et al. that LCH cells of self-healing or isolated cutaneous LCH (LCH-SS) have a more mature phenotype (with low expression of SHP-1) than those in disseminated disease (LCH-MS) [16]. SHP-1 is also useful for the differential diagnosis between LCH in lymph nodes and DLA. Organs which LCH involves are various. A lymph node may be a presenting and only site of LCH. LCH involves only skin and lymph nodes [23]. Those cases without characteristic features such as increased eosinophil levels give a diagnostic problem at the point of differential diagnosis with DLA containing proliferating LCs in lymph nodes [26].

Motheaten mice or viable motheaten mice (meV) lacks the SHP-1 expression [27]. meV shows normal LC numbers in the epidermis at birth, but the numbers decrease along with mouse maturation [28, 29]. SHP-1 might be necessary to maintain the LC number in the epidermis by maintaining immaturity of the mouse skin. Data on such mice LCs and human LCs in DLA may suggest that SHP-1 in the skin (keratinocytes) and/or SHP-1 in LCs themselves play a role in maintaining the immaturity of LCs.

Very recently, *BRAF* mutation was described in LCH including LCH-SS cases involving the lungs [9]. *BRAF* mutation is also related with many cancers [30]. Such data point out the neoplastic possibility of LCH as well as a clonal association between LCH and a lymphoblastic leukemia [5, 6]. It is an important question whether LCH-SS involving the lungs is neoplastic or nonneoplastic. Our data about SHP-1 expression of two cases LCH-SS involving the lungs looks same as in other LCH-SS cases, but two cases are not enough to talk about the role of SHP-1 expression in this differential diagnosis statistically. SHP-1 exists in some signaling pathways relating to BRAF [31, 32]. Thus, it is an important question whether SHP-1 relates or not with BRAF or mitogen-activated protein/extracellular signal-regulated kinase pathways in LCH. We are currently analyzing roles or functions of SHP-1 using transfectants derived from a cell line with LC character.

In conclusion, SHP-1 expressions were negative, low and high among DLA (nine patients), LCH-SS (21 patients), and LCH-MS (12 patients), respectively, with a significant difference. This difference can be used to provide insight into LCH and differential diagnosis among DLA, LCH-SS, and LCH-MS, especially between LCH in LNs and DLA.

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Conflict of interest We declare that we have no conflict of interest.

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CASE REPORT

Treatment of patients with hypothalamic-pituitary lesions as adult-onset Langerhans cell histiocytosis

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Abstract We report four cases of adult-onset Langerhans cell histiocytosis (LCH) with central nervous system (CNS) lesions in the hypothalamic-pituitary region. The first clinical symptoms were diabetes insipidus (two patients), hypothyroidism (one patient), and decreased libido/erectile dysfunction (one patient). Diagnosis was delayed as the CNS lesion was not initially suspected to be secondary to LCH, with a median time from symptom onset to treatment of 3.0 (range <1–5.3) years. In three patients, the tumor mass was effectively reduced by chemotherapy; however, all patients continue to exhibit hypopituitarism. Early diagnosis and initiation of treatment are required to improve the outcome of CNS-LCH in adult patients.

Keywords Langerhans cell histiocytosis · Medical oncology · Brain tumors · Hypothalamic-pituitary mass · Hypopituitarism

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1 Introduction

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of cells with the phenotype of activated Langerhans cells [1, 2]. About two-thirds of LCH cases develop in childhood while the remaining one-third develops in adulthood. LCH is a single or multi-system disease of the skin, bones, soft tissues, hematopoietic system and central nervous system (CNS) [2]. With regard to LCH with CNS involvement, diabetes insipidus (DI) is the most frequent symptom. It is diagnosed by magnetic resonance imaging (MRI) that reveals the absence of the posterior pituitary bright signal with or without a thickened pituitary stalk and/or space-occupying mass lesions at the hypothalamic-pituitary region (HPR) [3, 4]. However, even when such lesions are detected, LCH diagnosis is often delayed, particularly when the CNS lesion is the only LCH site. This is because such lesions can also be caused by other diseases [5–7]. Patients with LCH-induced lesions at the HPR and DI can eventually develop hypopituitarism [8], also known as anterior pituitary dysfunction. This has been observed in both children and adults [4, 9, 10]. However, reports of

adult cases are very limited, which make the treatment of adult patients further difficult.

LCH-induced DI has been considered not reversible in the majority of patients with this complication. It was shown recently that 2-chlorodeoxyadenosine (2-CDA) effectively induces a complete radiographic resolution of enhancing mass lesions in the CNS [11]. 2-CDA successfully reversed DI in a pediatric patient when it was given early [12]. While LCH-induced endocrine dysfunctions other than DI appear to be permanent and not reversible by any known treatment [9, 10], it remains to be determined whether the early introduction of 2-CDA or any specific therapy can reverse hypopituitarism and/or DI. Since the information on adult LCH is still fragmentary, we report here the cases of four adult-onset LCH patients with lesions at the HPR hoping that these case series may unravel critical issues to improve the outcome of the adult LCH in future.

