CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Lymphocytic Hypophysitis Presenting as Acute-onset Arginine Vasopressin Deficiency and Pituitary Stalk Thickening: A Case Report

Lian Zi Yang and Shanty Velaiutham

Endocrine Unit, Penang General Hospital, Pulau, Pinang, Malaysia

Abstract

Lymphocytic hypophysitis (LHy) is a rare autoimmune inflammatory process that selectively affects the neurohypophysis and infundibulum, typically presenting with arginine vasopressin deficiency (AVP-D). On magnetic resonance imaging (MRI) with contrast, there is a thickening of the pituitary stalk, enlargement of the neurohypophysis or both with homogeneous enhancement. LHy can be self-limiting and regression can be seen radiologically during follow-up.

A 22-year-old male presented with clinical findings consistent with AVP-D in 2016. MRI brain demonstrated enlargement of the pituitary stalk and absence of a posterior pituitary bright spot. He was given a trial of glucocorticoid treatment. His serial MRI brain showed a reduction of the pituitary stalk, but the AVP-D persisted. He was diagnosed with LHy.

LHy is characterized by lymphocytic infiltration, leading to eventual destruction of the pituitary tissue accompanied by varying degrees of pituitary dysfunction. Definite diagnosis can only be established via pituitary stalk biopsy. Due to the wide range of possible aetiologies, close monitoring is strongly recommended for the treatment of presumed cases lacking histopathologic confirmation. The response rate to glucocorticoids has been variable. Periodic monitoring of anterior pituitary function and pituitary MRI are essential in the management of this condition.

Key words: lymphocytic hypophysitis, arginine vasopressin deficiency, pituitary stalk, infundibulum

INTRODUCTION

Hypophysitis is a rare inflammatory disorder that affects the pituitary gland and infundibulum and aetiologies include autoimmune, infectious, neoplastic, infiltrative, immunoglobulin G4 IgG4, immunotherapy-induced or sometimes idiopathic.[1,2] LHy, one of the causes of primary hypophysitis, is a rare autoimmune inflammatory process that selectively affects the infundibulum and neurohypophysis, typically presenting with arginine vasopressin deficiency (AVP-D).[3] Magnetic resonance imaging (MRI) with contrast demonstrates thickening of the pituitary stalk, enlargement of the neurohypophysis, or both with homogeneous enhancement.[3,4] The inflammatory process in LHy can be self-limited and regression can be seen radiologically during follow-up.[4] This case report will illustrate the clinical and radiological course of a rare case of LHy who received glucocorticoid treatment and was closely monitored under our follow-up.

CASE

A 22-year-old male presented with a sudden onset of polyuria and polydipsia for 2 months in 2016. He developed a predilection for cold drinks with concomitant nocturia which occurred hourly incurring a total urine volume excreted in a day of approximately 9 litres. Symptoms such as headache, visual disturbances, fever, cough or weight loss were absent. He denied exposure to individuals infected with tuberculosis (TB). He had no remarkable past medical history or family history and was not taking any medications. On examination, he had normal secondary male characteristics, with a height of 1.78 m and a body mass index (BMI) of 25.2 kg/m^2. Clinically, he had an unremarkable respiratory, abdominal and neurological examination. There were no skin lesions, lymphadenopathy, bone pain or joint swelling. Renal profile was significant for hypernatremia (serum sodium 150 mmol/l) in the presence of dilute urine (urine specific gravity 1.005); the

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 5, 2024. Accepted: September 13, 2024.
Published online first: April 20, 2025.
https://doi.org/10.15605/jafes.040.01.08

Corresponding author: Lian Zi Yang, MD
Endocrine Unit, Penang General Hospital
Jalan Residensi, 10450 George Town, Pulau Pinang, Malaysia
E-mail: z.yang91@gmail.com
ORCiD: https://orcid.org/ 0009-0007-3293-814X

corresponding serum and urine osmolality were 321 mOsm/kg and 105 mOsm/kg, respectively. Water deprivation test was deferred due to the presence of marked hypernatremia. A trial of available oral desmopressin was given resulting in a significant reduction of polyuria. Overall, the clinical and laboratory findings were consistent with AVP-D.

Cranial MRI (Figure 1) demonstrated enlargement of the pituitary stalk (6 mm) and homogenous enhancement of both pituitary gland and stalk post-gadolinium contrast. The pituitary gland appeared normal and the posterior pituitary bright spot was absent. The patient refused the planned possible pituitary biopsy.

