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Lymphocytic hypophysitis presenting with diabetes insipidus in a 14-year-old girl: case report and review of the literature

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Abstract Lymphocytic hypophysitis is a rare disorder predominantly affecting females during the antepartum or postpartum period. It is characterized by destruction and lymphocytic infiltration of the pituitary gland, probably by an autoimmune process, leading to a pituitary mass lesion and/or various degrees of hypopituitarism. The lesion is usually confined to the adenohypophysis. Posterior pituitary gland or stalk involvement is rare, although patients presenting with diabetes insipidus have been reported. We describe a girl aged 13 years 9 months with lymphocytic hypophysitis who presented with diabetes insipidus and secondary amenorrhea. MRI of the brain revealed a 1 cm enhancing mass in the pituitary stalk. A biopsy of the mass by right periorbital craniotomy showed lymphocytic infiltration without neoplastic cells or granuloma formation. To our knowledge, this is the youngest reported patient with a diagnosis of lymphocytic hypophysitis. In this case report, her clinical presentation is discussed along with a review of the literature.

Conclusion We present the first childhood case of lymphocytic hypophysitis which is an autoimmune inflammatory disorder of the pituitary gland. Although this is a rare condition in adults, it also needs to be considered in the pediatric population. Conservative management is preferred unless there are signs of increased intracranial pressure. Most importantly, close monitoring for multiple hormone deficiencies is indicated in this condition.

Key words Lymphocytic hypophysitis · Diabetes insipidus · Hypopituitarism

Abbreviations DI diabetes insipidus · dDAVP deaminoo-arginine vasopressin · IGF-I insulin-like growth factor-I · IGFBP-3 insulin-like growth factor binding protein-3.

Introduction Lymphocytic hypophysitis is a rare inflammatory disorder of the pituitary gland first described by Goudie and Pinkelton in 1962 [14]. Nearly 60 cases have been described in the English literature most commonly affecting females and exclusively adult patients. Patients usually present with symptoms of a pituitary mass lesion and/or various degrees of hypopituitarism [1–7, 9–11, 13–39]. Pathologic findings of lymphocytic hypophysitis include lymphocytic infiltration of the pituitary gland without granuloma formation [1–5, 7, 10, 11, 13–29, 31–39]. We describe a nulliparous girl aged 9 years 13 months who presented with diabetes insipidus and secondary amenorrhea. After an extensive evaluation, a diagnosis of lymphocytic hypophysitis of the pituitary stalk was made. To our knowledge, this is the youngest patient reported in the English literature.

Case report A girl aged 13 years 9 months was referred to University of Michigan Pediatric Endocrinology Unit in August of 1994 with complaints of sudden onset of polyuria, polydipsia, fatigue, headaches and 10 lbs weight loss of 1 month duration (4.53 kg). Based on her history, she had been presumptively diagnosed with central diabetes insipidus (DI) and started on treatment with deamino-o-arginine vasopressin (dDAVP) by her primary physi-
cian 2 weeks prior to the referral to our clinic. Treatment with dDAVP resulted in remarkable improvement of her symptoms. She had regular menstrual periods since 11 years of age until 3 months prior to presentation to our clinic, when these ceased. Her past medical history was unremarkable and she had no history of visual disturbance, fatigue, cold intolerance, galactorrhea, loss of pubic or axillary hair. Family history was significant only for tall stature on her father's side.

On physical examination, her weight was 41.2 kg (10th percentile) and her height was 170.1 cm (95th percentile). Blood pressure was 119/64 mm Hg and pulse was 77/min. The thyroid gland was not palpable. She had stage 4 pubic hair and genital development. Neurologic examination was normal including visual acuity, visual fields to confrontation, pupillary size and reactivity, retina and optic discs on funduscopic examination and ocular alignment and movement. Visual fields were also normal by Goldman perimetry.

A lateral skull X-ray showed a normal calvarium with no evidence of lytic lesions or abnormal calcifications. However, MRI of the brain revealed a 1 x 1 x 1 cm mass lesion in the pituitary stalk and inferior hypophalamus that was isointense on T1-weighted images and enhanced homogeneously with gadolinium; consistent with a neoplastic or inflammatory process. Tumor markers, alpha fetoprotein and beta-HCG, were negative (Table 1) and evaluation for sarcoidosis and tuberculosis revealed a normal angiotensin converting enzyme level and negative tuberculin skin test. Moreover, no pulmonary lesions were found by thoracic CT. A brain MRI 3 months later showed slight decrease in the size of the lesion (6 x 5 x 8 mm). However, 6 months after its initial identification, the mass had again increased in size to 10 x 8 x 10 mm. The neurohypophysis lacked the hypointense signal on T1-weighted images seen in normal subjects.