2 Case report

2.1 Case 1

A 20-year-old girl first complained of polyuria/polydipsia and amenorrhea. Eight months later, she was diagnosed with hypopituitarism in association with a gadolinium (Gd)-enhanced mass at the HPR that was detected by a brain MRI (Fig. 1a). An immediate open biopsy of the mass confirmed the diagnosis of LCH. Localized irradiation (21 Gy) markedly reduced the mass. Two years later, the patient was referred to us with re-growth of hypothalamic mass, continued amenorrhea, poorly controlled DI and generalized cutaneous LCH, which was confirmed by biopsy. On admission, she was very obese (159 cm, 89.5 kg) with significantly low serum hormone levels (Table 1). Multiagents' chemotherapy was started, consisting of vinblastine (VBL; once a month), methotrexate (once a month), oral prednisolone (PSL; 5 days a month) and daily oral 6-mercaptopurine (6-MP), followed by a combination of vincristine/cytarabine/methotrexate/PSL with daily oral 6-MP for an additional 5 months. DDAVP and hormonal replacement therapy (estrogen/progesterone, thyroxin) were continued. The size of hypothalamic mass was reduced significantly (>50%) along with complete resolution of skin lesions (Table 1). Five years after LCH onset, her serum prolactin and estradiol levels returned to normal. Thereafter, she has become free from DDAVP, but without restoring of menstrual cycles.

2.2 Case 2

A 36-year-old female developed DI in association with amenorrhea and was placed on DDAVP. The thickened pituitary stalk detected by MRI remained under observation but was not treated because of a presumed diagnosis of lymphocytic hypophysitis. However, the thickened pituitary stalk progressed fairly rapidly into a Gd-enhanced mass at the HPR (Fig. 1b). One and a half years later after onset, a tumor biopsy revealed typical LCH histology. When referred to us, she was obese (156 cm, 87.0 kg) and had amenorrhea, fatty liver, reduced glucose tolerance and reduced hormone levels (Table 1). Five courses of 2-CDA (5 mg/day × 5 days) and PSL (20 mg/day) over 4.5 months, followed by daily oral 6-MP, significantly reduced the mass size (>50%) and pituitary stalk thickening. LCH lesions outside the CNS were not found. The patient remains markedly obese and diabetic.

2.3 Case 3

A 38-year-old male was first diagnosed with primary hypothyroidism. Nineteen months later, he developed the symptoms of thirst, fatigue and disturbed consciousness along with disorientation and abnormal behaviors. A brain MRI revealed a Gd-enhanced mass at the HPR (Fig. 1c).

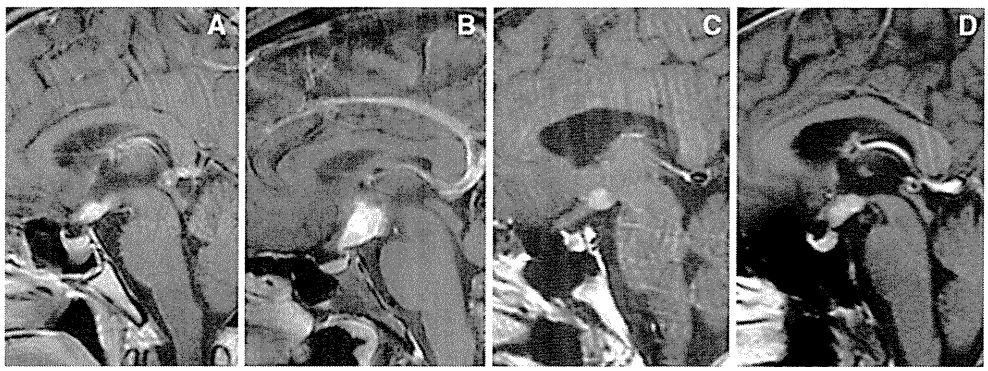

Fig. 1 Sagittal magnetic resonance imaging view of the gadolinium-enhanced mass at the hypothalamic-pituitary region in four adult patients at disease onset. **a–d** Cases 1–4, respectively

Table 1 Patient profiles

Cases	Age (years)/ sex	LCH type	Symptoms	Hormonal dysfunction[a]	Time (years) to biopsy of CNS mass from onset of symptoms	Time (years) to treatment from onset of symptoms	Treatment	Reduction of mass size[b] (%)
1	20/F	MS[1]	DI, amenorrhea, obesity, skin lesions	Reduced (LH, FSH, freeT4, ACTH, GH) Elevated (PRL)	0.7	<1.0	Irradiation (21 Gy), multiagents' chemo[c]	75.5
2	36/F	CNS alone	DI, amenorrhea, obesity	Reduced (GH, LH, FSH, freeT4) Elevated (PRL)	1.6	1.8	2-CDA/PSL, 6-MP	87
3	38/M	MS[2]	DI, polyendo-crinopathy, bone lesions	Reduced (GH, LH, FSH, ACTH) Elevated (PRL)	1.8	4.1	2-CDA/PSL, 6-MP	20
4	46/M	MS[3]	DI, decreased libido, erectile dysfunction, bone lesions	Reduced (LH, FSH, freeT4, ACTH) Elevated (PRL)	4.0	5.3	VBL/PSL 2-CDA/PSL, 6-MP	58