Other anterior pituitary hormones were within normal limits, except for mildly raised prolactin levels 1440 (86-324 mIU/L), equivalent to 67.7 ng/ml. Besides that, the anti-TPO level was elevated at 491 (<35 IU/ml). Investigations for secondary aetiologies including anti-neutrophil cytoplasmic antibodies (ANCA), alpha-fetoprotein (AFP), Beta-hCG (B-HCG), Immunoglobulin G4 (IgG4), Antinuclear antibody (ANA), Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), urine analysis, angiotensin converting enzyme (ACE) and imaging including skeletal survey, computed tomography (CT) thorax and serial chest radiographs were not significant. He was commenced on a trial of glucocorticoid treatment with oral prednisolone starting at 50 mg daily. This was tapered by 10 mg monthly until dose reached prednisolone 30 mg daily. This was followed by a 5 mg reduction monthly until oral prednisolone was 10 mg daily. This was tapered further to 7.5 mg daily for a month, then reduced further to another month of oral prednisolone at 5 mg daily before steroid treatment discontinuation. Despite high doses of glucocorticoid treatment, the AVP-D persisted and required regular doses of desmopressin. His serial pituitary MRI in 2017 (9 months after the initial MRI) and 2021 (5 years and 4 months from the initial MRI) showed a gradual reduction in the diameter of the pituitary stalk which measured 5 mm and 4.5 mm, respectively.

His other hormones were monitored during follow-up and remained unremarkable (Table 1). The short synacthen test performed in 2017 showed adequate cortisol response: 264 nmol/l (0 min), 476 nmol/l (30 min), 519 nmol/l (60 min). The previously mildly elevated serum prolactin normalised during subsequent visits. Signs and symptoms suggestive of secondary causes of LHy did not manifest during follow-up and his weight remained stable throughout

Table 1. Serial hormone assessments on the patient's follow-up

Hormones tested	2016	2021	2022
Free T4 (thyroxine) (Normal range: 12-22 pmol/L)	18.6 pmol/L	14 pmol/l	14 pmol/l
Cortisol nmol/l (Normal range: 133-537 nmol/L)	219 nmol/l	303 nmol/l	309 nmol/l
Testosterone (Normal range 8.64-29 nmol/L)	9.75 nmol/L	11.0 nmol/L	12.0 nmol/L
Insulin-like growth factor 1 (IGF-1) (Normal range: 115-340 ug/l)	203 ug/l		

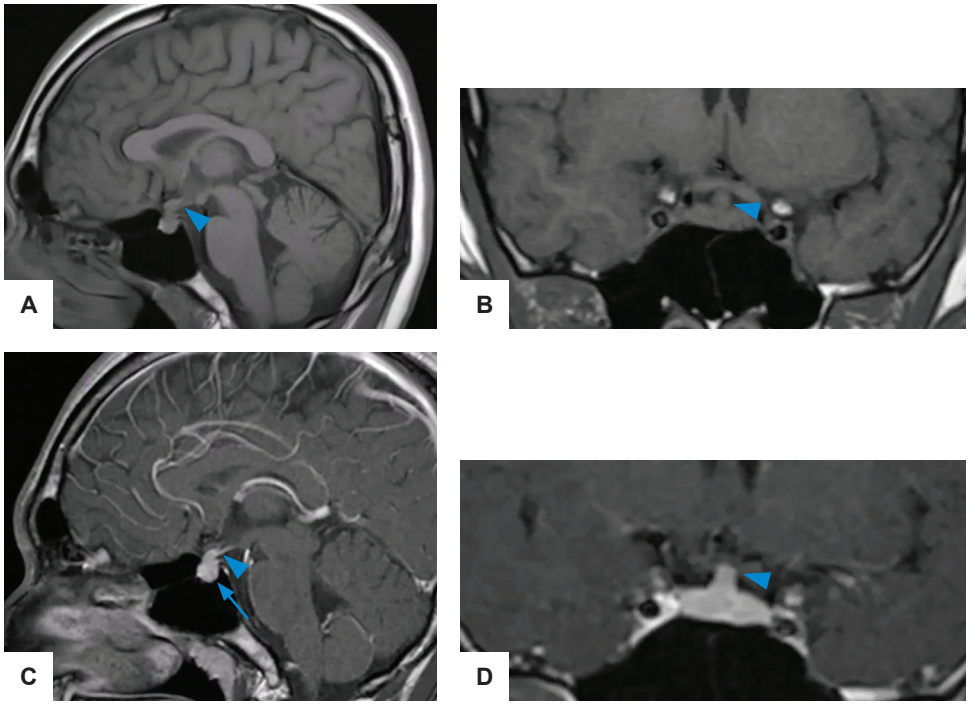

Figure 1. Magnetic resonance imaging of hypothalamic-pituitary regions in 2016 **(A-D)**. Thickening of pituitary stalk measuring 6 mm *(arrowheads)* and absence of posterior pituitary bright spot *(arrow)* at initial presentation **(A, B)** non-contrast T1-weighted; **(C, D)** contrast-enhanced.

