CASE REPORT

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

Yukino Shoji[1], Yuki Naruse[1], Naoko Iwata[2], Haruki Fujisawa[3], Atsushi Suzuki[3], Yoshihisa Sugimura[3], Masato Mori[1], Ryugo Hiramoto[1]

[1]Matsudo City General Hospital, Clinic of Pediatrics, Chiba, Japan
[2]Daido Hospital, Clinic of Endocrinology and Diabetes, Aichi, Japan
[3]Fujita Health University Faculty of Medicine, Department of Endocrinology and Diabetes, Aichi, Japan

What is already known on this topic?

Recently, anti-rabphilin-3A antibodies (RPH3A-Ab) have emerged as a promising diagnostic marker for lymphocytic infundibuloneurohypophysitis (LINH) in adults. However, few reports of this association 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 LINH based on a positive test for RPH3A-Ab. This case study illustrates the potential of RPH3A-Ab as an early diagnostic marker for pediatric-onset LINH.

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 but.there are few reports of this association in the pediatric population. We report the case of an 8-year-old boy with central diabetes insipidus (CDI) who was diagnosed clinically with LINH, based on RPH3A-Ab positivity. He was initially 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 the diagnosis of CDI, the patient tested positive for RPH3A-Ab. MRI performed nine months after CDI diagnosis revealed amelioration of the pituitary stalk enlargement, and this 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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Address for Correspondence: Yukino Shoji MD, Matsudo City General Hospital, Clinic of Pediatrics, Chiba, Japan
E-mail: snowdrop.6805@gmail.com **ORCID:** orcid.org/0000-0001-5668-0525

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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 associated with inflammatory/autoimmune conditions, such as lymphocytic hypophysitis or 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 measurement of alpha-fetoprotein (AFP), human chorionic gonadotropin-beta (HCG-β), and placental alkaline phosphatase (PLAP) have been shown to be useful in the diagnosis of GCTs (4). Imaging studies, including cranial 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 histopathological 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 (6,7,8). Here, we report a case in which a patient with CDI was clinically diagnosed with LINH using RPH3A-Ab testing shortly after diagnosis of CDI.

Case Report

The patient was an 8-year-old boy who presented with 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. However, 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 score (SDS) -1.5] and 22 kg (-0.8 SDS), respectively. His complete 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 resulted in 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, his 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 (Figure 1). Contrast-enhanced MRI revealed a uniform contrast effect in the pituitary gland.

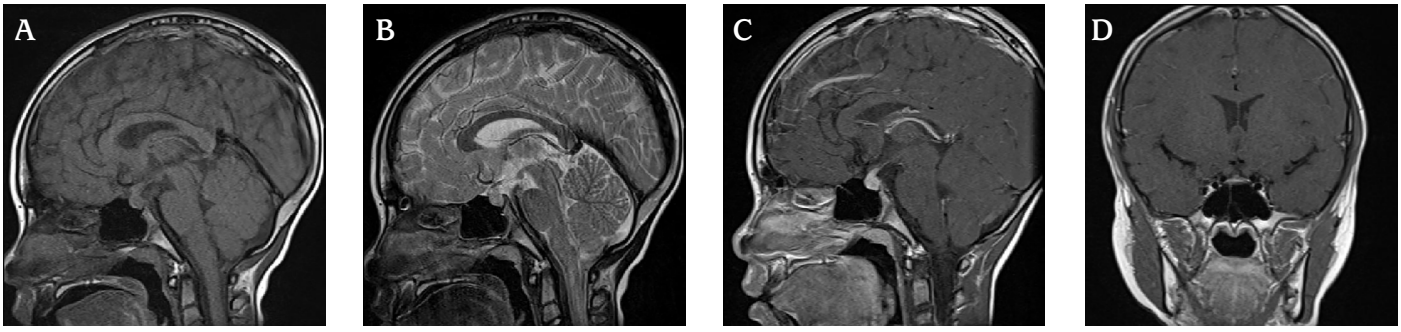

Figure 1. Pretreatment magnetic resonance images of the 8-year-old boy. A) Sagittal T1-weighted MRI at the time of diagnosis of CDI. B) Sagittal T2-weighted MRI at the time of diagnosis of CDI revealing loss of high signal intensity in the posterior lobe and enlargement of the pituitary stalk. C, D) Sagittal and coronal sections of T1-weighted contrast-enhanced MRIs at the time of diagnosis of CDI revealing a uniformly enhanced pituitary gland

MRI: magnetic resonance image, CDI: central diabetes insipidus

Anterior pituitary function tests revealed no abnormalities. Tumor markers associated with 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 in 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. Technetium-99m scintigraphy revealed no abnormal accumulations suggestive of LCH. Three months after the diagnosis of CDI, the patient tested positive for RPH3A-Ab, a potential marker for the diagnosis of LINH (Figure 2).

