

Case report

Lymphocytic Infundibuloneurohypophysitis Diagnosis Owing to Positive Anti-rabphilin-3A Antibody Test Result in an 8-year-old Boy with Early-onset Central Diabetes Insipidus

Short title: RPH3A-Ab+ CDI Child Diagnosed with LINH

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What is already known on this topic?

Recently, anti-rabphilin-3A antibodies have emerged as a promising diagnostic marker for lymphocytic infundibuloneurohypophysitis in adults; however, few such reports exist for the pediatric population.

What this study adds?

We report the case of an 8-year-old boy with central diabetes insipidus diagnosed with lymphocytic infundibuloneurohypophysitis based on anti-rabphilin-3A antibody positivity. Our case study illustrates the potential of anti-rabphilin-3A antibodies as an early diagnostic marker for pediatric-onset lymphocytic infundibuloneurohypophysitis.

Abstract

Childhood-onset lymphocytic infundibuloneurohypophysitis (LINH) has rarely been reported. Pathological evaluation via pituitary biopsy is necessary for a definitive diagnosis of LINH. However, pituitary biopsy is a highly invasive procedure. Recently, anti-rabphilin-3A antibody (RPH3A-Ab) has been reported as a promising diagnostic marker for LINH in adults; however, there are few such reports in the pediatric population. We report the case of an 8-year-old boy with central diabetes insipidus (CDI) who was clinically diagnosed with LINH based on RPH3A-Ab positivity. He was diagnosed with CDI using a water deprivation test combined with desmopressin administration. Serum and cerebrospinal fluid tumor markers were negative, and T1-weighted magnetic resonance imaging (MRI) revealed the absence of high signal intensity in the posterior pituitary gland and an enlarged pituitary stalk. Anterior pituitary function tests revealed no abnormalities. No pituitary biopsy was performed because of its invasive nature, and desmopressin treatment was initiated. Three months after CDI onset, the patient tested positive for RPH3A-Ab. MRI performed 9 months after CDI onset revealed amelioration of the pituitary stalk enlargement, and the clinical course corroborated our diagnosis of LINH. RPH3A-Ab may be useful as an early diagnostic tool for LINH in the pediatric population.

Keywords: Central diabetes insipidus, lymphocytic infundibuloneurohypophysitis, rabphilin-3A antibody, lymphocytic hypophysitis, pituitary

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Introduction

Central diabetes insipidus (CDI) may occur in children and adolescents in the absence of a known underlying disease (idiopathic), or with inflammatory/autoimmune conditions (lymphocytic hypophysitis and immunoglobulin G4 [IgG4]-related diseases), Langerhans cell histiocytosis (LCH), intracranial germ cell tumors (GCTs), infectious and vascular diseases, trauma resulting from surgery or an accident, and, rarely, metastasis. (1) Lymphocytic hypophysitis is classified into lymphocytic adenohypophysitis, lymphocytic infundibuloneurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH), based on the site of involvement and clinical symptoms. (2)

Magnetic resonance imaging (MRI) of a patient with CDI often reveals an absence of high signal intensity of the posterior pituitary gland and an enlarged pituitary stalk. The most common causes of an enlarged pituitary stalk in children are GCTs, LCH, and LINH.

(3)

Serum alpha-fetoprotein (AFP), human chorionic gonadotropin beta (HCG-beta), and placental alkaline phosphatase (PLAP) concentrations have been shown to be useful in the diagnosis of GCTs. (4) Imaging studies, including head MRI and computed tomography (CT), should be performed when LCH is suspected. These tests are important for the differential diagnosis of children with CDI, whereas pituitary biopsy plays an important role in the definitive and pathological diagnosis of these conditions.

Serum rabphilin-3A antibody (RPH3A-Ab) testing has been reported as a useful noninvasive method for the diagnosis of LINH.

(5) However, to the best of our knowledge, there are few reports on the use of RPH3A-Ab in the pediatric population. (6-8) Here, we report a case in which a patient with CDI was clinically diagnosed with LINH using RPH3A-Ab testing shortly after CDI onset.

Case report

Our patient, an 8-year-old boy, had a 2-month history of polyuria and polydipsia. Two years before admission, his urine specific gravity was >1.030, and his frequency of urination was 3–4 times a day.

Two months prior to admission, he experienced polydipsia (2–4 L/day) and frequent urination at night. He was referred to our

hospital for further investigation and treatment of persistent polyuria.

Upon initial examination, no headaches or visual field defects were observed. The patient had no history of head injury. His mother and maternal grandmother had a history of aldosteronism.