this period. He got married and fathered a child naturally the next year. However, anti-TPO was still elevated (215 IU/ml), suggesting an associated autoimmune disorder. Ultimately, a diagnosis of LHy was made and the patient continued to be monitored closely. He was switched from oral to sublingual desmopressin when it became available in our center. His condition remains stable on sublingual desmopressin 180 mcg, 120 mcg, 180 mcg thrice a day, with development of polyuria with delayed or missed doses and serum sodium ranging from 139 to 140 mmol/l during follow-up.

DISCUSSION

Hypophysitis is a rare inflammatory disorder that affects the infundibulum and pituitary gland. Diagnosis is usually made based on clinical presentation, dedicated magnetic resonance imaging, laboratory findings and, in some cases, biopsy. Hypophysitis can be further categorised according to its anatomical involvement, whereby inflammation can affect the anterior pituitary (adenohypophysitis), entire pituitary (panhypophysitis), infundibulum and posterior pituitary (infundibulo-neurohypophysitis).

Hypophysitis can also be categorised according to its aetiology as primary or secondary. Primary hypophysitis is characterised by autoimmune and other infiltrative or inflammatory forms of isolated pituitary involvement of unknown aetiology. Secondary hypophysitis is characterised by a reaction due to a local process, infection, drug, systemic disease or malignancy. Alternatively, hypophysitis can be categorised using its histological features including lymphocytic, granulomatous, IgG4-related, xanthomatous, necrotizing and mixed forms. The most common form is lymphocytic hypophysitis.[1]

Hypophysitis usually presents with symptoms related to the deficiency of pituitary hormones with or without mass effect symptoms, such as headaches and vision disturbances. AVP-D is common.[2] Various imaging characteristics can be seen. The most common MRI finding is a thickened, non-deviated pituitary stalk or associated symmetric pituitary gland enlargement.[1] The evaluation of a patient with thickening of the pituitary stalk involves assessing the function of both the anterior and posterior pituitary gland and identifying the underlying cause. Other possible aetiologies include neoplastic lesions and metastases, inflammatory conditions such as Langerhans cell histiocytosis, neurosarcoidosis and infections such as tuberculosis.[1,5] Biopsy may be the only modality for definitive diagnosis and is useful in establishing the histopathological type and in excluding other secondary aetiologies.[1] However, aside from being invasive, biopsy carries risks such as hypopituitarism, bleeding and infection. Currently, there are no established criteria for pituitary biopsy. Because the differential diagnosis is broad,