CNS central nervous system, *MS* multisystem type ([1]CNS + skin lesions, [2]CNS + multiple bone lesions, [3]CNS + spinal bones), *DI* diabetes insipidus, *VBL* vinblastine, *6-MP* 6-mercaptopurine, *PSL* prednisolone, *2-CDA* 2-chlorodeoxyadenosine, *GH* growth hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *ACTH* adrenocorticotropic hormone, *PRL* prolactin

[a] Plasma antidiuretic hormone levels were within normal ranges at onset but later dropped markedly in all cases

[b] Mass size change was calculated based on the 3-dimensional (axial, sagittal and coronal) MRI findings, for the recurred CNS mass in Case 1 with use of VBL-containing multiagents' chemotherapy, and for the primary CNS mass in Cases 2–4 with use of 2-CDA/PSL

[c] See text

He also showed complicated polyendocrinopathy consisting of DI, hypogonadism, hyperthyroidism, adrenal crisis and severe orthostatic hypotension (Table 1). The mass was presumptively diagnosed as pilocytic astrocytoma on the basis of an endoscopic biopsy. DDAVP was started together with corticosteroid, thiamazole and testosterone propionate. Four years later, osteolytic bone lesions appeared on the right femur and left clavicle, which was diagnosed as LCH by a biopsy. Eventually, the histology of the CNS mass was confirmed to be a LCH lesion. The patient received five courses of 2-CDA/PSL chemotherapy, followed by daily oral 6-MP. However, these treatments only minimally (<50%) reduced the mass size.

2.4 Case 4

A 46-year-old male first presented with decreased libido and erectile dysfunction 7 years after total gastrectomy for gastric adenocarcinoma. Four years later, a Gd-enhanced mass at the HPR was detected (Fig. 1d). Until then, he had ignored his polydipsia/polyuria symptoms. The CNS mass biopsy led to a diagnosis of LCH. A systemic MRI survey also revealed multiple spinal involvements. Based on the patient's hormone deficiency (Table 1), hormonal replacement therapy with human chorionic gonadotropin, follitropin alpha and human growth hormone was started. The patient also had loss of concentration and short-term memory deficits that were suggestive of mild neurodegenerative disease. Eventually, chemotherapy (VBL/PSL) was given but stopped after three courses because liver dysfunction grade 2 was observed. However, a year later, the patient decided to receive five courses of 2-CDA/PSL followed by daily oral 6-MP. This markedly reduced the CNS mass size (>50%).

3 Discussion

LCH-induced hypopituitarism has been described in both adults and children [4, 9, 10, 13]. In most cases, the initial symptoms are the polyuria/polydipsia signs of DI. As LCH-induced hypopituitarism, while children generally show growth hormone deficiency [14], adults are often associated with additional deficiencies of sex hormone or hypogonadism and hyperprolactinemia besides growth hormone deficiency [10, 13]. Indeed, all four adult patients described here had LH–FSH deficiency and hyperprolactinemia. The initial symptoms of Cases 1 and 2 were DI and amenorrhea, Case 3 presented with hypothyroidism, and Case 4 had decreased libido and erectile dysfunction (for some reason, the diagnosis of DI in the two male patients was delayed). Although not common, primary hypothyroidism associated with LCH-induced DI has been described previously [15, 16]. The female patients had problematic morbid obesity.

When a CNS lesion at the HPR is found as an apparent sole disease, it is critical to have histological confirmation of LCH by biopsy because several possibilities besides LCH should be considered, including germ cell tumors, lymphocytic hypophysitis [7], Erdheim–Chester disease, and juvenile xanthogranulomatosis [4–6]. However, a biopsy of CNS mass needs to be decided under careful consideration. In cases of histiocytic disorders like LCH, extra-CNS lesions may exist at the onset of disease, thus a systemic survey should always be performed before CNS mass biopsy. Also, it is possible that extra-CNS LCH lesions develop later. Of our cases, the CNS mass of Case 1 was immediately biopsied, although the patient also had eczematous scalp lesions which were highly suspicious of LCH. Case 2 had no extra-CNS lesions, thus a CNS biopsy was performed after observation until mass grew. Cases 3 and 4 developed bone LCH after CNS mass biopsy. Notably, the diagnosis of LCH was significantly delayed in the latter three cases, probably because LCH was thought uncommon in adults, thus other causes were searched.