The patient's height and weight were 121.5 cm (standard deviation [SD], -1.5) and 22 kg (-0.8), respectively. His blood count and serum chemistry profile were normal: serum sodium concentration, 140 mEq/L and plasma arginine vasopressin (AVP) concentration, 0.5 pg/mL. His plasma osmolality, urinary osmolality, and urine relative density were 282 mOsm/kg, 47 mOsm/L, and 1.002, respectively. Urine test results were negative for glucosuria and pyuria.

A water deprivation test revealed a maximum urine osmolality of 128 mOsm/kg, with a low AVP concentration, even though the plasma osmolality increased to 290 mOsm/kg. Two hours after administration of subcutaneous desmopressin, the patient's urine osmolality increased to 499 mOsm/kg, and a diagnosis of CDI was made.

T1-weighted MRI revealed the absence of high signal intensity of the neurohypophysis and diffuse enlargement of the pituitary stalk (Fig. 1). Contrast-enhanced MRI revealed a uniform contrast effect in the pituitary gland.

Anterior pituitary function tests revealed no abnormalities. Tumor markers specific to GCTs were not elevated: the patient's serum AFP concentration was 2 ng/mL (normal range: 0–7 ng/mL), his serum carcinoembryonic antigen concentration was 2 ng/mL (normal range: 0–5 ng/mL), and both HCG- β and PLAP antibody tests on the cerebrospinal fluid were negative. IgG4 concentrations were not elevated. The myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA), proteinase 3-ANCA, and T-SPOT test results were negative. ^{99m}Tc scintigraphy revealed no abnormal accumulations suggestive of LCH. Three months after the onset of CDI, the patient tested positive for RPH3A-Ab, a potential marker for the diagnosis of LINH (Fig. 2).

Based on the above results, we diagnosed the patient with LINH. We did not perform a pituitary biopsy because of its highly invasive nature; rather, we planned to closely observe the patient. He was treated with desmopressin, and his polyuria and polydipsia improved. Considering the possibility of a tumor, no steroid therapy was administered. Nine months after CDI onset, brain MRI revealed shrinking of the enlarged pituitary stalk (Fig. 3) and no elevation in tumor markers was found. The patient was not exposed to radiation, including via a CT scan, during the course of the disease. His CDI symptoms persisted after shrinking of the enlarged pituitary stalk.

Discussion

We presented a case of a patient with CDI who tested positive for RPH3A-Ab 3 months after onset of the disease. His anterior pituitary hormonal function and tumor markers were normal. Follow-up pituitary MRI revealed amelioration of the pituitary enlargement, and RPH3A-Ab positivity indicated a diagnosis of LINH.

Pituitary biopsy is required for the definitive diagnosis of LINH; however, its high degree of invasiveness is problematic. Recently, RPH3A-Ab was reported as a noninvasive diagnostic marker of LINH in adults. However, its use in the diagnosis of LINH at the onset has not been clarified.

RPH3A is expressed in the posterior pituitary gland and supraoptic nucleus of the hypothalamus, where AVP-expressing neuronal cell bodies are located, but rarely in the anterior pituitary gland. RPH3A-Ag has been reported as a pathogenic antigen in which T cells specific for RPH3A are involved in the pathogenesis of neurohypophysis. (5)

Measurement of RPH3A-Ab in serum was performed as follows, at the Fujita Health University. A vector containing the full-length human rabphilin 3A gene was transfected into HEK293FT cells to produce a recombinant human rabphilin-3A protein. As a control,

the same vector but without the rabphilin 3A gene was transfected into HEK293FT cells. RPH3A-Ab in the serum was detected by Western blotting using the recombinant human rabphilin-3A protein lysate as the antigen and the serum as the primary antibody. A protein band of 76 kDa appeared in the lysate of cells transfected with rabphilin-3A protein but not in that of control cells, which was considered to be positive for RPH3A-Ab, as reported previously. (9)

Murai et al. reported the sensitivity and specificity of RPH3A-Ab in pituitary diseases. Sensitivity was 100%, 11.1%, and 80.0% for LINH, LAH, and LPH, respectively. The overall specificity of the sellar/suprasellar mass was 97.4%. (10) Moreover, Iwama et al. reported that RPH3A-Ab was detected in 5 of 41 samples from healthy control subjects (sensitivity, 88%). (9) Therefore, RPH3A-Ab could be useful to diagnose LINH.

