Neurodegenerative central nervous system disease as late sequelae of Langerhans cell histiocytosis. Report from the Japan LCH Study Group

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ABSTRACT

Clinical features, brain magnetic resonance imaging findings and EDSS scores of 11 patients with neurodegenerative central nervous system Langerhans cell histiocytosis were analyzed in Japan. All patients initially had multi-system-type Langerhans cell histiocytosis; 8 at 1-2 years of age and 3 at a later age. Neurodegenerative central nervous system largermans cell histiocytosis disease developed after a median time interval of 3.9 years from initial diagnosis. With a median follow-up of 4.5 years, 6 patients showed progression of disease with an EDSS score >3. This study demonstrates the importance of early detection of neurodegenerative central nervous system Langerhans cell histiocytosis by brain magnetic resonance imaging, particularly in the follow-up of patients who developed multi-system-type Langerhans cell histiocytosis in early infancy.

Key words: Langerhans cell histiocytosis, late sequelae, neurodegenerative central nervous system disease

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Introduction

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder characterized by abnormal proliferation of Langerhans cells, which results in the formation of lesions primarily in the skin, bone, liver, spleen, and lymph nodes.[1] The disease also affects the central nervous system (CNS), where it frequently manifests as diabetes insipidus, and, rarely, as late sequelae involving cerebral, cerebellar/ spinocerebellar or pyramidal cells. These late sequelae CNS diseases, which include cerebellar ataxia and other neurological defects, have previously been observed in case reports or case studies,[2-11] and are now recognized as neurodegenerative CNS-LCH (ND-CNS-LCH) disease.[7-11] The diagnosis of ND-CNS-LCH disease is made by characteristic brain MRI findings and/or symptoms of cerebral or cerebellar neurologic dysfunction.[7-12]

The long-term outcome of ND-CNS-LCH disease is bleak. However, longitudinal follow-up studies from the initial LCH episodes in such cases have rarely been reported. Careful analysis of clinical features is essential to understand how the disease occurs and how it progresses with time. A multi-institutional case study was, therefore, conducted and we report 11 cases of ND-CNS-LCH collected through the Japan LCH Study Group (JLSG) registry.

Design and Methods

ND-CNS-LCH was defined as a prior history of LCH, together with detection of characteristic brain MRI patterns at the cerebellar dentate nuclei, basal ganglia, and/or pons, and cerebellar/ cerebral white matter, with or without the development of

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symptoms of neurological dysfunction. The JLSG study, approved by the IRB at the Kyoto Prefectural University of Medicine where the registration center is located, was carried out in accordance with institutional ethical standards and the Helsinki Declaration. In the Japan LCH registry, 150 multi-system-type LCH patients were registered from 1996 to 2004 for the JLSG study.[13] We identified 11 cases of ND-CNS-LCH; 9 patients registered during the above study period and 2 more cases from the period before the start of JLSG registration (Table 1).

The initial LCH lesions were treated using the JLSG-96 protocol (VCR/AraC/PSL) in 5 patients, and by individual protocol (VBL/PSL or other regimens) in the other 6. LCH onset occurred before 2 years of age in 9 patients, 4.8 years in 1 patient, and at 16 years of age in the oldest. At the time of ND-CNS-LCH diagnosis, 5 patients were diagnosed by abnormalities in their MRI in the absence of neurological symptoms (Group 1), while the other 6 already had neurological deficits at the time of diagnosis (Group 2). In the latter group, MRI abnormalities were confirmed later. During the clinical course, 4 of the 11 patients received intravenous immunoglobulin (IVIG) treatment for longer than 12 months (Table 1, Figure 1). Expanded disability status scale (EDSS) scores,[14] determined by the physician-in-chief at each institute, were used to evaluate the grade of ND-CNS-LCH diseases.