In three of these 4 adult patients, we observed >50% CNS mass reduction with use of chemotherapy including VBL (Case 1) and 2-CDA/PSL (Cases 2 and 4); however, in none of the patients hormonal deficiencies reversed. These results made us to conclude that we were able to control mass lesions in the HPR with chemotherapies such as VBL or 2-CDA but late mass reduction is not sufficient enough to reverse endocrine dysfunction. In other words, benefits of such treatment are questionable for adult LCH patients with already existing endocrine deficits. Thus, the most critical question is, are LCH-associated endocrine disorders reversible if they are treated early and appropriately? Although rare and controversial, some reports suggest that DI can be reversed [12, 17, 18]. Particularly, a previous report indicated that hypothalamic-pituitary radiation therapy can effectively reverse DI if it is provided early, namely <14 days after DI diagnosis [18].With regard to anterior pituitary dysfunction, while most reports suggest that it cannot be reversed [6, 9, 10], Makras et al. [19] have described the case of a 35-year-old female who resumed normal menstruation following steroid administration. Case 1 became free from DDAVP several years after treatments with immediate hypothalamic-pituitary radiation therapy for the primary mass and rapid introduction of multiagents' chemotherapy for the recurred CNS mass, but not resumed menstruation. With regard to 2-CDA treatment, the HPR lesions were reported to respond well to it [6, 11]. Of our three cases treated with 2-CDA/PSL, two responded quite well (the tumor size was reduced by >50%), the remaining patient responded minimally. In these cases, no hormonal recovery has yet been attained.

As typically seen in this report, for CNS lesions in LCH, reducing a LCH-related HPR mass lesion has been one of the therapeutic goals, which is achievable with different options including radiation therapy and/or systemic chemotherapy. However, in the majority of the patients, such trials were too late to reverse endocrine dysfunction which already exists. Thus, to ward off such undesirable situation, introducing early treatment in association with rapid diagnosis and with the CNS mass reduction as early as possible is essential [20]. However, a major obstacle associated with adult patients with LCH is that they are reluctant to take a long leave of absence from their jobs for examination/treatment. This often prevents the disease from being evaluated fully or being treated sufficiently with chemotherapy. Indeed, three of our patients only took one week off during their 4-week 2-CDA treatment. Given the adverse effects of 2-CDA, this limited treatment schedule forced us to give smaller 2-CDA doses (5 mg/day × 5 days a month). This may have been partly responsible for the limited responsiveness to 2-CDA that we observed. Nevertheless, the treatment still caused grade 2 adverse hepatic effects (two cases) and neutropenia and thrombocytopenia (one case). A rapid diagnosis and novel measures are needed to improve the outcome of adult-onset LCH-induced DI and hypopituitarism. For that purpose, future studies must clarify the preventive role of systemic treatment with respect to reversal of endocrine deficits with controlled prospective trials, although the numbers are too small that international collaboration is required on adult patients with LCH lesions at the HPR.

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ORIGINAL ARTICLE

Analysis of 43 cases of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus registered in the JLSG-96 and JLSG-02 studies in Japan

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Abstract To determine the ability of recent systemic chemotherapy protocols to reduce the incidence of central diabetes insipidus (CDI) in Langerhans cell histiocytosis (LCH), 43 CDI cases that belonged to a cohort of 348 pediatric patients with multi-focal LCH who were treated with the JLSG-96/-02 protocols were analyzed. The overall incidence of CDI was 12.4%, but in 24 cases CDI was already present at the time LCH was diagnosed. Thus, CDI developed during or after systemic chemotherapy over a follow-up period of 5.0 (0.2–14.7) years in only 19 patients (5.9%), with 7.4% at 5-year cumulative risk by Kaplan–Meier analysis. In two cases, complete resolution of CDI was noted. Anterior pituitary hormone deficiency was detected in 13 cases, while CDI-associated neurodegenerative disease was observed in six cases. The JLSG-96/-02 protocol appears to effectively reduce the occurrence of CDI. However, novel therapeutic measures are required to reverse pre-existing CDI and to prevent CDI-associated neurological complications.

Keywords Central diabetes insipidus · Langerhans cell histiocytosis · Anterior pituitary hormone dysfunction · Neurodegenerative disease

1 Introduction

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of cells with the phenotype of activated Langerhans cells. It is thought to be the major cause of central diabetes insipidus (CDI) in children. Although LCH develops most often at extra-cranial sites such as the skin, bones, and lymph nodes as a multi-focal disease, LCH lesions can also arise in the hypothalamic–pituitary region (HPR), which can induce arginine vasopressin (AVP) deficiency and trigger CDI [1, 2]. In early studies of LCH, CDI was reported in 15–50% of patients [3]. However, since the advent of modern systemic chemotherapy, CDI has been observed in 7–20% of patients [4]. Notably, CDI can develop before, concurrently with, or subsequent to the

For Japan LCH Study Group.