Based on the above results, the patient was diagnosed 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 diagnosis, brain MRI revealed shrinking of the enlarged pituitary stalk (Figure 3) and no elevation in tumor markers was found. The patient was not exposed to radiation, including CT scans, during the course of the disease. His symptoms of CDI persisted after shrinking of the enlarged pituitary stalk.

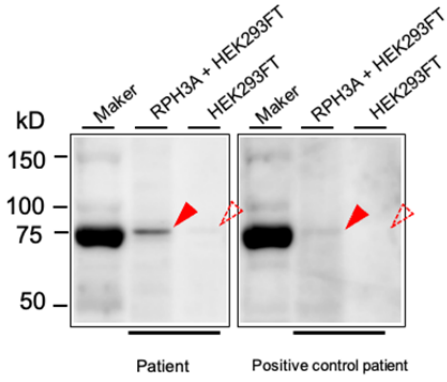

Figure 2. Detection of anti-rabphilin-3A antibodies by Western blotting

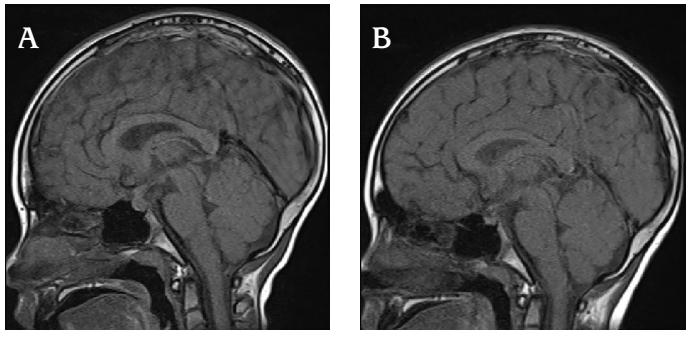

Figure 3. (A, B) Pre- and posttreatment magnetic resonance images of the 8-year-old boy

Discussion

This report describes a case of a pediatric patient with CDI who tested positive for RPH3A-Ab three months after diagnosis of CDI. His anterior pituitary hormonal function and tumor markers were normal. Follow-up pituitary MRI revealed amelioration of the earlier pituitary enlargement, and RPH3A-Ab positivity suggested a diagnosis of LINH.

Pituitary biopsy is required for the definitive diagnosis of LINH but its is highly invasive and thus problematic, especially in children. Recently, RPH3A-Ab was reported as a noninvasive diagnostic marker of LINH in adults. However, its use in the diagnosis of LINH early in the condition 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 autoantigen in which T cells specific for RPH3A are involved in the pathogenesis of neurohypophysis (5).

Measurement of RPH3A-Ab in serum was performed at the Fujita Health University. Briefly, 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 patient 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. (10) 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%. Moreover, Iwama et al. (9) reported that RPH3A-Ab was detected in 5 of 41 samples from healthy control subjects (sensitivity, 88%). Therefore, RPH3A-Ab may be useful to diagnose LINH.

We are aware of only three case reports of RPH3A-Ab positivity in pediatric patients with CDI (6,7,8). The patients tested positive for RPH3A-Ab at six and eight months, and nine years after CDI onset. All had growth hormone deficiency, which is suggestive of LPH. In the presented case, the patient tested positive for RPH3A-Ab three months after diagnosis of CDI.

To the best of 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 cannot 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 should result in fewer invasive investigations and also early treatment, which may improve prognosis.

The cause of the shrinking of the enlarged pituitary stalk in the presented patient is unclear. The inflammatory process in LINH may be self-limiting, and radiological follow-up may 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 six months (11). A previous study reported a patient who was diagnosed with LINH by pituitary biopsy, however, the pituitary stalk swelled, tumor marker levels 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 monitoring hormonal assessments.

Conclusion

This report describes an 8-year-old boy diagnosed with LINH because of the presence of serum RPH3A-Ab, first detected three months post-CDI diagnosis. His clinical course was consistent with such a diagnosis. This case study illustrates the potential of RPH3A-Ab as an early diagnostic marker for pediatric-onset LINH. However, the utility of these antibodies as a diagnostic marker needs to be validated with more cases in the future.

Ethics

Informed Consent: Informed consent form was obtained from the patient's family.

Presented in: Previous presentation of the content of the manuscript: The 55th Annual Scientific Meeting of the Japanese Society for Pediatric Endocrinology on 02.11.2022 in Kanagawa, Japan.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Yukino Shoji, Yuki Naruse, Concept: Yukino Shoji, Yuki Naruse, Masato Mori, Ryugo Hiramoto, Design: Yukino Shoji, Yuki Naruse, Data Collection or Processing: Yukino Shoji, Yuki Naruse, Naoko Iwata, Haruki Fujisawa, Atsushi Suzuki, Yoshihisa Sugimura, Analysis or Interpretation: Yukino Shoji, Yuki Naruse, Naoko Iwata, Haruki Fujisawa, Atsushi Suzuki, Yoshihisa Sugimura, Literature Search: Yukino Shoji, Writing: Yukino Shoji.

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