Langerhans Cell Histiocytosis: 40 Years' Experience

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Objectives: Our study analyzes 40 years' experience with pediatric Langerhans cell histiocytosis patients.

Materials and Methods: Between June 1968 and December 2009, 121 patients (79 males, 42 females; median age 4.13 y) were diagnosed at our center (74% monosystemic disease; 26% multisystemic), treated according to current protocols. We evaluated the response, the survival, and the neuroendocrinological sequelae.

Results: Overall survival (OS) for all patients was 93% at 10 years from diagnosis, event-free survival (EFS) 77%. OS for patients younger than 2 years and older than or equal to 2 years was 82% and 97% ($P = 0.003$); EFS 48% and 87% ($P = 0.001$). OS for patients diagnosed before and after April 1, 1991 was 84% and 98% ($P = 0.007$), EFS 66% and 85% ($P = 0.03$). OS for monosystemic and multisystemic disease was 100% and 71% ($P < 0.001$); EFS 88% and 45% ($P < 0.001$). OS for "risk" patients (involvement of bone marrow, spleen, liver, lungs) and "low-risk" patients was 50% and 94% ($P = 0.007$), EFS 37% and 54% ($P = 0.06$). Fourteen patients developed diabetes insipidus, 7 patients growth hormone deficiency, 2 hypothyroidism, and 1 neurodegeneration.

Conclusions: Our study confirms improvement of pathogenetic knowledge and treatment over the last 20 years. Age at diagnosis older than or equal to 2 years and standardized treatment are associated with improved prognoses. Multisystemic involvement, especially with "risk" organs seem to be correlated to a worse outcome.

Key Words: LCH, children, risk organs, diabetes insipidus, neurodegeneration

(*J Pediatr Hematol Oncol* 2012;34:353–358)

Langerhans Cell Histiocytosis (LCH) is a rare group of disorders with a wide range of clinical presentations,[1] that affects about 5 to 6 per million children per year: more than 50% of cases are diagnosed between 1 and 15 years of age, with a peak between 1 and 4 years.[2]

Because of its unknown etiology, LCH had originally been called histiocytosis X in 1953 by Linchenstein, grouping 3 different entities[3]: Letterer-Siwe disease, Hand-Schuller-Christian disease, and eosinophilic granuloma.[2,3] Suggested hypothesis is an irregular and uncontrolled proliferation of lymphocytes and histiocytes after viral infections or gene mutation. Mutation could be somatic or germinal: the latter might explain familiar cases of LCH.[4,5] Some authors think that a dysregulation in interaction between Langerhans cells is probably implicated in LCH pathogenesis.[6]

Whether LCH represents a reactive or a neoplastic disease is still a matter of debate. Probably LCH is the only pathologic combination between oncogenesis and chronic immune dysregulation.[7]

Various studies have contributed to further understanding of the pathobiology of LCH and over the years have established a classification based on the organ involvement and dysfunction.

The initial classification proposed by the Histiocyte Society in 1987 divides histiocytic syndromes into 3 classes: class I and class II include reactive forms, based on proliferation of Langerhans cells and non-Langerhans cells, respectively, and class III includes rare neoplastic forms. Class I is the most frequent and represents the old entity of histiocytosis X.[8] More recently, a revised classification scheme included a division into: (1) dendritic cell-related disorders—LCH, secondary dendritic processes, juvenile xanthogranuloma, and solitary histiocytomas with a dendritic phenotype; (2) macrophage-related disorders; (3) malignant histiocytic disorders; and (4) dendritic cell or macrophage-related histiocytic sarcoma.[9]

LCH may involve bone, skin, lymph nodes, or parenchymal organs such as liver, spleen, lungs, bone marrow and may cause endocrinological disorders [such as diabetes insipidus (DI), growth hormone (GH) deficiency, and hypothyroidism] or neurological deficit.