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diagnosis of LCH on the basis of various extra-cranial lesions; it can also arise during chemotherapy for systemic LCH or after therapy has concluded. Thus, it should be kept in mind that the aforementioned incidences of CDI represent all occurrences of CDI. To clarify whether a particular treatment regimen can prevent the development, or produce a resolution of CDI, it is necessary to perform an appropriately designed randomized prospective trial; however, due to small numbers of LCH patients, no such data are available to date. As an alternate way, a comparison could be made for the incidence of CDI that develops after chemotherapy or off therapy with those in previous reports.

In terms of LCH-induced CNS complications, it has been reported that an anterior pituitary hormone deficiency (APHD) may develop following CDI during life-long follow-up [3, 5, 6]. In addition, it has been reported that neurodegenerative (ND) disease can occur [7, 8].

The present study investigated whether the JLSG-96/-02 protocols for pediatric patients with multi-focal LCH in Japan can significantly reduce the incidence of LCH-induced CDI or related neurological complications by analyzing data obtained by these protocols that were performed in the last 14 years [9, 10]. To this end, the details of patients participating in these studies who developed LCH-induced CDI were analyzed retrospectively.

2 Patients and methods

The JLSG study was approved by the institutional review board of the Kyoto Prefectural University of Medicine, where the registration office is located. The study was performed in accordance with institutional ethical standards and the tenets of the Helsinki Declaration. In total, 348 multi-focal LCH cases including 222 multi-system (MS) disease and 126 cases of single system multi-focal (SS-m; 116 bone and 10 skin or lymph node) disease were studied. These included 91 and 257 cases that were registered in the 1996–2001 JLSG-96 study and the 2002–2009 JLSG-02 study, respectively. These treatment protocols involved essentially the same drug combinations (vincristine, cytosine arabinoside, prednisolone, methotrexate and 6-mercaptopurine), but the latter protocol differed from the earlier protocol in terms of a mild modification and by involving a longer treatment period (7.5 months as opposed to 12 months) [9, 10]. Continuing prospective data collection of the therapeutic results of the registered patients revealed that by March, 2010, CDI was found in a total of 43 patients, of whom 12 and 31 patients had been registered in the JLSG-96 and JLSG-02 studies, respectively, where diagnosis of CDI was made either by clinical features alone or by water deprivation test.

The median age of these 43 CDI patients at the time LCH was diagnosed was 2.6 (range 0.4–17.0) years, and the male/female ratio was 0.8. All of these patients had multi-focal LCH, of which 72% had cranio-facial bone lesions. The median follow-up period for all 348 LCH cases in the two studies was 5.0 (range 0.2–14.0) years, with the shortest follow-up of surviving patients being 0.8 years from the initiation of treatment.

The prospectively collected data sheets of the 43 CDI cases that were recorded during the follow-ups (6 weeks, 6 months and 1 year, and thereafter every year) were analyzed for the cumulative risk of CDI by the Kaplan–Meier method [11]. In addition, to clarify clinical features of CDI cases, the data from newly prepared CDI-oriented questionnaires that were sent to each physician-in-chief who was taking care of the LCH patients with CDI were analyzed in details including CDI-related neurological consequences. The questionnaires asked are summarized in Supplementary Table.

Complete and partial CDI were defined with modified criteria of Sands et al. [12]. The response of CDI to any type of chemotherapy was evaluated as complete remission (CR), namely no need for 1-deamino-8-D-arginine vasopressin (DDAVP) or normalization of MRI findings including recovery of the posterior bright spot; partial remission (PR), namely >50% reduction in DDAVP dosage or improvement in MRI findings with resolution of the stalk thickening; or no response (NR), namely persistent symptoms of polydipsia/polyuria with dependence on DDAVP. The diagnosis of ND disease was based on the criteria described by Wnorowski et al. [7]. Statistical analysis was performed with the Chi-square test. p values less than 0.05 were considered to be significant.

3 Results

3.1 Incidence of CDI

In all, CDI occurred in 12.4% (43/348), which consisted of 15.8% (35/222) in MS and 6.3% (8/126) in SS-m diseases ($p = 0.01$). Between JLSG-96 and JLSG-02 studies, the incidence of total CDI did not differ significantly (12/91 vs. 31/257; $p = 0.78$). Thus both studies were combined and analyzed. In 55.8% (24/43) of CDI cases, CDI was already detectable at the time LCH was diagnosed. The remaining 44.2% (19/43) developed after the initiation of treatment, with the overall incidence of late-onset CDI (namely, during chemotherapy or off therapy) was only 5.9% (19/348−24 = 324). The cumulative risk of CDI after treatment was estimated as 7.4% at 5 years and 12.8% at 10 years, respectively, with use of Kaplan–Meier method