We are aware of only three case reports of RPH3A-Ab positivity in pediatric patients with CDI. (6-8) The patients tested positive for RPH3A-Ab 6 months, 8 months, and 9 years after CDI onset. All of them had growth hormone deficiency, which is suggestive of LPH. In our case, the patient tested positive for RPH3A-Ab 3 months after CDI onset.

To our knowledge, this is the first report of a pediatric patient with LINH who tested positive for RPH3A-Ab so soon after CDI onset. In our case, RPH3A-Ab testing during the early stages of CDI led to a diagnosis of LINH. However, we could not rule out other causes of CDI as pituitary biopsy was not performed. There is no strong evidence to support the utility of glucocorticoids as first line LINH treatment, however, the use of glucocorticoids has been associated with complete disease regression in some cases. (11) Early diagnosis of LINH leads to fewer invasive investigations and may result in early treatment to improve prognosis.

The cause of shrinking of the enlarged pituitary stalk is unclear. The inflammatory process in LINH can be self-limiting, and radiologic follow-up can show regression. CDI in patients with LINH may be permanent, likely due to neuronal destruction. (12) The management and follow-up of LINH requires repetitive MRI scans every 6 months. (11) A previous study reported the case of a patient who was diagnosed with LINH by pituitary biopsy, however, the pituitary stalk swelled, the tumor markers increased, and the patient was ultimately diagnosed with GCT. (13) Pituitary biopsy should be considered if tumor markers are elevated and pituitary stalk swelling does not improve. In addition, as there is a possibility that hypopituitarism may occur, we intend to perform hormonal assessment.

Conclusion

We presented the case of an 8-year-old boy diagnosed with LINH owing to serum RPH3A-Ab positivity, 3 months post-CDI onset. His clinical course was in line with such a diagnosis. Our case study illustrates the potential of RPH3A-Ab as an early diagnostic marker for pediatric-onset LINH. This needs to be validated with more cases in the future. This needs to be confirmed with more cases in the future.

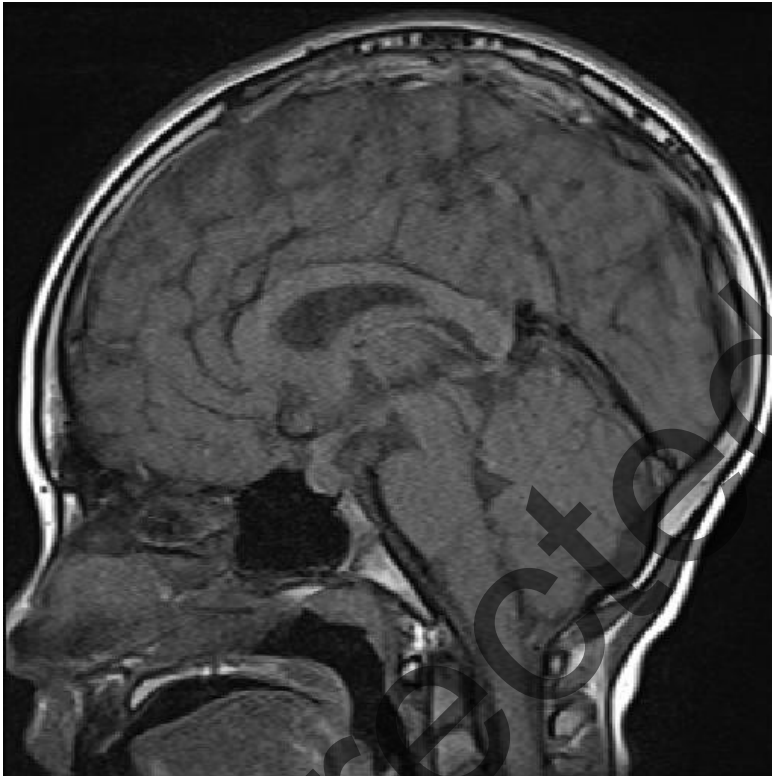
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Figure 1. Pretreatment magnetic resonance images of the 8-year-old boy