Depending on which organs are implicated, LCH may prove rapidly fatal or develop a chronic reactivating but therapy-responsive pattern or resolve spontaneously.[10]

Diverse therapeutic approaches may be considered depending on the affected organ, including surgery, radiotherapy, and chemotherapy.[11]

To date there is no optimal treatment protocol for multifocal/multisystemic forms or risk organ disease, carrying a high-reactivation rate.[12]

The purpose of our study was to review the experience of the last 40 years analyzing the improvement of treatment and comparing different groups of patients and their outcome.

MATERIALS AND METHODS

Patients

We considered 121 patients affected by LCH, treated in our institution from June 1968 to December 2009 (median follow-up: 5.27 y; range, 0 to 24.37 y). They were 79 males (65%) and 42 females (35%) and the median age at diagnosis was 4.13 years (range, 12 d to 15 y).

Received for publication February 3, 2011; accepted March 27, 2012.
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A histologic diagnosis by surgical biopsy was performed in 110/121 (91%) patients; the diagnosis was based on clinical and radiologic findings in 11 cases (9%), because of surgical risk due to the vertebral site of the disease.

We used the classification proposed by Histiocyte Society in 1987 based on histopathologic characteristics which distinguishes 2 forms of disease: *monosystemic* (skin or lymph nodes or monofocal/multifocal bone involvement) and *multisystemic* (involving "risk" organs: bone marrow, spleen, liver, lungs, or "low-risk" organs—skin, lymph nodes, bone). The patients diagnosed before 1987 were classified retrospectively.

Treatment

Before 1991, when the LCH-I protocol started (first standardized protocol in Italy for the treatment of LCH), the patients were treated in a nondefinite way.

Since 1991 3 standardized protocols were successively activated.

The LCH-I protocol compared the efficacy (response, failure, and morbidity) of monotherapy with vinblastine or etoposide, without showing significant difference between the 2 arms, in neither to the initial response and the probability of relapse, nor mortality.[13]

The LCH-II protocol compared 2 treatment arms, the 2-drug arm A with prednisone and vinblastine and the 3-drug arm B with prednisone, vinblastine, and etoposide. To date, etoposide has not shown any additional therapeutic benefit to response, survival, or relapse rate, nor as it shown any benefit as monotherapy or in combination with vinblastine and prednisone.[14]

In LCH-III protocol, the patients are stratified into 3 groups: group 1 (multisystemic "risk" patients), group 2 [multisystemic "low-risk" patients), and group 3 (monosystemic multifocal bone disease and localized "special site" involvement (central nervous system lesions with intracranial soft tissue extension or vertebral lesions with intraspinal soft tissue extension)]. Patients with bone monofocal LCH and monosystemic skin or lymph nodes LCH do not receive any treatment, but only "wait and see" follow-up.

Response

Disease status was recorded as "*Complete regression of disease*"—related signs and symptoms after diagnosis (CR1) or after first, second, third, or fourth reactivation of the disease (CR2,3,4,5); "*Reactivation*" was defined as the appearance of new lesions; all "*Deaths*" were considered as due to LCH, otherwise the cause of death will be specified.

The patients had yearly endocrinological follow-up (clinical examination and laboratory tests) and neurological follow-up [clinical examination, magnetic resonance imaging (MRI) of brain, and psychological tests at the time of diagnosis and then upon clinical request].

Statistics

Data were analyzed as of December 31, 2009. Overall survival (OS) was calculated from diagnosis to death for any causes by Kaplan-Meier statistics.[15] Event-free survival (EFS) was defined as the length of time from diagnosis to the reactivation of LCH. The differences between curves were calculated by log-rank test.[16] The following variables were analyzed for their impact on outcome: site of disease (monosystemic or multisystemic), period of diagnosis (before April 1, 1991 or after April 1, 1991), age at diagnosis (age younger than 2 y or older than or equal to 2 y). The statistical analysis for dichotomic variables was performed through the Fisher exact test per $P < 0.05$.[17] All statistical analyses were performed with SPSS software Version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Patients

Extension of Disease

In 90/121 (74%) patients, LCH was monosystemic; in 31/121 (26%) LCH was multisystemic. In the first group, 56/90 patients (62%) presented monofocal bone localizations, 17 (19%) multifocal bone lesions, 14 (15.5%) had skin localizations, and 3 (3.5%) had lymph node LCH.