Table 1 Incidence of CDI in LCH; Comparison of our data with historical data

Author (reference)	Cohorts	Incidence of CDI		
		Simple calculation/KM		
		Total (%)	At LCH Dx (%)	After treatment (%)
Dunger et al. ([1])	$N = 52$ (SS-m 20, MS 32)	28.8 (15/52)	13.3 (2/15)	26 (13/50)
				42 (KM 4 years)
Grois et al. ([3])[a]	$N = 199$ (SS-s 93, SS-m + MS 166)	9.5 (19/199)	42.1 (8/19)	5.8 (11/191)
				11 (KM 5.3 years)
Grois et al. ([4])[b]	$N = 1741$, Of which 1183 (SS-s 509, SS-m 154, MS 520) were studied for CDI after treatment	12 (212/1741)	48.1 (102/212)	9.3 (110/1183)
				16 (KM 5 years
				20 (KM 10 years)
Current study	$N = 348$ (SS-m 126, MS 222)	12.4 (43/348)	55.8 (24/43)	5.9 (19/324)
				7.4 (KM 5 years)
				12.8 (KM 10 years)

SS-s single system single site, *SS-m* single system multi-sites, *MS* multi-system, *Dx* diagnosis, *KM* Kaplan–Meier analysis

[a] DAL-HX83 study (1983–1993)

[b] DAL-HX83/90 + LCH-I + LCH-II studies

(Table 1; Fig. 1). Clinical features of the 43 CDI cases are summarized in Table 2.

3.2 Diagnosis of LCH/CDI

In all but three cases, LCH was diagnosed on the basis of biopsies of extra-cranial lesions. In remaining three cases in which CDI developed early as the only sign of LCH, the lesion at the HPR was biopsied. One of these cases was first diagnosed as low grade glioma, but a second biopsy performed 2 years later revealed it to be LCH. CDI was diagnosed in two-thirds of the cases by water deprivation/hyperosmolar salt loading tests. The plasma AVP and plasma osmolarity (pOSM) levels at onset were determined in 14 cases: the median AVP value was 0.45 (range <0.15–1.5) pg/ml and the median pOSM value was 285 (range 273–311) mOsm/kg H_2O.

3.3 Characteristics of CDI and treatment response

In terms of the MRI abnormalities that were noted at the onset of CDI, a thickened stalk was observed in 72.1% (31/43), while loss of a hot signal (T1-weighted MRI) in the pituitary posterior lobe was observed in at least 95.0% (41/43) and a hypothalamic mass was noted in 18.6% (8/43) of the cases, either on its own or in combination with the loss of the hot signal. All CDI patients except one received nasal DDAVP, most often at a dose of 5–10 μg. Although the JLSG-96/02 chemotherapy was largely effective for LCH at extra-cranial sites [9, 10], it was

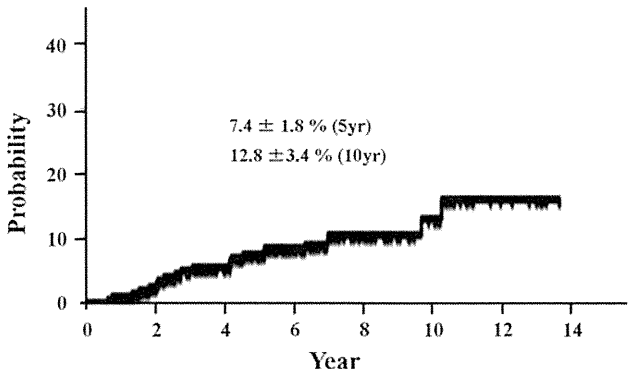

Fig. 1 Cumulative incidence and risk of CDI after treatment in 323 patients with multi-focal LCH disease, analyzed by Kaplan–Meier method

unable in the majority of cases to reverse CDI that was present before or at the time of the diagnosis of LCH: of these 25 cases, only two attained a CR (Table 3). It is worth commenting that both patients had partial CDI at the time LCH was diagnosed. One of these patients exhibited clinical improvement of CDI symptoms within 2 weeks of commencing the JLSG-96 protocol, prior to the introduction of DDAVP; this was associated with the normalization of the pituitary stalk thickening within 1.5 months of JLSG-96 treatment (figure not shown). The other case was first treated with JLSG-02 and then with 2-chlorodeoxyadenosine/cytosine arabinoside over a period of 2.8 years, which resulted in a CR along with the recovery of the hot signal in the posterior lobe after 3 years (Fig. 2). With regard to the late-onset CDI cases, where CDI arose during

Table 2 Clinical features of the 43 patients with LCH-induced CDI

	n
Diagnosis of CDI	
With laboratory test	26
Clinically	14
Unknown	3
Type of CDI at onset	
Complete	23
Partial	10
Unknown	10
Onset of CDI	
Early-onset CDI	24
(alone/with other sites)	(12/12)
Late-onset CDI	19
(during/off chemotherapy)	(6/13)
(alone/with other sites/unknown)	(6/12/1)
MRI findings at onset of CDI	
Thickened stalk	31
Loss of hot signal	41
Hypothalamic mass	8
No abnormal	1
No MRI	1
DDAVP (μg/day) for CDI	
<5	10
5–10	17
10–20	8
>20	3
Unknown	5
Effect of JLSG-96/02 on early-onset CDI	
CR	2
PR	3
NR	17
Unknown[a]	3
Effect of Rx on late-onset CDI	
CR/PR	0/1
NR	14
Un-evaluable	1
Unknown[a]	2
APHD	
Yes	13
No	30
Pattern of APHD	
GH	10
TSH	6
LH–FSH	3
ACTH	3
Neurodegenerative disease (ND)	
Yes	6
No	36
Unknown	1

