

### Lymphocytic infundibuloneurohypophysitis with positive anti-rabphilin-3A antibodies nine years post-onset of central diabetes insipidus

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**Abstract.** Childhood-onset lymphocytic infundibuloneurohypophysitis (LINH) due to infiltration of autoimmune lymphocyte in the neurohypophysis is rarely reported. Its definitive diagnosis requires a pituitary biopsy, which is an invasive procedure. Recently, anti-rabphilin-3A antibody has been reported as a potential diagnostic marker for LINH in adults; however, only a few cases have been reported in children. Here, we present a case of childhood-onset LINH in a 10-yr-old boy identified as anti-rabphilin-3A antibody positive during chronic phase, 9 yr post-onset of central diabetes insipidus (CDI). T1-weighted magnetic resonance imaging (MRI) revealed pituitary stalk thickening and absence of posterior pituitary bright signal spot, and the hormonal responses of the adenohypophysis to GHRH, TRH, CRH, and LHRH revealed no abnormalities during the first admission. MRI at 5 mo post-onset indicated reduced stalk swelling; however, replacement treatment with intranasal desmopressin was continued to counter unimproved CDI. Additionally, GH replacement therapy was also initiated to counter its deficiency. Pituitary re-enlargement was not observed in the subsequent routine MRI, and no increase was observed in the levels of tumor markers during follow-up, which was considered clinically consistent with LINH. Our case study suggests that anti-rabphilin-3A antibody may be considered as a useful diagnostic marker for LINH in children.

**Key words:** autoimmune hypophysitis, neurohypophysis, diabetes insipidus, GH, rabphilin-3A

#### Introduction

Pituitary inflammation may occur in the primary (lymphocytic, granulomatous, and xanthomatous) or secondary (tumors or drug-induced) hypophysitis (1). Lymphocytic hypophysitis caused by the infiltration of autoimmune lymphocytes leads to adenohypophysis and/or neurohypophysis hypofunction.

Patients with lymphocytic infundibuloneurohypophysitis (LINH) having posterior pituitary lesions often present with central diabetes insipidus (CDI) at onset, and T1-weighted magnetic resonance imaging (MRI) reveals the absence of posterior pituitary bright signal spot and enlarged pituitary stalk. CDI may be permanent; although pituitary stalk swelling is reduced over time. It is rarer in children than

in adults; therefore, its effective treatment and long-term prognosis in children are unclear. As LINH is intended to be differentiated from secondary hypophysitis such as tumors, the detection of anti-rabphilin-3A antibody has been reported as a useful noninvasive method (2, 3). However, reports on the usefulness of anti-rabphilin-3A antibodies for the diagnosis of LINH in pediatric population are limited. Here, we report a case study in which the patient developed LINH at the age of 10, and was identified as anti-rabphilin-3A antibody-positive during the chronic phase 9 yr post-onset.

#### Case Report

A 10-yr-old boy presented to our institute with nocturia, thirst, and polyurea (> 5000 mL/d). His height

