to record LCH cases as well as it records hematopoietic malignancies, using cancer registry methodology, despite the relatively scattered cases. This study, based on 5-year national registration of LCH, has shown the main features of LCH incidence in the overall population and was consistent with previous studies. Cooperation between the NRCH and F-LCH-SG should help to ensure the quality of the clinical data, enabling further elucidation of the natural history of LCH and study of potential risk factors for that rare disease.

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References

1. Senechal B, Elain G, Jeziorski E, et al. Expansion of regulatory T cells in patients with Langerhans cell histiocytosis. PLoS Med 2007;4:e253.

2. Glotzbecker MP, Carpentieri DF, Dormans JP. Langerhans cell histiocytosis: clinical presentation, pathogenesis, and treatment from the LCH etiology research group at the children's hospital of Philadelphia. University of Pennsylvania Orthopaedic Journal 2002;15:67-73.

3. Hamre M, Hedberg J, Buckley J, et al. Langerhans cell histiocytosis: an exploratory epidemiologic study of 177 cases. Med Pediatr Oncol 1997;28:92-97.

4. Bhatia S, Nesbit ME, Egeler RM, et al. Epidemiologic study of Langerhans cell histiocytosis in children. J Pediatr 1997;130:774-784.

5. Fritz, Percy, Andrew, Shanmugaratnam, Sobin, Parkin, Sharon., editors. International Classification of Disease for Oncology Third Edition. Geneva: World Health Organization; 2000.

6. Clavel J, Goubin A, Auclerc MF, et al. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: National Registry of Childhood Leukaemia and Lymphoma, 1990-1999. Eur J Cancer Prev 2004;13:97-103.

7. Donadieu J, Rolon MA, Thomas C, et al. Endocrine involvement in pediatric-onset Langerhans' cell histiocytosis: a population-based study. J Pediatr 2004;144:344-350.

8. Barthez MA, Araujo E, Donadieu J. Langerhans cell histiocytosis and the central nervous system in childhood: evolution and prognostic factors. Results of a collaborative study. J Child Neurol 2000;15:150-156.

9. Chu, D'Angio, Favara, et al. Histiocytosis syndromes in children. Lancet Neurol 1987;1:208-209.

10. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. J Pediatr 1995;127:1-11.

11. International Working Group for Disease Monitoring and Forecasting. Capture-recapture and multiple-record systems estimation II: Applications in human diseases. International Working Group for Disease Monitoring and Forecasting. Am J Epidemiol 1995;142:1059-1068.

12. Carstensen H, Ornvold K. The epidemiology of Langerhans cell histiocytosis in children in Denmark, 1975-1989. Med Pediatr Oncol 1993;21:387-388.

13. German Childhood Cancer Registry. Annual Report 2005 (1980-2004). Institute for Biostatistics, Epidemiology and Informatics (http://info.imsd.uni-mainz.de/K_Krebsregister/english/) University of Mainz .

14. Karis J, Bernstrand C, Fadeel B, Henter JI. The incidence of Langerhans cell histiocytosis in children in Stockholm county, Sweden 1992-2001.

15. Alston RD, Tatevossian RG, McNally RJ, et al. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. Pediatr Blood Cancer 2007;48:555-560.

16. Weitzman, Egeler., editors. Histiocytic disorders of children and adults. Basic science, clinical features and therapy. Cambridge University Press; 2007.

17. Minkov M, Prosch H, Steiner M, et al. Langerhans cell histiocytosis in neonates. Pediatr Blood Cancer 2005;45:802-807.

18. Donadieu J. Histiocytose langerhansienne. Encyclopedie Orphanet. (http:www.orpha.net/data/patho/FR/fr-histyocytose.pdf), 2003.

19. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. Arch Dis Child 1996;75:17-24.

20. Jubran RF, Marachelian A, Dorey F, Malogolowkin M. Predictors of outcome in children with Langerhans cell histiocytosis. Pediatr Blood Cancer 2005;45:37-42.

21. Gadner H, Grois N, Arico M, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. The Journal of Pediatrics 2001;138:728-734.

TABLE I. Distribution of LCH by subtype, gender and age at diagnosis.