In 16/31 (52%) patients a "risk" system was involved: 3/16 presented bone multifocal lesions associated with skin, lymph node, and liver involvement; 6 had lymph nodal disease associated with hepatic and splenic lesions; in 2 patients LCH involved the liver, lungs, skin, and lymph node; 2 presented skin, lungs, and multifocal bone lesions; 1 had hepatic and lymph nodal disease; 2 presented bone marrow involvement associated with bone and liver, respectively. In 15/31 patients (48%) LCH affected "low-risk" systems: 10/15 presented with bone and skin lesions; 2 presented lymph node and skin LCH; and 3 had involvement of bone, skin, and lymph nodes.

Age at Diagnosis

As shown in Table 1, 33/121 (27%) patients were under 2 years of age and 88 (73%) wereolder than or equal to 2 years. In the first group, 9/33 presented bone disease (3 had monofocal lesions and 6 multifocal), 9/33 presented monosystemic skin or lymph node LCH, 15/33 had multisystemic disease (7/15 with "risk" organs). In the second group, 64/88 presented bone disease (53/64 monofocal and 11/64 multifocal), 8 patients presented monosystemic skin or lymph node lesions, 16 multisystemic disease (9/16 involved "risk" organs).

TABLE 1. Distribution Clinical Presentation of Disease in all 121 Patients in Relation to the Age at Diagnosis

	Age < 2 y		Age ≥ 2 y			
Clinical Presentation	**N**	**%**	**N**	**%**	**All N**	***P***
Bone monofocal	3	9.1	53	60	56	0.0001
Bone multifocal	6	18.2	11	13	17	NS (0.3)
Skin or Lymph node monosystemic	9	27.3	8	9	17	0.02
Multisystemic 'low risk'	8	24.2	7	8	15	0.03
Multisystemic 'risk'	7	21.2	9	10	16	NS (0.1)
All	33	100	88	100	121	

TABLE 2. Distribution of Clinical Presentation of Disease in all 121 Patients in Relation to the Period of Diagnosis

	Before April 1, 1991		After April 1, 1991			
Clinical Presentation	**N**	**%**	**N**	**%**	**All N**	***P***
Bone monofocal	20	38	36	53	56	NS (0.1)
Bone multifocal	11	21	6	9	17	NS (0.1)
Skin or Lymph node monosystemic	7	13	10	14.5	17	NS (0.2)
Multisystemic 'low risk'	5	9	10	14.5	15	NS (0.2)
Multisystemic 'risk'	10	19	6	9	16	NS (0.1)
All	53	100	68	100	121	

Period of Diagnosis and Treatment

As shown in Table 2, in 53/121 (44%) patients the diagnosis was made before April 1, 1991 and in 68 cases (56%) after.

In the first group, 31/53 patients were affected by bone disease (20 monofocal, 11 multifocal), 7 had skin or lymph node lesions, 15 had multisystemic LCH (10/15 with "risk" organs). Four/53 (7.5%) patients received no treatment ("wait and see"), 5/53 (9.5%) received only curettage, 11/53 (21%) patients underwent curettage and telecobalt therapy, 33/53 (62%) were treated with chemotherapy (vinblastine, etoposide, methotrexate, cyclophosphamide, and prednisone) at variable doses and duration.

In the second group, 42/68 had bone disease (36 monofocal and 6 multifocal), 10 had skin or lymph node disease, 16 patients presented multisystemic LCH (6 with "risk" organs). Seventeen/68 (25%) patients were treated according to the LCH-I protocol (April 1, 1991 to April 30, 1996), 17/68 patients (25%) with the LCH-II protocol (May 1, 1996 to March 30, 2001) and 34/68 (50%) were treated according to the LCH-III protocol (since April 1, 2001). In LCH-III, 10/34 (29%) patients were only followed with "wait and see" due to their monofocal lesions, in 18/34 (53%) patients with monofocal bone disease a curettage was performed, 1/34 (3%) patient was treated according to group 1 treatment of LCH-III protocol, 2/34 (6%) were included in group 2, and 3/34 (9%) in group 3.

