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].

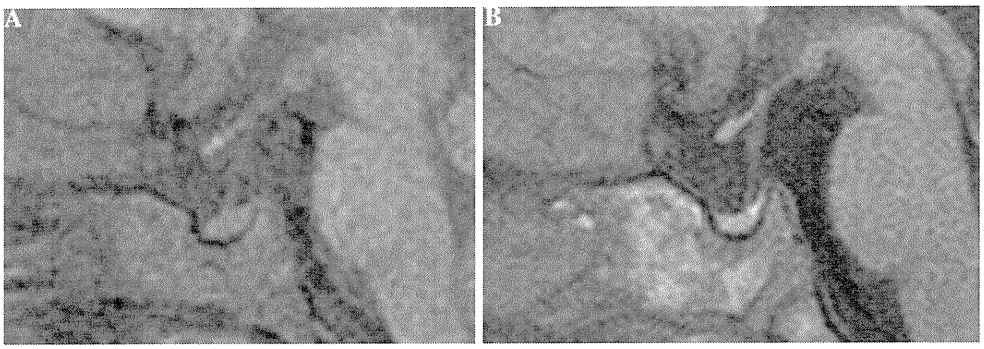

Fig. 2 MRI (T1-weighted) findings, in a patient who had CDI at the time LCH was diagnosed and attained a CR on chemotherapy. **a** Pre-therapy and **b** post-therapy. In **b**, a high signal at the posterior lobe can be seen clearly

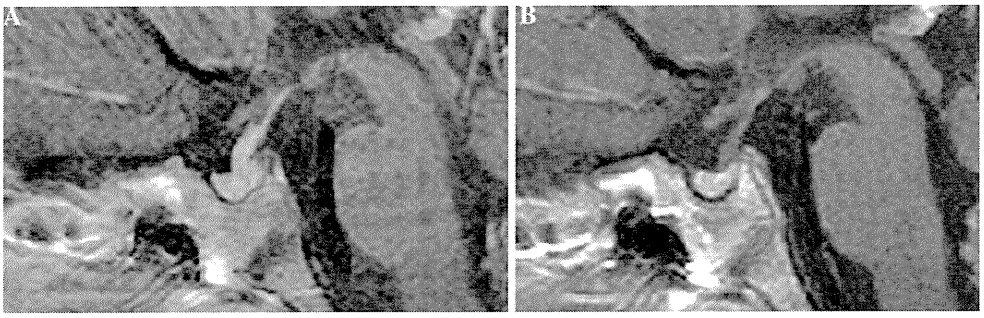

Fig. 3 MRI (T1-weighted with Gadolinium enhancement) findings, in a patient who attained a PR (the thinning of the pituitary stalk), with 2-chlorodeoxyadenosine treatment. **a** Pre-therapy and **b** post-therapy

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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