CDI central diabetes insipidus, *Rx* treatments consisting of various chemotherapies, including JLSG96/02 and 2-chlorodeoxyadenosine, *APHD*, anterior pituitary hormone deficiency, *DDAVP* 1-deamino-8-D-arginine vasopressin, *GH* growth hormone, *TSH* thyroid stimulating hormone, *LH–FSH* luteinizing hormone–follicle stimulating hormone, *ACTH* adrenocorticotropic hormone

[a] Treatment response data were not obtained from all cases

($n = 5$) or after therapy ($n = 13$), none attained a CR. In particular, the patients who developed CDI during the treatment were reported to be non-responsive to chemotherapy, including to 2-chlorodeoxyadenosine ($n = 2$) and the C protocol of JLSG-96/02 ($n = 2$), except for a patient who showed a PR after the treatment with 2-chlorodeoxyadenosine, as shown in Fig. 3. In this series, none of the patients received irradiation to the HPR.

3.4 APHD and ND disease

Of the 43 CDI cases, APHD was noted in 13 cases (incidence, 30.2%). Ten exhibited GH deficiency, six had TSH deficiency, three were LH–FSH deficient and three showed ACTH-deficiency. Five cases already had APHD at the onset of CDI and seven developed APHD after CDI. In the remaining case, it was unclear whether CDI preceded APHD or vice versa. Six patients (incidence among CDI cases, 14%) were diagnosed with ND disease, five on the basis of clinical signs and symptoms and one on the basis of MRI findings alone. Three of these cases developed ND disease and CDI at the same time, while the remaining three developed ND disease 19 months, 3 and 4 years after CDI, respectively.

4 Discussion

The main purpose of this study was to determine whether the JLSG-96/-02 protocols significantly reduce LCH-induced CDI and other neurological complications. For this, the data of patients with LCH-induced CDI who participated in the JLSG-96/-02 studies were analyzed. Systemic chemotherapy or radiation therapy has long been tried to generate a CR or to prevent LCH-induced CDI [1, 5, 13–15, 18]. Unfortunately, it appears that, at present, CDI is generally irreversible once it is established, probably because the damage to the HPR occurs early in the disease and, by the time an MRI lesion is noted, it is too late to reverse the process. Supporting this is that at the time of CDI diagnosis, approximately 70% of cases exhibit

Table 3 Cases that attained a complete response of CDI

Cases	ID	Age (years) at onset/ gender	Features of LCH at onset	Time CDI was detected	Type of CDI (AVP/pOSM)[a]	MRI at onset (follow-up)	Rx	Duration (months) of CDI
1	96–122	2.2/M	Skin, skull, orbita, rib, lung lesions, and CDI	At LCH onset	Partial (0.6/280)	Thickened stalk and loss of hot spot (improved)	JLSG-96	<1.5
2	02–241	1.1/F	Skin, skull, LS/S/BM/GI, oral mass lesions, and CDI	At LCH onset	Partial (1.0/282)	Loss of hot spot (improved)	JLSG-2002 2CDA + AraC	37

Rx treatment, *CDI* central diabetes insipidus, *LS/BM/GI* liver/spleen/bone marrow/gastrointestinal tract, *2CDA* 2-chlorodeoxyadenosine, *AraC* cytosine arabinoside

[a] Units of AVP = pg/ml, units of pOSM (plasma osmolarity) = mOsm/kg H_2O

a thickened stalk on MRI [13]. Indeed, a thickened stalk was demonstrated in 72.1% of the cases in the present study. On the other hand, there still exists an important question if the early introduction of recent systemic chemotherapy for LCH can prevent the new development of CDI. In the present study, the data of 43 patients with LCH-related CDI were analyzed. The overall incidence of CDI was 12.4% over a median of 5.0 years of follow-up.

The total incidence, incidence of CDI at the diagnosis of LCH and that after treatment are compared with previous publications in Table 1. Particularly, the incidence of CDI after therapy was compared by simple calculation and/or Kaplan–Meier analysis. As can be seen, the largest cohort study by Grois et al. [4] showed that it was 9.3%, with 16 and 20% cumulative risk at 5 and 10 years after treatment, respectively. By contrast, our data showed a lower incidence in which it was 5.9%, with 7.4 and 12.8% cumulative risk at 5 and 10 years, respectively. This supports the notion that our systemic chemotherapy protocol effectively reduces the incidence of CDI.