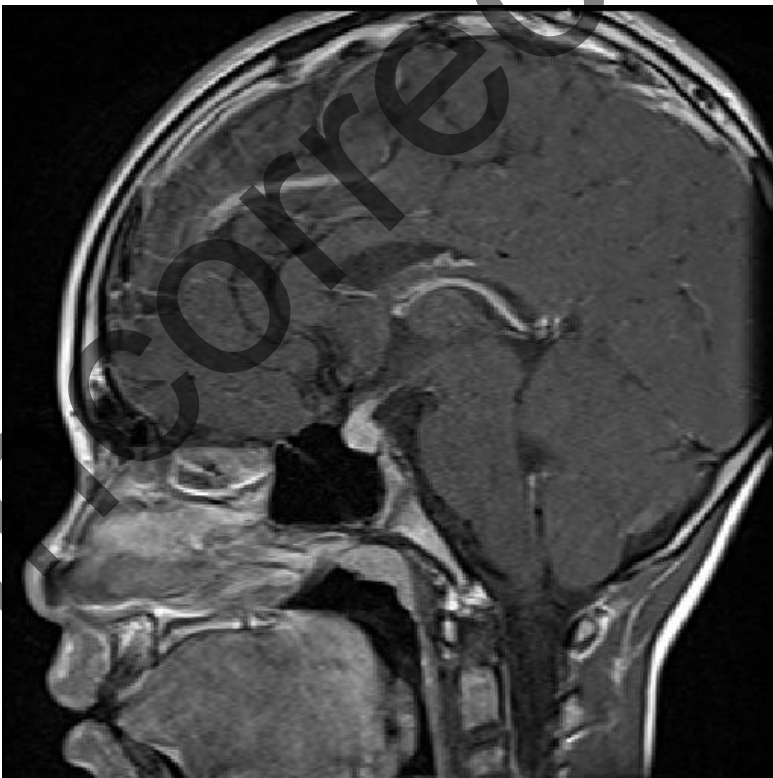
A



B



C



D

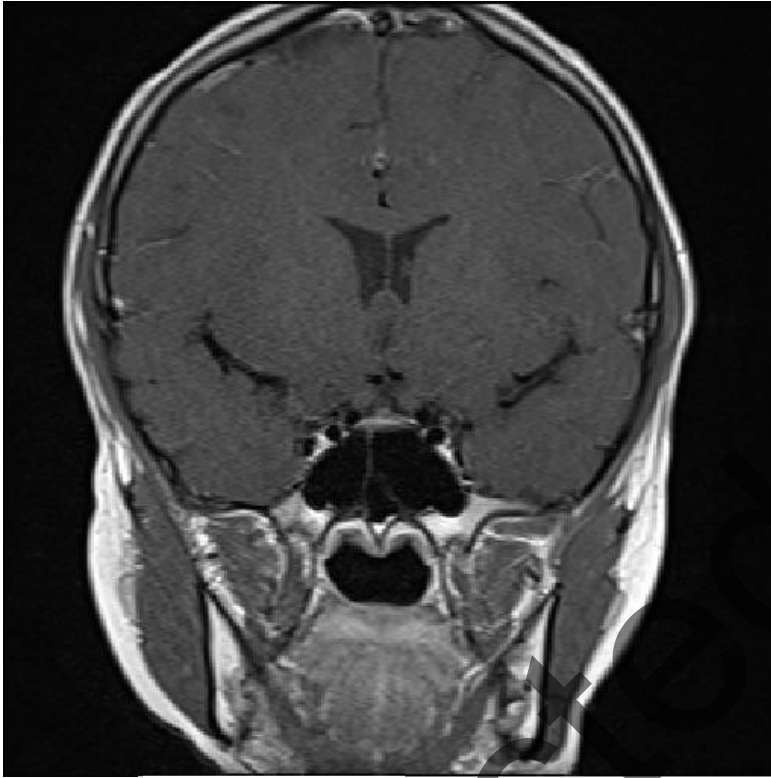


Figure 2. Detection of anti-rabphilin-3A antibodies by Western blotting.