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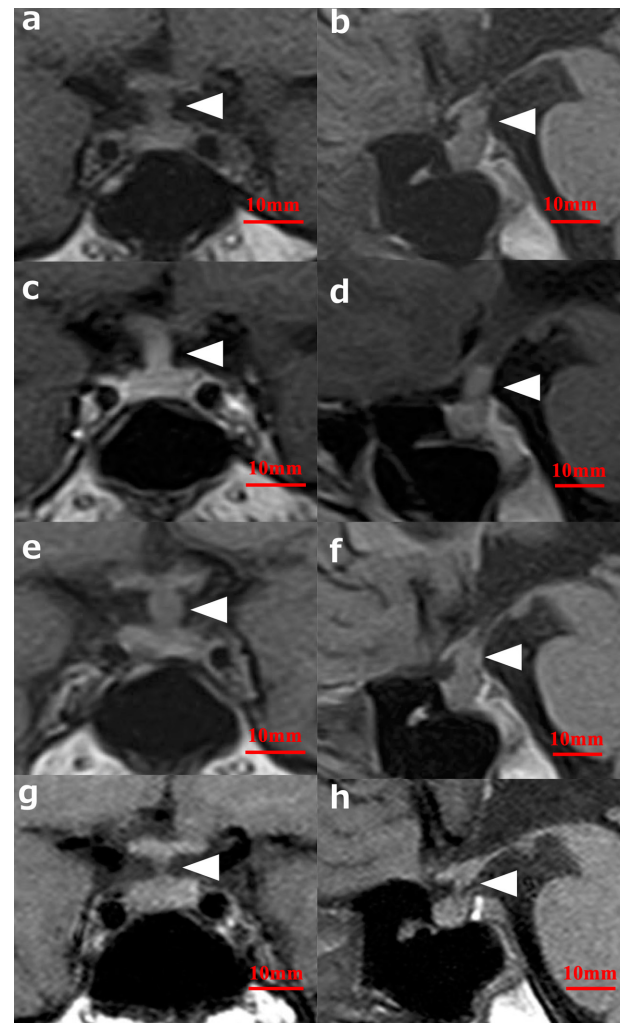


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and weight were 136 cm (standard deviation [SD],  $-0.7$ ) and 28.4 kg ( $-1.0$  SD), respectively. He had no problem in growth until then and reported no headache or visual disturbance during the first visit. He was exhausted because of sleep disorders and increasing thirst as a result of nocturia and polyuria. Blood count and serum chemistry profile were normal; plasma arginine vasopressin level was 0.4 pg/mL at serum sodium level of 144 mEq/L. Plasma osmolality, urinary osmolality, and urine relative density were measured to be 289 mOsm/L, 76 mOsm/L, and less than 1.005 respectively, thereby indicating polyuria and impaired urinary concentrating ability. T1-weighted pituitary MRI revealed absence of high-intensity signal from the neurohypophysis and a diffuse enlargement of the pituitary stalk (Figs. 1a, 1b). Contrast-enhanced MRI revealed a uniform contrasting effect of the adenohypophysis and the stalk (Figs. 1c, 1d). Based on the MRI findings, CDI secondary to pituitary lesions was suspected. Because of life-threatening effects of severe dehydration, treatment with intranasal desmopressin administration was initiated from day 3 of diagnosis, without a water deprivation test and hypertonic saline infusion test. As a result, increase in urine osmolality ( $>3\ 00$  mOsm/L) and decrease in daily urine volume ( $<3\ 000$  mL/d) were observed in routine urinalysis; therefore, the case was clinically diagnosed as CDI. The hormonal responses of the anterior pituitary gland to GHRH, TRH, CRH, and LHRH revealed no abnormalities (Table 1). Serum alpha-fetoprotein (AFP) and serum beta-human CG ( $\beta$ -hCG) test, and tuberculin reaction were negative. IgG (1022 mg/dL), IgG4 (15 mg/dL), and angiotensin-converting enzyme (8.4 IU/mL) were within the normal range. Anti-pituitary, antinuclear, anti-mitochondrial, anti-smooth muscle antibodies, and MPO-ANCA and PR3-ANCA were measured during first admission and all test results were found negative. Gallium scintigraphy revealed absence of distant metastasis and systemic granulomatosis; ophthalmic and dermatology examination results were negative for sarcoidosis and Langerhans cell histiocytosis. Although pituitary biopsy could not be performed because written informed consent was not obtained, clinical symptoms and imaging findings were consistent with those of LINH. Prednisolone (1 mg/kg/d) was administered from day 10 for the treatment of LINH; its concentration reduced by 0.25 mg/kg every 2 wk. Urine volume and urine osmolality were controlled after increasing the dose of desmopressin to 15  $\mu$ g daily, and the patient was discharged on day 20 (Fig. 2). Two months later, the pituitary MRI revealed enlargement of the pituitary stalk (Figs. 1e, 1f); however, it was temporary as the pituitary MRI at 5 mo post-onset showed reduced swelling. The pituitary stalk swelling was further reduced at 12 mo post-onset. Three years after the onset, the pituitary stalk nearly returned to its normal size, as revealed by contrast-enhanced MRI. (Figs. 1g, 1h). Replacement treatment with desmopressin was continued to counter unimproved CDI. During follow-up examination, the tumor markers levels