Historically, LCH-induced CDI was treated by irradiation [5]. However, in view of the risk of radiation-related late effects, irradiation has not recently been generally recommended as the treatment of choice for CDI, particularly in children [3, 13, 15]. Thus, a question arises if early introduction of systemic chemotherapy may reverse newly onset as well as once established CDI. Regarding reversibility of CDI, one study found that, without irradiation, established CDI was not reversed or ameliorated by any treatment [3], however, anecdotal cases of the regression of CDI after chemotherapy with etoposide or 2-chlorodeoxyadenosine have been reported [16, 17]. In this study, we also noted that two of the 25 CDI cases obtained a CR after treatment (Table 3), of which one was reversed rapidly and the other after 37 months of treatment. Unfortunately, few cases of PR were reported in our study, which may reflect the lack of repeat MRI studies. To improve the frequency of PR/CR in CDI, it is critical that the response to chemotherapy is evaluated precisely. To this end, it is important to perform repeat MRI studies and confirm the recovery of posterior lobe bright spot [13].

In the present series, the incidences of APHD (30.2%) and ND disease (14%) in CDI cases were also lower than the respective incidences of 58 and 32% that were reported previously [13]. This is probably due in part to effective chemotherapy. However, it is possible that these incidences may become higher if the follow-up period of our series is much longer than the current median 5 years. In terms of ND disease, our previous analysis of patients with LCH-induced ND disease revealed that only half had CDI [19]. Thus, the six ND disease cases that were detected here in association with CDI do not account for all neurologically impaired cases in the cohorts of the JLSG-96/-02 studies [20].

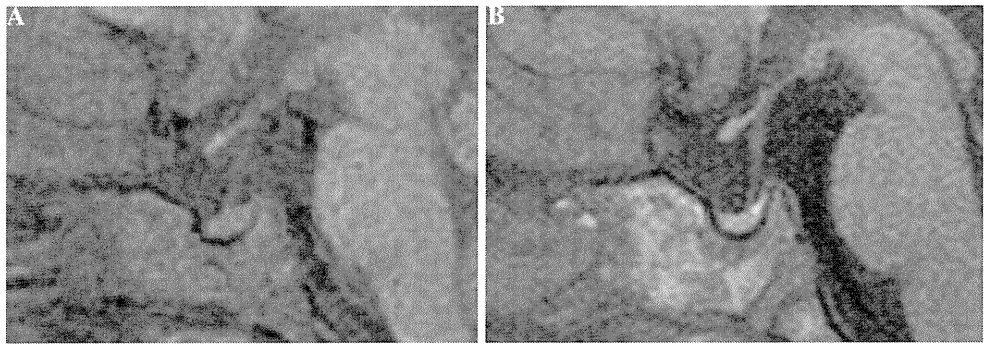

Fig. 2 MRI (T1-weighted) findings, in a patient who had CDI at the time LCH was diagnosed and attained a CR on chemotherapy. **a** Pre-therapy and **b** post-therapy. In **b**, a high signal at the posterior lobe can be seen clearly

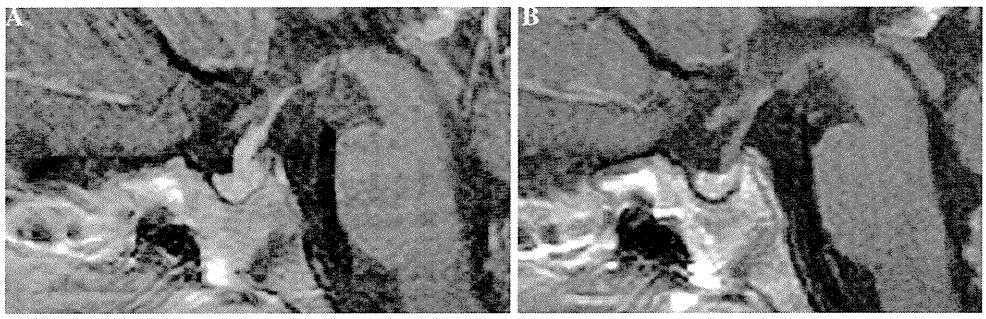

Fig. 3 MRI (T1-weighted with Gadolinium enhancement) findings, in a patient who attained a PR (the thinning of the pituitary stalk), with 2-chlorodeoxyadenosine treatment. **a** Pre-therapy and **b** post-therapy

The present observations indicate that the rapid diagnosis of CDI and the prompt institution of systemic chemotherapy are needed to further lower the incidence of CDI and to generate CR more frequently. It should be kept in mind that patients with multi-system LCH lesions on the craniofacial bones are at high risk of CDI [1, 3–5, 10, 13]. Once CDI develops, it becomes rapidly irreversible in most patients, who will then need life-long DDAVP treatment. Thus, to better control CDI as well as to reverse it, CDI should be diagnosed as early as possible on the basis of suspicious symptoms of polyuria/polydipsia and with the assistance of brain MRI [13]. In addition, novel measures that may prevent the progression of LCH-induced CDI to APHD as well as to ND disease should be explored.

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Conflict of interest The authors declare no financial conflicts of interest.

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