Response and Survival

OS at 10 years from diagnosis for all patients cohort was 93%, EFS was 77%.

For patients younger than and older than or equal to 2 years at diagnosis OS at 10 years from diagnosis was 82% and 94% ($P = 0.003$), respectively (Fig. 1); EFS was 48% and 87% ($P = 0.001$).

As shown in Table 3, 27/33 (82%) patients younger than 2 years at diagnosis were alive at last follow-up (December 31, 2009); 16/33 (48.5%) in CR1, 5 (15.5%) in CR2, 4 (12%) in CR3, 1 (3%) in CR4, 1 (3%) on therapy, and 6/33 (18%) were dead. In the group of patients older than or equal to 2 years at diagnosis 85/88 (96.5%) were alive, 77/88 (87.5%) in CR1, 4 (4.5%) in CR2, 1 (1%) in CR3, 2 (2.5%) in CR4, 1 (1%) in CR5, and 3/88 (3.5%) were dead.

For patients diagnosed *before and after April 1, 1991*, OS at 10 years was 84% and 98% ($P = 0.007$), respectively (Fig. 2), whereas EFS was 66% and 85% ($P = 0.03$), respectively. As shown in Table 3, at last follow-up 45/53 (85%) patients diagnosed *before April 1, 1991* were alive, 35/53 (66%) were in CR1, 6 (11%) in CR2, 1 (2%) in CR3, 3 (6%) in CR4, and 8/53 (15%) were dead. In the group of patients diagnosed *after April 1, 1991*, 67/68 (98.5%) were alive, 58/68 (85%) were in CR1, 3 (4.5%) in CR2, 4 (6%) in CR3, 1 (1.5%) in CR5, 1 (1.5%) was in treatment with indomethacin, and 1/68 (1.5%) was dead.

All the patients with monosystemic disease were alive at the time of the last follow-up (December 31, 2009). As shown in Figure 3, when we considered patients with *monosystemic* LCH versus *multisystemic* patients the OS at 10 years was 100% and 71% ($P < 0.001$), and EFS was 88% and 45%, respectively ($P < 0.001$). OS at 10 years for *multisystemic* "*risk*" patients and "*low-risk*" patients was 50% and 94%, respectively ($P = 0.007$), EFS was 37% and 54% ($P = 0.06$).

At last follow-up, all patients with *bone monofocal* disease were alive in CR: 54/56 (96%) in CR1, 1 (2%) in CR2, and 1 (2%) in CR4. The 5.3% presented reactivation of disease and then complete regression after second-line treatment. Eleven/17 patients (65%) with *bone multifocal* disease were in CR1, 4 (23%) in CR2, 1 (6%) in CR4, and 1 (6%) in CR5. Fourteen/17 patients (82%) with *skin or lymph node* disease were in CR1, 1 (6%) in CR2, 1 (6%) in CR3, and 1 (6%) in CR4.

Six of 17 (35%) bone multifocal patients presented reactivation of disease while only 3/17 (18%) patients with skin or lymph node disease.

In the *multisystemic* group, at last follow-up 8/15 (53%) "*low-risk*" patients were in CR1, 3 (20%) in CR2, 2 (13%) in CR3, and 1 (7%) was having indomethacin; 1/15 (7%) was dead. Six/16 (38%) "*risk*" patients were in CR1, 2 (12%) in CR3, and 8/15 (50%) patients were dead.