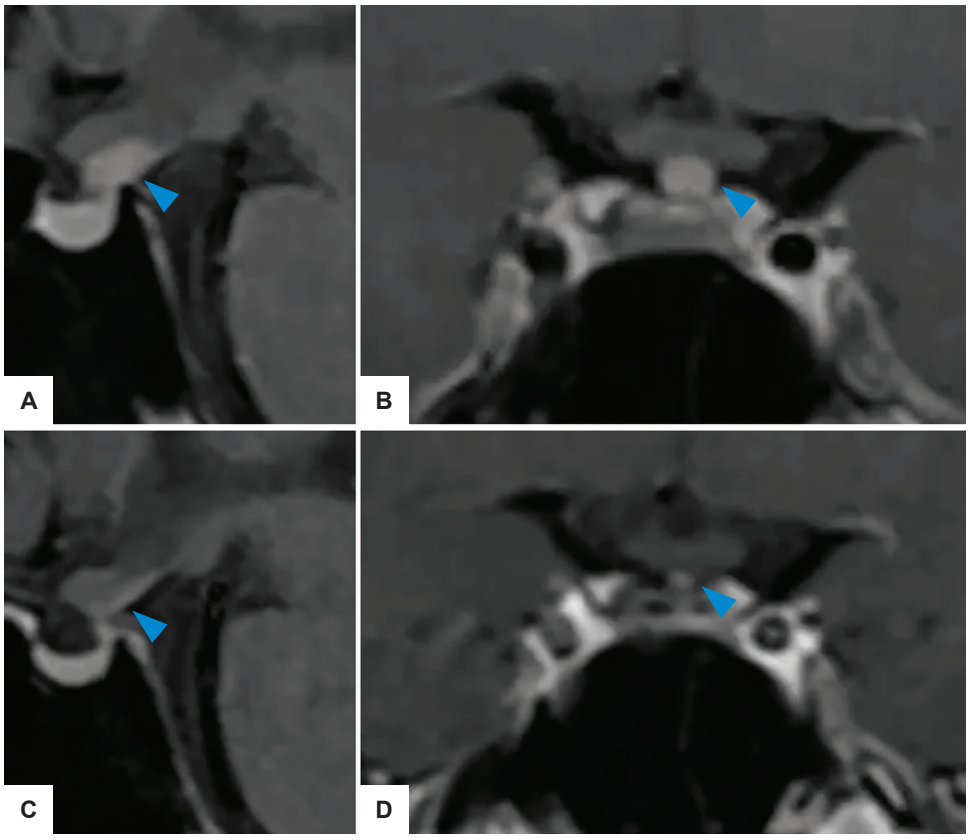

Figure 2. Magnetic resonance imaging of hypothalamic-pituitary regions (contrast-enhanced T1-weighted) during follow-up **(A-D)**. Pituitary stalk *(arrowheads)* was less thickened in 2017, measuring 5 mm **(A, B)** and the pituitary stalk diameter was further reduced in 2021, measuring 4.5 mm **(C, D)**.

it is crucial to establish a presumptive diagnosis based on non-invasive investigations given that histopathology is not always available for confirmation.[2]

Specific investigations such as IgG4, ANCA, ACE, ANA, B-HCG, AFP and tuberculin skin test can be performed to exclude other causes. Occasionally, whole-body computed tomography or fluorodeoxyglucose-positron emission tomography (FDG- PET) can be useful to delineate the underlying aetiology.[1] Rabphilin-3A is reported to be a predominant auto-antigen in LHy. There are recent studies that demonstrated the utility of anti-rabphilin-3A antibodies as sensitive markers of LHy in patients with AVP-D. Testing for anti-rabphilin-3A antibodies could be useful in distinguishing LHy from other pituitary disorders, potentially eliminating the need for invasive pituitary biopsy in the future.[6,7] A trial of empiric high-dose glucocorticoid treatment could be considered if all investigations are negative, as most inflammatory and infiltrative lesions will respond to glucocorticoid treatment. While the mass effects will likely improve with administration of glucocorticoid, the pituitary function is unlikely to return to normal.[1]

Approximately two-thirds of cases of primary hypophysitis are found to be lymphocytic hypophysitis. It is frequently associated with autoimmune diseases such as autoimmune thyroid disease, primary biliary cirrhosis, lupus and celiac disease. LHy is characterized by lymphocytic infiltration, leading to eventual destruction of the pituitary tissue accompanied by varying degrees of pituitary dysfunction. In LHy, AVP-D is the main and most pronounced symptom due to lymphocytic infiltration of the neurohypophysis and infundibulum.[4,8] Mass effect symptoms such as headache can occur. The anterior pituitary function is frequently intact, with occasional mild and transient involvement of the anterior pituitary function. Radiologically, LHy is characterised by diffuse thickening of the infundibulum and marked gadolinium enhancement of the stalk, with a diameter exceeding 3.5 mm at the level of the median eminence of the hypothalamus. The usual neurohypophyseal "bright spot" is also lost.[4] This case is likely a case of lymphocytic hypophysitis based on its clinical course, imaging features and absence of clinical features suggestive of secondary causes during follow-up. Although tuberculosis (TB) was considered due to its endemic presence in the region, the absence of related clinical signs, symptoms and radiological features at diagnosis and during follow-up suggested that TB was unlikely to be the cause.

While glucocorticoid treatment is efficacious, its dose, duration and benefits are still of much contention. There are reports of mixed outcomes such as cured cases of LHy with glucocorticoids and cases with spontaneous regression without glucocorticoids.[8,9] This case showed that despite early initiation of steroids at high doses, the AVP-D persisted even when imaging features improved. Since no randomised controlled trials have been conducted due to the rarity of this condition, it is uncertain whether glucocorticoids can lead to better pituitary function recovery compared to observation alone in the treatment of hypophysitis.[1,2] It is reported that the response rate to glucocorticoids in primary hypophysitis varies widely, ranging from 20% to over 95% for partial or complete improvement in radiological and hormonal response.[1] Hypophysitis is regarded as severe if mass effects, such as headache, cranial nerve palsy or visual field defects, occur. This requires administration of glucocorticoids and consideration of pituitary biopsy.[1,2] However, it is important to evaluate the benefits and risks of glucocorticoid treatment in treating mild cases of primary hypophysitis given the wide range of potential glucocorticoid side effects.[1] A recent meta-analysis observed a more marked improvement with very high dose intravenous glucocorticoid and for a longer treatment duration (>6.5 weeks). It is also suggested that those who did not respond to glucocorticoids had longer symptom duration and irreversible fibrosis may have occurred.[10] Nevertheless, periodic clinical assessment for the recovery of pituitary function is required and pituitary MRI surveillance can be performed at 3 to 6 months, initially.[1,5] Some suggest repeating MRI surveillance annually for 5 years and at the same time evaluating for anterior pituitary function yearly. Due to the wide range of possible aetiologies, caution and close monitoring are strongly recommended for the treatment of presumed cases lacking histopathologic confirmation.[1,2]