Laboratory tests were performed to evaluate the patient's hormonal status (Table 1). ACTH deficiency was not present, since the early morning cortisol level was normal upon presentation and remained normal during follow up. The free T4 and TSH levels were both normal initially but decreased towards the lower end of the normal range during follow up, suggesting the need to be vigilant about the potential for the development of secondary hypothyroidism. FSH, LH and estradiol levels were all below the assay sensitivity, consistent with hypogonadotropic hypogonadism. Interestingly, the patient's prolactin level was elevated initially, but later decreased to normal levels. It is possible that the pituitary lesion identified by the MRI decreased the tonic inhibition signals traversing this region into the anterior pituitary, thus explaining the initial elevation of prolactin levels and return to the normal range as the lesion decreased in size. IGF-1 (insulin-like growth factor-1) and IGFBP-3 (insulin-like growth factor binding protein-3) were obtained to indirectly assess growth hormone (GH) secretion. IGF-1 was low for a 14-year-old girl and the IGFBP-3 level was normal for her age. Bone age was 14 years. Since there was no clinical indication for GH treatment, GH provocative tests were not performed.

In view of the increasing size of the pituitary stalk lesion, biopsy of the pituitary stalk by right periorbital craniotomy was obtained 8 months after the initial MRI. Histologic examination of the specimen showed chronic inflammation with an inflammatory infiltrate composed predominantly of lymphocytes along with some plasma cells and eosinophils. The lymphocytes were positive for the common leukocyte antigen and an occasional cell was also positive for Ki-1 (or CD-56, which stains monocyte cells) indicating normal lymphocytic infiltration without neoplastic cells (Fig. 1). The pituitary stalk mass has persisted on subsequent MRIs, showing slight fluctuations in size and shape from scan to scan. On the most recent MRI, 21 months from diagnosis, it measured 9 x 6 x 9 mm with slight extension toward the left side of the hypothalamus (Fig. 2). Clinically, the patient has not developed any neurologic signs or symptoms. She has gained 15 lbs (6.8 kg) while on dDAVP treatment and has been started on estrogen/progesterone cyclic hormonal replacement for her hypogonadotropic hypogonadism.

### Table 1 Laboratory findings of the patient on initial evaluation and 18 months after diagnosis (ACE angiotensin converting enzyme)

<table>
<thead>
<tr>
<th></th>
<th>Presentation</th>
<th>18 months after diagnosis</th>
<th>Normal values</th>
</tr>
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<tbody>
<tr>
<td><strong>Evaluation for DI Etiology</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Beta-HCG (mU/ml)</td>
<td>&lt; 5</td>
<td></td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Alpha-fetoprotein (IU/l)</td>
<td>&lt; 3.8</td>
<td></td>
<td>&lt; 3.8</td>
</tr>
<tr>
<td>ACE (units/l)</td>
<td>90</td>
<td></td>
<td>50-150</td>
</tr>
<tr>
<td><strong>Hormonal evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (ug/dl)</td>
<td>22.8</td>
<td>18</td>
<td>10-25</td>
</tr>
<tr>
<td>FreeT4 (ng/dl)</td>
<td>1.1</td>
<td>0.98</td>
<td>0.73-1.8</td>
</tr>
<tr>
<td>TSH (IU/l)</td>
<td>1.5</td>
<td>0.68</td>
<td>0.3-6.5</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>&lt; 1.0</td>
<td>3-26</td>
<td></td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>&lt; 2.0</td>
<td>2-105</td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>&lt; 20</td>
<td>20-375</td>
<td></td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>31</td>
<td>14</td>
<td>0-17</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>277</td>
<td>286-660</td>
<td></td>
</tr>
<tr>
<td>IGFBP-3 (mg/l)</td>
<td>3.3</td>
<td>2.2-5.9</td>
<td></td>
</tr>
<tr>
<td><strong>Autoimmune evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticimicrosomal Ab</td>
<td>&lt; 1:100</td>
<td>&lt; 1:400</td>
<td></td>
</tr>
<tr>
<td>Antithyroglobulin Ab</td>
<td>&lt; 1:100</td>
<td>1:100</td>
<td></td>
</tr>
<tr>
<td>Antidiuretic Ab</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Antiparical Ab</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>511</td>
<td>&gt; 225</td>
<td></td>
</tr>
</tbody>
</table>

*a.m. level

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**Discussion**

Central DI in children is most commonly idiopathic. Tumors of the hypothalamus or pituitary region constitute only 30% of the pediatric cases. Other infiltrative or infectious lesions, such as sarcoidosis or tuberculosis, are very rare causes of DI [8]. In our patient, the 1 cm mass lesion in the pituitary stalk and inferior hypophalamus region led to the exploration of possible CNS neoplasm or inflammatory process. A biopsy of the lesion revealed findings consistent with lymphocytic hy-
pophysis and excluded glioma, germinoma or other neoplastic lesions, as well as sarcoidosis, tuberculosis and Langerhans cell histiocytosis.