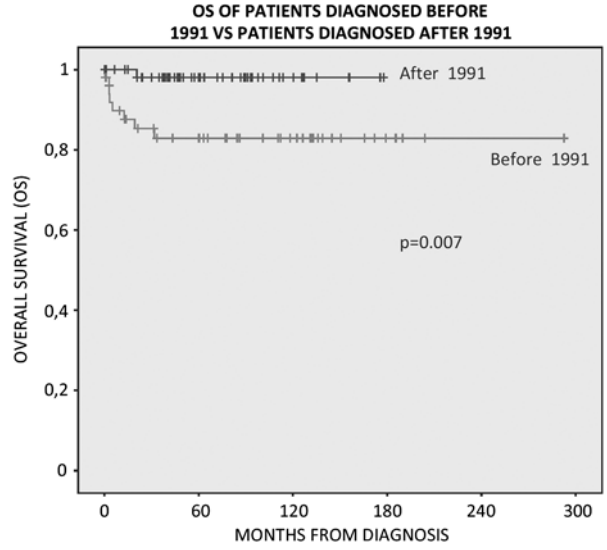

FIGURE 1. Overall survival for patients <2 years at diagnosis versus ≥ 2 years.

TABLE 3. Status of 121 Patient at Last Follow-up (December 31, 2009) in Relation to the Period of Diagnosis (Before and After April 1, 1991) and the Age at Diagnosis (< and ≥ 2 y old)

	Before April 1, 1991		After April 1, 1991		Age < 2 y		Age ≥ 2 y		
	N	%	N	%	N	%	N	%	All N
Alive	45	85	67	98.5	27	82	85	96.5	112
First CR	35	66	58	85	16	48.5	77	87.5	93
Second CR	6	11	3	45	5	15.5	4	4.5	9
Third CR	1	2	4	6	4	12	1	1	5
Fourth CR	3	6	0	0	1	3	2	2.5	3
Fifth CR	0	0	1	1.5	0	0	1	1	1
In chemotherapy	0	0	1	1.5	1	3	0	0	1
Dead	8	15	1	1.5	6	18	3	3.5	9
All	53	100	68	100	33	100	88	100	121

LCH Neuroendocrinological Sequelae

Fourteen of 121 (11.5%) patients developed DI at 0 to 36 months from diagnosis (median 14 mo): 7/14 (50%) had monosystemic bone LCH (3 monofocal and 4 multifocal), and 7 were multisystemic "low-risk" patients. Seven/14 (50%) patients showed at least 1 lytic scalp lesion. EFS at 10 years for patients who developed DI was 62% versus 83% for nonaffected patients ($P = 0.02$).

Seven of 121 patients (6%) presented *GH deficiency* at 16 to 64 months (median 27 mo): all were multisystemic patients (1 had "risk" organ involvement).

Two patients (1.5%) developed asymptomatic *hypothyroidism*, 17 months and 23 months after the diagnosis of LCH, respectively: 1 patient presented bone monofocal disease and the other patient, with "risk" LCH, developed also GH deficiency, 6 months after the onset of hypothyroidism.

In our cases, only 1 patient developed *neurodegeneration*. LCH presented with mucocutaneous lesions at 3 months of age, followed by 3 reactivations, the first 1 with bone localizations (occipital bone), 3 months after the diagnosis, and the 2 subsequent skin reactivations 13 months and 19 months after the diagnosis. After treatment with LCH-I protocol for the third reactivation, the patient developed DI (26 months from LCH diagnosis) and at the age of 13 years presented neuropsychiatric symptoms with behavior abnormalities, attempted suicide, episodes of escape and wandering, bad language, alcohol abuse, and balance deficits. MRI of the brain showed no significant findings.

DISCUSSION

Intrinsic characteristics of LCH, the poor knowledge about it and the possible diagnostic difficulties explain the length of time to achieve such brilliant and encouraging improvement, in terms of both prognosis and quality of life of the patients.

The aim of our study was to follow the evolution of LCH over 40 years at our center, considering the diagnostic, therapeutic, and prognostic aspects.

First diagnostic approach may be a surgical biopsy in the greater part of the patients because the most common site of disease is the bone and the surgical biopsy represents also the therapeutic act for monofocal bone patients. A complete staging study permitted to correctly diagnose other sites of LCH and to schedule treatment plan.