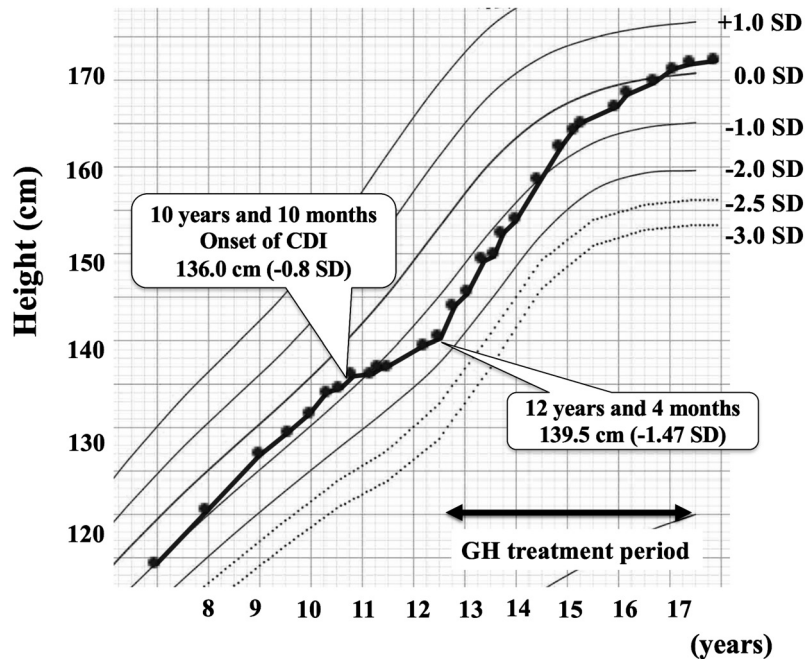


**Fig. 1.** Changes in magnetic resonance imaging (MRI) findings over time. (a, b) T1-weighted MRI images at the onset of central diabetes insipidus (CDI), showing no high-intensity signal for the posterior lobe and a diffuse enlargement of the pituitary stalk (arrowheads). The width of the stalk is 6.3 mm for coronal section and 5.3 mm for sagittal section. (c, d) Contrast-enhanced T1-weighted MRI images at the onset of CDI, showing uniform contrasting effect of the anterior pituitary and the stalk (arrowheads). The width of the stalk is 6.3 mm for coronal section and 5.2 mm for sagittal section. (e, f) T1-weighted MRI images at 2 mo post-onset, showing diffuse enlargement of the pituitary stalk (arrowheads). The width of the stalk is 6.9 mm for coronal section and 5.8 mm for sagittal section. (g, h) Contrast-enhanced T1-weighted MRI images at 3 yr post-onset, showing reduced pituitary stalk swelling (arrowheads). (a, c, e, g) Sagittal section, (b, d, f, h) coronal section.

were not elevated. The patient's yearly growth rate was  $<-1.5$  SD for 2 yr; therefore, an arginine stimulation test was performed at 1 yr and 6 mo post-onset (at the age of 12 yr and 4 mo). The peak level of GH was low (3.22 ng/mL); therefore, the patient was diagnosed with GH deficiency and GH replacement therapy was initiated. At the age of 13 yr and 7–10 mo, the findings suggested

**Table 1.** Results of the hormonal responses of the anterior pituitary gland to GHRH, TRH, CRH, and LHRH

Loading hormones	Adenohypophyseal hormones	Basal value	Peak value
GHRH	GH (ng/mL)	0.15	13.76
TRH	TSH ( $\mu$ IU/mL)	2.58	12.84
	PRL (ng/mL)	12.8	42.5
CRH	ACTH (pg/mL)	13.0	48.1
	Cortisol ( $\mu$ g/dL)	5.9	15
LHRH	LH (mIU/mL)	< 0.1	1.9
	FSH (mIU/mL)	0.1	0.6