	Histiocytosis									
	unifocal		multifocal		disseminated		total			
	N	IR	N	IR	N	IR	N	IR	SR	ASR
Male										
< 1 year	14	7.2	4	2.1	8	4.1	26	13.4		
1-4 years	29	3.8	23	3.0	8	1.1	61	8.1		
5-9 years	23	2.5	7	0.8	1	0.1	31	3.4		
10-14 years	18	1.9	2	0.2	2	0.2	22	2.3		
0-14 years	**84**	**3.0**	**36**	**1.3**	**19**	**0.7**	**140**	**4.9**		5.3
Female										
< 1 year	17	9.2	5	2.7	10	5.4	32	17.3		
1-4 years	16	2.2	22	3.0	6	0.8	45	6.2		
5-9 years	20	2.3	6	0.7	0		26	3.0		
10-14 years	10	1.1	4	0.4	0		15	1.6		
0-14 years	**63**	**2.3**	**37**	**1.4**	**16**	**0.6**	**118**	**4.3**		4.7
Total										
< 1 year	31	8.2	9	2.4	18	4.7	58	15.3	0.8	
1-4 years	45	3.0	45	3.0	14	0.9	106	7.2	1.3	
5-9 years	43	2.4	13	0.7	1	0.1	57	3.2	1.2	
10-14 years	28	1.5	6	0.3	2	0.1	37	2.0	1.5	
0-14 years	**147**	**2.6**	**73**	**1.3**	**35**	**0.6**	**258**	**4.6**	**1.2**	5.0

N: number of cases, IR: incidence rate per million per year, ASR: age standardized rate per million per year, SR: ratio of the number of cases in males to that in females

Table II. Primary LCH sites

	Bone		Skin		CNS*		Hemato**		Liver		Spleen		Lung		Other		N
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Unifocal LCH																	
<1 y	3	(10)	24	(77)	0	(0)									4	(13)	31
1-4 y	36	(80)	8	(18)	0	(0)									1	(2)	45
5-9 y	40	(93)	1	(2)	2	(5)									0	(0)	43
10-14 y	24	(86)	1	(4)	3	(11)									0	(0)	28
0-14 y	**103**	**(70)**	**34**	**(23)**	**5**	**(3)**									**5**	**(3)**	**147**
Multifocal LCH																	
<1 y	7	(78)	8	(89)	0	(0)									3	(33)	9
1-4 y	43	(96)	16	(36)	11	(24)									5	(11)	45
5-9 y	13	(100)	2	(15)	2	(15)									0	(0)	13
10-14 y	5	(83)	1	(17)	1	(17)									1	(17)	6
0-14 y	**68**	**(93)**	**27**	**(37)**	**14**	**(19)**									**9**	**(12)**	**73**
Disseminated LCH																	
<1 y	8	(44)	14	(78)	1	(6)	9	(50)	6	(33)	7	(39)	9	(50)	15	(83)	18
1-4 y	10	(71)	10	(71)	1	(7)	4	(29)	5	(36)	4	(29)	8	(57)	5	(36)	14
5-9 y	1	(100)	0	(0)	1	(100)	0	(0)	0	(0)	0	(0)	1	(100)	0	(0)	1
10-14 y	1	(50)	1	(50)	1	(50)	0	(0)	0	(0)	0	(0)	2	(100)	2	(100)	2
0-14 y	**20**	**(57)**	**25**	**(71)**	**4**	**(11)**	**13**	**(37)**	**11**	**(31)**	**11**	**(31)**	**20**	**(57)**	**22**	**(63)**	**35**

** Central nervous system; ** Hematologic dysfunction; N: number of cases*

Table III. Distribution of LCH cases enrolled in clinical trials LCH-II or LCH-III by subtype and age at diagnosis

	Histiocytosis							
	unifocal		multifocal		disseminated		Total	
	N		*N*		*N*		*N*	
< 1 y	4	15%	7	78%	15	83%	26	49%
1-4 y	6	15%	17	41%	10	71%	33	34%
5-9 y	5	13%	2	17%	1	100%	8	16%
10-14 y	4	17%	1	20%	2	100%	7	23%
Total	19	15%	27	40%	28	80%	74	32%

N: number of cases

Table IV. Publication on the descriptive epidemiology of LCH.

Authors	Period	Place	Source	Age of cases	No. of cases	IR	Publication
Karis et al.	1992-2001	Stockholm county	Department of Pediatrics, Karolinska Hospital	<15 years	29	8.9	abstract
Muller et al.	1981-2000	Hungary	Hungarian Childhood Cancer Registry	<18 years	111		abstract
Carstensen& Ornvold	1975-1989	Denmark	All Danish departments of pediatrics, pathology, dermatology, radiation oncology, orthopedic surgery, neurosurgery, ear-nose-throat and dentistry	<15 years	90	5.4	abstract
Alston et al.	1954-1998	Northwest England	Manchester Children's Tumour Registry	<15 years	101	2.6	article

IR: incidence rate per million per year