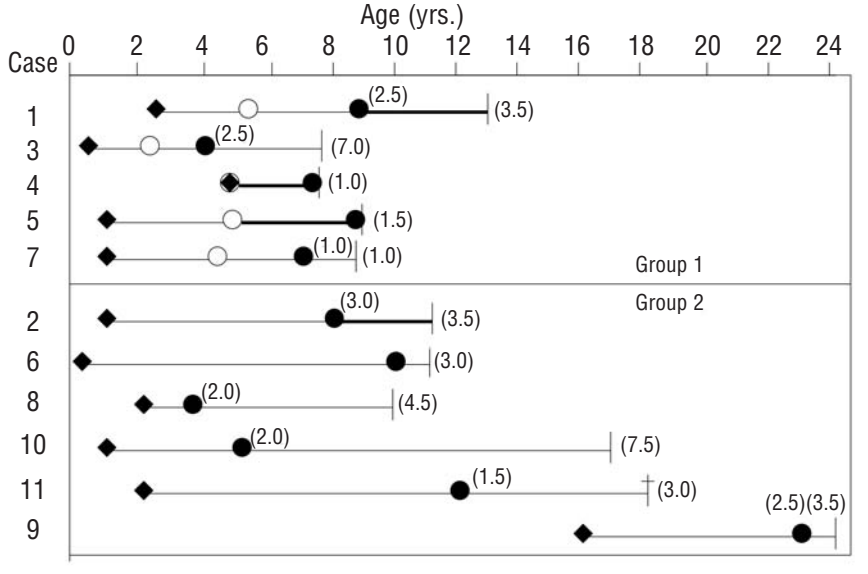

Figure 1. Clinical course of each patient. Closed diamonds, the onset of LCH, open circles, time of first detection of abnormal MRI findings, closed circles, time of detection of neurological symptoms, stop mark, last follow-up. Numbers in brackets indicate EDSS scores. Duration indicated by bold lines show IVIG treatment. Case 11 died of unknown causes.

Table 1. Clinical characteristics of 11 patients with ND-CNS-LCH.

Case N.	*Age/ sex at Dx of LCH*	*Type of LCH at Dx/ CNS-Risk lesions*	*Protocol used for treatment of LCH*	*Time from LCH-Dx to first detection of ND (EDSS)*	*Age when neurological signs noted (symptoms)*	*IVIG therapy (>12 mo)*	*Age at the last follow-up**	*EDSS at ND-Dx/ at the last visit (follow-up periods)*	*Yearly increase of EDSS*
1	2.6 yrs / M	MS/yes	Individual	2.9 yrs (0**)	8.8 yrs (ataxia)	yes	12.7 yrs	0/ 2.5 (3.3 yrs) 2.5/ 3.5 (3.9 yrs)***	0.76 0.26
3	0.4 yrs/ M	MS/no	JLSG-96	2.1 yrs (0)	3.9 yrs (ataxia) 5.0 yr (dysarthria)	no	7.8 yrs	0/ 7.0 (5.3 yrs)	1.32
4	4.8 yrs/ M	MS/yes	JLSG-96	0 yrs (0)	7.7 yrs (minor)	yes	7.7 yrs	0/ 1.0 (2.9 yrs)	0.34
5	1.1 yrs/ M	MS/yes	JLSG-96	3.9 yrs (0)	9.2 yrs (minor)	yes	9.2 yrs	0/ 1.5 (4.2 yrs)	0.36
7	1.1 yrs/ M	MS/yes	JLSG-96	3.4 yrs (0)	7.0 yrs (minor)	no	9.0 yrs	0/ 1.0 (4.5 yrs)	0.22
2	1.1 yrs/ M	MS/yes	JLSG-96	6.9 yrs (3.0)	8.0 yrs (ataxia) 10 yrs (strabismus)	yes	11.2 yrs	3.0/ 3.5 (3.2 yrs)	0.16
6	0.2 yrs/ M	MS/yes	Individual	9.6 yrs (2.0)	9.8 yrs (ataxia)	no	10.8 yrs	2.0/3.0 (1.0 yrs)	1.00
8	2 yrs/ F	MS/yes	Individual	1.5 yrs (2.0)	3.5 yrs (gait dis) 5.0 yrs (strabismus) 6.0 yrs (ataxia)	no	10.0yr	2.0/4.5 (6.5 yrs)	0.38
10	1 yrs/ M	MS/no	Individual	4 yrs (3.0)	5.0 yrs (ataxia)	no	17.0yr	3.0/7.5 (12 yrs)	0.38
11	2 yrs/ M	MS/yes	Individual	10 yrs (1.5)	12 yrs (dysarthria)	no	18.0yr	1.5/3.0(6 yrs)	0.25
9	16 yrs/ M	MS/no	Individual	7 yrs (2.5)	23 yrs (ataxia) 23 yrs (dysarthria)	no	24.0yr	2.5/3.5 (1.0 yrs)	1.0