**Fig. 2.** Growth curve showing growth rate of the patient.

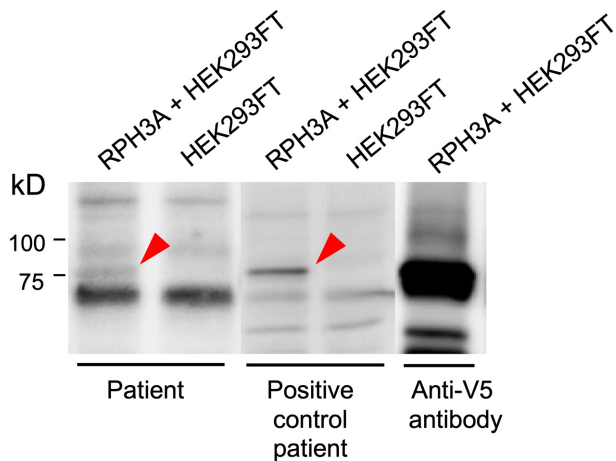
pubertal development in the patient, including testicular enlargement (> 4 mL), Tanner Stage II external genitals, and elevated serum testosterone level (149.5 ng/dL). His height improved to 166.1 cm (−0.5 SD) at the age of 15 yr and 9 mo (Fig. 2). During follow-up examination, no abnormality was observed in other pituitary hormones. At the age of 17 yr and 4 mo, the bone age was judged as “adult”, and therefore GH treatment was discontinued. Arginine stimulation test was performed 2 mo after the cessation of medication; the peak GH value was 8.08 ng/mL. Therefore, GH treatment was not continued for adult GH deficiency.

The latest MRI (at the age of 19 yr and 6 mo) revealed no pituitary re-enlargement; however, desmopressin was continued to counter CDI. At the age of 19 yr, the patient was found positive for the presence of anti-rabphilin-3A antibody (Fig. 3), which is a potential marker in the diagnosis of LINH (2). The serum of a patient previously diagnosed with LINH by biopsy and other investigations, was labeled as positive control (4) (Fig. 3). Presently, he has no evidence of any abnormality, including a pituitary tumor.

## Discussion

We present a case of LINH diagnosed without a pituitary biopsy, based on the development of CDI, the pituitary MRI findings, and the clinical course. Follow-up pituitary MRI revealed absence of pituitary re-enlargement, and the levels of tumor markers, including AFP and HCG $\beta$ , were not elevated in 9 yr. Furthermore, the presence of anti-rabphilin-3A antibody found 9 yr post-onset of CDI suggested LINH.

Lymphocytic hypophysitis is classified into lymphocytic adenohypophysitis (LAH), LINH, and lymphocytic panhypophysitis (LPH) based on the location of the pituitary inflammation and clinical symptoms (5). Lymphocytic hypophysitis occurs more frequently in adult pregnant women (sex ratio approximately 3:1) (1, 3). A literature review by Vellener Gellner et al. showed a slightly higher proportion of girls (56%, 14/25), being diagnosed with childhood-onset lymphocytic hypophysitis at a median age of 12 yr, and included three cases associated with pregnancy. Histological diagnosis prediction was 56% (14/25) (6).



**Fig. 3.** Detection of anti-rabphilin-3A antibody by western blotting. Recombinant full-length human rabphilin-3A (RPH3A, left lanes) expressed in the HEK293FT cells or the total cell lysate from the HEK293FT cells transfected with an empty vector (HEK293FT, right lanes) was probed with the serum of the present patient and a lymphocytic infundibuloneurohypophysitis (LINH) patient diagnosed previously (positive control patient). The arrowhead indicates the presence of anti-rabphilin-3A antibody. Recombinant full-length human rabphilin-3A expressed in the HEK293FT cells was also probed with an anti-V5 antibody as positive control (Anti-V5 antibody).