From 1968 to 2009, treatment has progressively improved and became more methodical and based on standardized protocol, stratifying patients according to involved sites and risk organs, ranging from surgery alone to multidrugs chemotherapy. Our results confirm a wide range of clinical

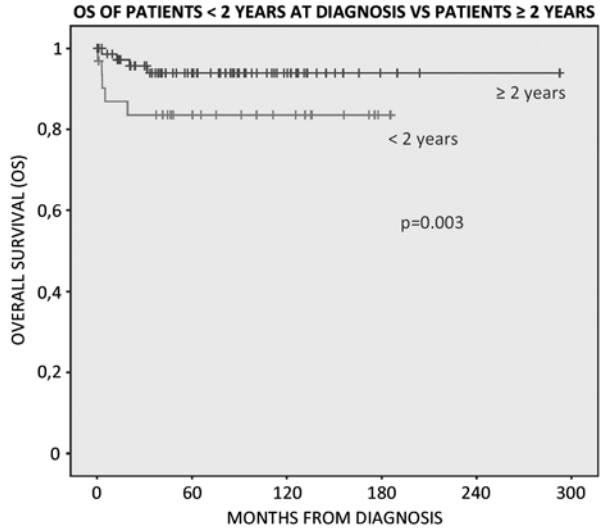

FIGURE 2. Overall survival for patients diagnosed before 1991 versus after 1991.

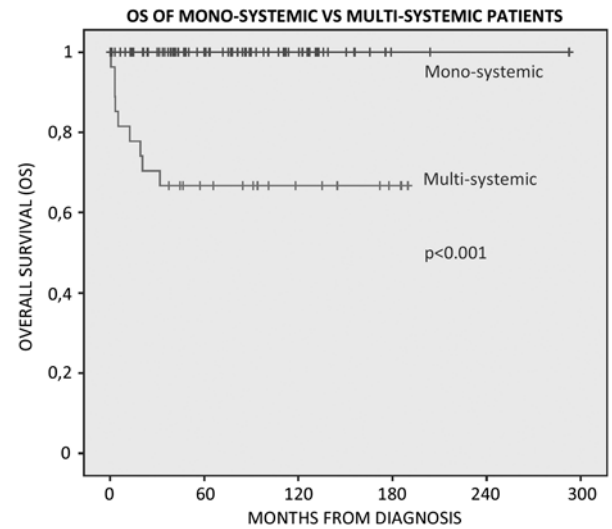

FIGURE 3. Overall survival for monosystemic patients versus multisystemic.

presentations and generally good prognosis, related to some variables already known.

In 1990, Greis and Hankin[18] reported the experience of 20 patients affected by isolated bone LCH showing that 100% of patients were in CR at the end of the study. Generally, authors point out that monofocal bone lesions have good response to all kinds of treatment and functional deficits rarely remain.[19] Patients with monosystemic LCH of skin or lymph nodes or bone (even if skeletal involvement is multifocal) have excellent survival chances. In contrast, patients with multisystemic LCH may have a more unpredictable course, including rapid deterioration with fatal outcome.

In our cases, all monosystemic patients had very good outcome, with low-reactivation rate. OS and EFS were higher for monosystemic than multisystemic patients and for "low-risk" than "risk" disease. In fact, all cases of death have been observed in multisystemic patients, with a proportion of 50% in "risk" cases, confirming also that involvement of "risk organs" is a well-established unfavourable prognostic indicator in multisystemic LCH.[20] Multisystemic LCH is associated with high mortality also when patients are younger than 2 years, as reported by Gadner et al.[21]

In 1993, Wysocki et al[22] described 20 LCH patients (median age 11 mo) showing worse prognosis in those who presented dysfunction of at least 1 organ and younger than 2 years, and Carstensen and Ornvold[23] confirmed poor outcomes for patients with organ dysfunction and noted that organ dysfunction was more frequent in patients younger than 2 years.

In our study, we reported lower OS and EFS for the group younger than 2 years at diagnosis, with a higher percentage of multisystemic disease in this group.