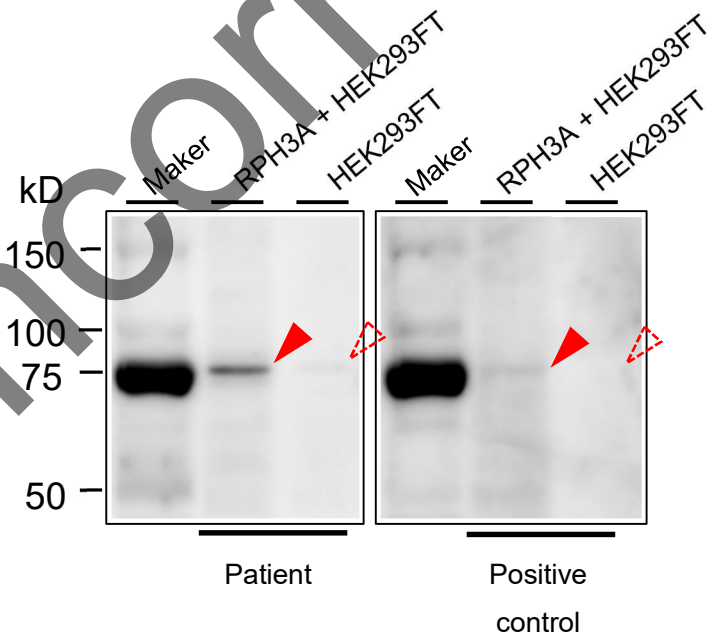
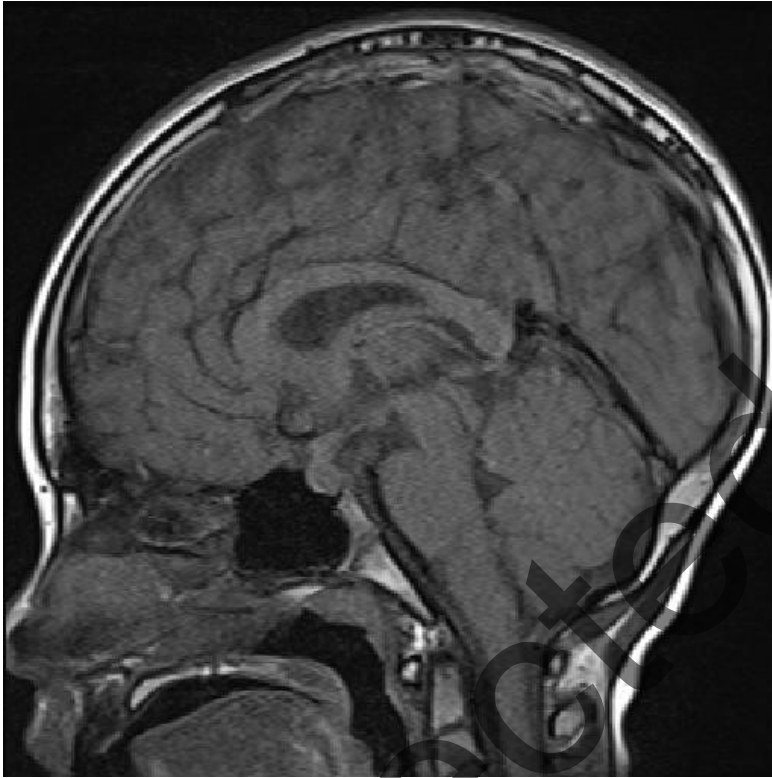
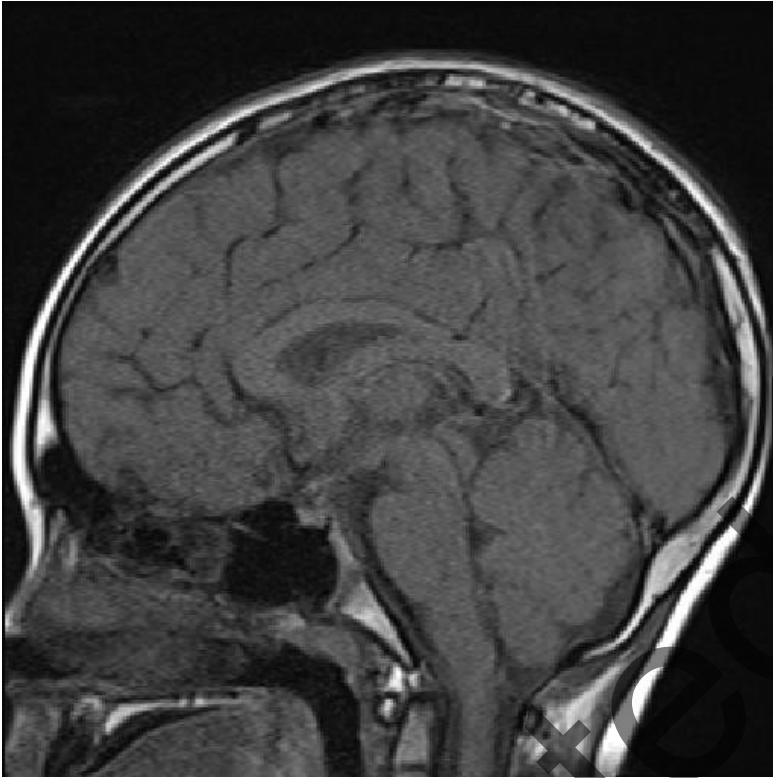


Figure 3. Pre- and posttreatment magnetic resonance images of the 8-year-old boy

A



B



The maximum DPI for MRI images at our hospital is 127.

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Uncorrected proof