**At the end of 2006, Dx=diagnosis, ND=neurodegenerative disease, MS=multi-system disease, minor=minor neurological abnormality, gait dis =gait disturbance, **Dx was made only by MRI abnormalities. ***IVIG-treatment period was separately calculated.*

Results and Discussion

Clinical characteristics

The clinical features of the 11 patients in this study are summarized in Table 1 and Figure 1. Initial characterization of LCH indicated that the median age of onset of LCH was 1.1 years of age (range, 0.2-16 years), with 8 at 1-2 years of age and 3 at a later age. All of the 11 patients had multi-system (MS)-type LCH, and skin as well as skull osteolytic lesions (including "CNS-Risk" area) were most common (n=8). The initial diagnosis was made early at a young age (median 2.9; range 2.5-5.5 years) by MRI findings in 5 Group 1 patients who later developed minor neurological symptoms or ataxia after an interval of a median 2.9 (range 1.4-4.5) years. The 6 Group 2 patients, in whom no MRI was performed until neurological signs developed, were neurologically diagnosed at an older age (3.5, 5, 8, 9.9, 12, and 23 years of age) with an interval of a median 7 years from the onset of LCH (see Figure 1). One patient (case #11) died of unknown causes at 18 years of age.[15]

Magnetic resonance imaging findings and neurological symptoms

Brain MRI revealed strong signals in the area of the cerebellar dentate nuclei (Figure 2) in 7 patients, strong signal spots at the basal ganglia in 5 patients, intense signal spots in the cerebral white matter area in 3 patients, severe cerebral atrophy in 1 patient, and cerebellar atrophy in 3 patients. Of the 11 patients, 7 showed cerebellar ataxia, of which 2 are currently unable to walk and need wheelchair assistance (cases #3, 10). Three patients have had minor neurological abnormalities (cases #4, 5, 7) including mild spastic gait, four had dysarthria (cases #1, 3, 9, 11), and 2 received ophthalmological surgery for double vision due to convergent strabismus caused by the cerebellar impairment (cases #2, 8) (Table 1).

EDSS evaluation during the clinical course

The time interval from the detection of abnormal MRI findings to the appearance of neurological symptoms was 1.4-3.3 years in the 5 Group 1 patients (Table 1). The disease was found to progress over time once the disease became symptomatic in all patients except for case #7. At the last visits, the Group 1 patients had a median EDSS score of 1.5 (range 1.0-7.0) with a follow-up of a median 4.5 (range 2.9-7.2) years. By contrast, the Group 2 patients had a median EDSS score of 3.5 (range, 3.0-7.5) with a follow-up of a median 4.6 (range, 1.0-12) years. Thus, EDSS scores at the last follow-up were higher for Group 2 than for Group 1 patients. Although only 4 of the 11 patients received IVIG-containing regimens for longer than 12 months (15), to see the treatment effect, the increase in EDSS score/year was compared for the IVIG-treated period in 4 patients and the non-IVIG-treated period in the 8 patients. Data (mean values; 0.28/year *vs.* 0.69/year) indicated that the progression of the disease was somewhat delayed in patients undergoing IVIG treatment although this was not statistically significant (Mann-Whitney test). At the last follow-up, 5 patients maintained an EDSS score <3 and 6 patients a score >3 (of which 2 had score 7 or higher).