GH deficiency was observed in 76% of the patients diagnosed with lymphocytic hypophysitis and was often associated with LINH (7). The clinical features of LINH in children are still unclear. We searched for studies that used the Japan Medical Abstracts Society Online Database “Ichushi Web”, and found 7 case reports and 34 conference proceedings in Japan, which included 35 cases of childhood-onset lymphocytic hypophysitis, excluding duplicates. The average age of 33 patients, whom age and sex were known, was 7.2 yr, and the number of boys was slightly higher than of girls (57.5%, 19/33) (8, 9). Only three patients underwent biopsy due to progressive swelling of the pituitary stalk and for differential diagnosis. The parameters associated with anterior pituitary hormone deficiency were GH deficiency, GH and TSH deficiencies, and GH, TSH, LH and FSH deficiencies in 9, 1, and 2 cases, respectively.

The effects of lymphocytic hypophysitis treatment remain controversial. Although pituitary stalk swelling may resolve spontaneously, symptomatic patients with severe headache and optic nerve compression may require treatment with steroids, immunosuppressants, and biologicals (9–12). The present case was also administered steroids for early improvement of the pituitary stalk swelling and CDI. Nevertheless, the improvement of pituitary stalk swelling was gradual and CDI persisted.

As the etiology of pituitary stalk thickening is diverse (13), nasal pituitary biopsy is required for the

definitive diagnosis of lymphocytic hypophysitis to differentiate it from tumor (germinoma, adenoma, and craniopharyngioma), granulomatosis, and Rathke cleft cyst. Some patients were diagnosed with germinoma after the clinical diagnosis of lymphocytic hypophysitis (14, 15); however, it is often difficult to determine whether to perform a pituitary biopsy, which is an invasive procedure, considering the potential for spontaneous regression of the pituitary stalk swelling (1).

Our case was clinically diagnosed without biopsy; therefore, the patient needed to be monitored for the possible presence of germinoma. Follow-up MRI revealed absence of tumor for a long time and relapse of pituitary swelling after steroid administration, indicating a high possibility of LINH. Recently, anti-rabphilin-3A antibody has been reported as a beneficial marker for LINH in adults; however, the usefulness of anti-rabphilin-3A antibody for LINH diagnosis at the onset has not yet been reported. Rabphilin-3A antibody was expressed in neurohypophysis and hypothalamic vasopressin neurons excluding adenohypophysis. Anti-rabphilin-3A antibodies were detected in all the four patients with histologically confirmed LINH (sensitivity 100%) and in 22 of 29 patients with LINH (sensitivity, 76%), including those clinically diagnosed. In addition, none of the 34 patients with sellar or parasellar masses were positive for anti-rabphilin-3A antibody (specificity, 100%). However, there were anti-rabphilin-3A antibody-positive cases in healthy control samples (12.2%, 5 of 41), and the usefulness of LINH diagnosis in pediatric population and others needs further investigation (2).

The limitation of the present case study was that the anti-rabphilin-3A antibody could not be observed in the sample at the time of onset. However, considering that the patient was positive for anti-rabphilin-3A antibody in the chronic phase (without tumor findings, including germinoma) 9 yr after the onset of CDI, this case study supported rabphilin-3A as the main autoantigen even in childhood-onset LINH. Anti-rabphilin-3A antibody may serve as a useful diagnostic marker for childhood-onset LINH. Establishing a serological diagnostic method that does not require biopsy for LINH, would reduce the mental and the physical burden on patients and their families.

In conclusion, we present a rare case of childhood-onset LINH diagnosed with anti-rabphilin-3A antibody 9 yr post-onset of CDI. Our case study suggests anti-rabphilin-3A antibody as a diagnostic marker for childhood-onset LINH that can be used without performing an invasive procedure.

**Informed Consent:** Verbal informed consent was obtained from the patient for this article and has been recorded in the medical chart.

**Potential Conflict of Interest:** The authors have nothing to declare.

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