In 2007, Alston et al[2] published a study of 101 LCH patients registered in Great Britain from 1954 to 1998, showing better OS for those diagnosed after 1991. Our data confirm that patients treated and followed after 1991 had lower reactivation rate and mortality than patients diagnosed before, probably related to systematic diagnostic approach and standardized treatment.

In addition, we analyzed endocrinological and neurological sequelae of LCH: DI is the most common and risk factors for developing it include multisystemic disease and craniofacial bone lesions, particularly involving frontal bones, orbits, middle ears, and mastoids. The risk is also significantly increased when LCH is active for a prolonged period of time and with disease reactivations.[24] Prosch et al[25] in 2004 described DI as possible presenting symptom of LCH; Amato et al[26] in 2006 reported 46 cases of LCH: 10/46 (22%) patients developed DI, in 4/10 associated to GH deficiency and in 2/4 to hypogonadism. In fact, patients with LCH and DI have a high risk of progression to anterior pituitary dysfunction, with a 54% 10-year risk of GH deficiency[27] and lesser, but significant risk of deficiency of the other anterior pituitary hormones. Abla et al[28] in 2009 suggested that patients with new onset of DI may benefit from prolonged low-dose systemic chemotherapy in an attempt to prevent secondary consequences (anterior pituitary dysfunction and neurodegeneration) associated with posterior pituitary involvement by LCH.

In our study, DI occurred in 11.5% of cases: all patients had at least 1 bone lesion (50% lytic scalp lesion), confirming data reported in literature. Affected patients had lower EFS, confirming that patients who have reactivation of LCH have a higher risk of DI and suggesting a closer follow-up for these patients.

Neurodegeneration is a further dramatic consequence of LCH. Wnorowski et al[29] in 2008 described 83 LCH patients in whom brain MRI was performed at least twice for various clinical indications. Fifty-seven percent of these patients had radiologic LCH—neurodegeneration (median 34 mo), late neurological effect of systemic diffusion of LCH, or an autoimmune process.

The pathogenesis of neurodegeneration remains unclear. Van't Hooft et al[30] in 2008 proposed that neurodegenerative inflammatory reaction in LCH could be associated with an immune response to a neurotrophic agent causing secondary tissue damage.

Some authors have suggested that an equivalent of a paraneoplastic syndrome might be responsible for cytokine or autoimmune-induced tissue damage.[31,32]

Martin-Duverneuil et al[33] in 2006 specifically analyzed the MRI presentation of neurodegeneration in 13 LCH patients. The posterior fossa was involved in 12 patients and a cerebellar atrophy was observed in 8 cases. Surprisingly, the involvement of pontine white matter was not always related to severity of the alterations of cerebellar white matter and of nuclei dentate, more associated to the neurological deficit. The supratentorial region was involved in 11 patients, the globus pallidus in 8 patients. A diffuse cortical atrophy was present in 3 cases and a marked focal atrophy of the corpus callosum in 3 cases. The few reported pathologic examinations revealed focal areas of demyelination with gliosis, a loss of neuronal cells in the granular and Purkinje layers of the cerebellar cortex, with no evidence of typical $CD1a^+$ histiocytic infiltration that does not support a direct effect of the LCH cells on central nervous system.

We report 1 patient with symptomatic neurodegeneration, without significant MRI alterations: the prognosis is extremely poor, considering the impossibility of efficacious treatment. Although it is an isolated case, it is worthy of note.

In conclusion, our study confirms improved prognosis for LCH patients with monosystemic disease in particular bone monofocal lesions, in line with other published data; multisystemic disease and age younger than 2 years remain subgroups with worse outcome, due to their unfavourable localizations and the involvement of "risk" organs. Collaboration between all centers and between orthopedics, oncologists, neurologists, and endocrinologists is warranted to identify new prognostic factors to modulate future treatment strategies. A long-term follow-up for LCH patients is necessary in light of the possible endocrinological deficit and onset of neurodegeneration, with dramatic consequence.

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