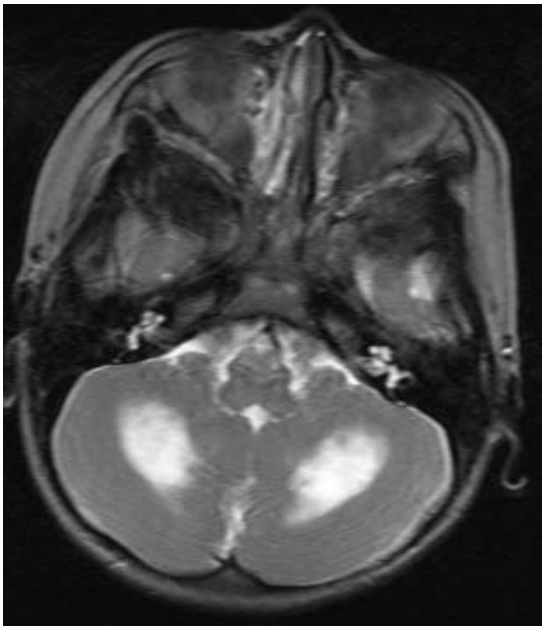

Figure 2. Representative magnetic resonance FLAIR imagings show strong signals in the region of the cerebellar dentate nuclei (Case 3).

This study showed that the median age of LCH onset was 1.1 (range, 0.2-16) years, and that ND-CNS-LCH disease developed after a median time interval of 3.9 (range, 0-10) years. In terms of the time of initial diagnosis of ND-CNS-LCH, first detection of MRI abnormalities could be made at around 3 years from the LCH onset, based on the data in Group 1 patients. The fact that 8 of the 11 ND-CNS-LCH patients had a history of MS-type LCH in infancy indicates a need for long-term follow-up of infantile MS-type LCH patients, particularly for CNS sequelae. Regarding 1 very late-onset case, adult onset ND-CNS-LCH cases have so far been sporadically reported.[3,16,17] Whether these patients really did have adult onset LCH lesions or whether LCH had been missed in infancy is not known.

In this study, EDSS scores were used to evaluate the progression of ND-CNS-LCH. It should be noted that in 3 of the 5 patients in whom abnormal MRI findings were detected prior to the development of neurological symptoms, the EDSS scores remained in the range of 1.0-1.5. By contrast, EDSS scores were >3.0 in the 6 patients who were symptomatic at diagnosis. However, since there is a greater emphasis on gait or walking ability in the EDSS score evaluation, future studies will require detailed assessments other than the EDSS score to improve evaluation of neurological symptoms in these patients.[18]

The usefulness of brain MRI, particularly T2W1 and

FLAIR imaging, to detect the strong signals at the cerebellar dentate nuclei, as well as severe cerebellar atrophy, has been well established in the diagnosis of ND-CNS-LCH disease.[7-12] In this series, only 5 patients had a chance to be diagnosed early from characteristic brain MRI findings prior to the development of neurological symptoms (Group 1). Since the remaining 6 patients in Group 2 were not examined by MRI in their follow-up until when neurological symptoms were noted, any comparison between these two groups is problematic. However, EDSS scores at the last follow-up were higher in Group 2 than in Group 1. Our data suggest the potential benefit of early diagnosis of ND-CNS-LCH and the need for future research to find an effective treatment to prevent or delay the progression of the disease.

With this aim, we previously reported therapeutic results with a combination therapy of IVIG and chemotherapy in pediatric ND-CNS-LCH patients,[12] since LCH CNS lesions share some common features with the pathogenesis of multiple sclerosis, and the efficacy of IVIG therapy has been reported in patients with multiple sclerosis.[19,20] Extended observation observed a trend for the delayed progression of the disease in the IVIG treated patients as seen from the change in the EDSS scores. However, these preliminary results need to be confirmed prospectively in a larger number of patients. Exploration of novel prophylactic or therapeutic measures is mandatory in the management of patients with ND-CNS-LCH.

Authorship and Disclosures

SI and AM co-designed the study, enrolled patients, analyzed results, wrote the manuscript and contributed to the data registration and quality control at the JLSG office. YS, RK, GH, HF, SS, HW, AO, ON, NF, TM, KK, and YT enrolled patients, analyzed results and critically revised the manuscript. All authors approved the final version of the manuscript. The authors reported no potential conflicts of interest.

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