CONCLUSION

This case shows that a diagnosis of LHy can be made with close monitoring with hormonal and radiological assessment and long-term follow-up in the absence of a highly invasive pituitary biopsy. There are no evidence-based guidelines on the management of LHy due to its rarity. Glucocorticoid response rate has been variable. An individualised approach is warranted. A conservative medical approach is often used as LHy is often self-limiting, especially when symptoms of mass effect are absent.

Ethical Considerations
Patient consent was obtained before the submission of the manuscript.

Statement of Authorship
All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement
LZY: Conceptualization, Investigation, Resources, Writing - original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **SV:** Investigation, Resources, Writing – review and editing, Supervision.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

References

1. Langlois F et al. Hypophysitis, the growing spectrum of a rare pituitary disease. J Clin Endocrinol Metab. 2022;107(1):10-28. PMID: 34528683 PMCID: PMC8684465 DOI: 10.1210/clinem/dgab672
2. Faje A. Hypophysitis: Evaluation and management. Clin Diabetes Endocrinol. 2016;2:15. PMID: 28702249 PMCID: PMC5471685 DOI: 10.1186/s40842-016-0034-8
3. Gubbi S, Hannah-shmouni F, Verbalis JG, Koch CA. Hypophysitis: An update on the novel forms, diagnosis and management of disorders of pituitary inflammation. Best Pract Res Clin Endocrinol Metab. 2019;33(6):101371. PMID: 31866206 PMCID: PMC7078033 DOI: 10.1016/j.beem.2019.101371
4. Rivera JA. Lymphocytic hypophysitis: Disease spectrum and approach to diagnosis and therapy. Pituitary. 2006;9(1):35-45. PMID: 16703407 DOI: 10.1007/s11102-006-6598-z
5. Turcu AF, Erckson BJ, Lin E, et al. Pituitary stalk lesions: The Mayo Clinic experience. J Clin Endocrinol Metab. 2013;98(5):1812-8. PMID: 23533231 DOI: 10.1210/jc.2012-4171
6. Arihara Z, Sakurai K, Niitsuma S, et al. Studies on anti-rabphilin-3A antibodies in 15 consecutive patients presenting with central diabetes insipidus at a single referral center. Sci Rep. 2022;12(1):4440. PMID: 35292721 PMCID: PMC8924241 DOI: 10.1038/s41598-022-08552-y
7. Iwama S, Sugimura Y, Kiyota A, et al. Rabphilin-3A as a targeted autoantigen in lymphocytic infundibulo-neurohypophysitis. J Clin Endocrinol Metab. 2015;100(7):E946-54. PMID: 25919460 PMCID: PMC5393526 DOI: 10.1210/jc.2014-4209
8. Hasebe M, Shibue K, Honjo S, Hamasaki A. A case of lymphocytic infundibulo-neurohypophysitis exhibiting spontaneous regression. JCEM Case Rep. 2023;1(2):luad020. PMID: 37908468 PMCID: PMC10580413 DOI: 10.1210/jcemcr/luad020
9. Inaba H, Susuki S, Shigematsu S, et al. Lymphocytic infundibuloneurohypophysitis: Long-term follow-up of a case cured with glucocorticoid. Med Princ Pract. 2010;19(1):79-81. PMID: 19996626 DOI: 10.1159/000252841
10. Krishnappa B, Shah R, Memon SS, et al. Glucocorticoid therapy as first-line treatment in primary hypophysitis: A systematic review and individual patient data meta-analysis. Endocr Connect. 2022; 12(2):e220311. PMID: 36445257 PMCID: PMC9874965 DOI: 10.1530/EC-22-0311

JAFES

Clinical controversies and disease updates are also welcome. Instructions to Authors available at www.ASEAN-endocrinejournal.org.