The clinical characteristics of the female patients diagnosed with lymphocytic hypophysitis and reported in the English literature are summarized in Table 2 [1–3, 5–19, 21–29, 31–33, 35–38]. It was not previously described in a child before this report. The youngest patient in the literature is a 17-year-old young woman who developed isolated ACTH deficiency 10 weeks following birth of her second child [9]. A few cases have been described in postmenopausal women [13, 16, 20, 30, 34, 36, 37] as well as in men [1, 2, 29, 31, 34]. Most of the cases in young females, by far, are associated with pregnancy [3–7, 9–11, 14, 15, 18, 22, 25–28, 31, 32, 35, 36].

Lymphocytic hypophysitis is considered to be an autoimmune process because of its frequent association with other autoimmune disorders [15, 16, 18, 21, 23, 26, 33, 35, 36], especially with Hashimoto thyroiditis [6, 9, 11, 16, 19, 25, 33, 35, 36]. In a recent study performed in hamsters, injection of rubella virus membrane-associated E1 and E2 glycoproteins were shown to induce lymphocytic hypophysitis; neonatal thymectomy prevented the development of the disease. This suggests the involvement of cellular immune system in the disease process [39]. Prevalence of hypophysitis during pregnancy or the postpartum period, when the immune system is altered [12], also supports the autoimmune pathogenesis of the disease.

The inflammatory process seen in lymphocytic hypophysitis is most often confined to the adenohypophysis. Depending on the size and exact localization of the lesion, it may cause visual abnormalities or symptoms of increased intracranial Pressure along with permanent or temporary hypopituitarism [1–7, 9–11, 13–39]. Multiple deficiencies of anterior pituitary hormones are found in about 73% of reported cases but isolated deficiency of ACTH may occur as well [6, 19, 33] and may be an important clue in the differential diagnosis. Our patient had DI and unrecognized anterior pituitary involvement manifesting as hypogonadotrophic hypogonadism in addition to low-normal TSH and free T4 levels at follow up.

Two possible explanations for DI in patients with lymphocytic hypophysitis exist: (1) extension of the mass into the hypothalamus suppressing synthesis of vasopressin and/or; (2) direct involvement of the pituitary

Fig. 1 Photomicrographs of the pituitary stalk biopsy specimens obtained by transphenoidal approach. Panel A is a hematoxylin and eosin stain (H&E, ×330) of tissue section showing dense lymphocytic infiltration. Panel B is a common leukocyte antigen (CLA, ×330) preparation which stains B- and T-lymphocytes. None of these stains revealed presence of histiocytes, neoplastic cells or granuloma formation, making the pathologic diagnosis lymphocytic hypophysitis.

Fig. 2 Coronal T1-weighted MRI images of the brain after intravenous administration of gadolinium. The arrow points to a strongly and homogeneously enhancing mass in the pituitary stalk, extending towards the left side of the hypothalamus.
Table 2 Clinical characteristics, treatment and outcome of all female patients reported in the literature with a diagnosis of lymphocytic hypophysitis*. We include our patient's findings for comparison

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>17–25 years</th>
<th>25–45 years</th>
<th>&gt; 45 years</th>
<th>Patient in this report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients according to age</td>
<td></td>
<td></td>
<td>13 years 9 months</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>10</td>
<td>37</td>
<td>5</td>
<td>52</td>
</tr>
</tbody>
</table>
| Biopsy           | 7           | 30          | 2          | 39                     +
| Autopsy          | 2           | 5           | 2          | 39                     -
| Clinical         | 1           | 2           | 1          | 4                      -
| Relation to Pregnancy |               |            |            |                        |
| Antepartum       | 3           | 9           | -          | 12                     -
| Postpartum       | 5           | 20          | -          | 25                     -
| Unrelated        | 2           | 8           | 5          | 15                     +
| Presentation     |             |            |            |                        |
| Isolated gonadotropin deficiency | 1          | 1           | -          | 2                      -
| Isolated GH deficiency | -          | -           | -          | -                      -
| Isolated ACTH deficiency | -          | 3           | -          | 3                      -
| Isolated TRH deficiency | -          | -           | -          | 2                      -
| Panhypopituitarism* | 8          | 26          | 4          | 38                     -/+|
| DT               | -           | 4           | 3          | 7                      +
| hyperprolactinemia | 3           | 15          | 2          | 20                     +
| Increased ICP*   | 4           | 26          | -          | 30                     -
| Autoimmune Disorders |             |            |            |                        |
| Hashimoto thyroiditis | 3          | 7           | 3          | 13                     -
| Adrenalitis      | 1           | 1           | -          | 2                      -
| Atrophic gastritis/PA* | -          | 1           | 1          | 2                      -
| IDDM/pancreatitis | 1           | 1           | -          | 2                      -
| Anti-SM antibodies* | 1           | -           | -          | 1                      -
| Treatment        |             |            |            |                        |
| surgery*         | 6           | 29          | 2          | 37                     -
| steroids*        | 2           | 8           | 1          | 11                     -
| conservative     | 4           | 4           | 2          | 10                     +
| Outcome          |             |            |            |                        |
| Spontaneous recovery | 2           | 7           | 1          | 10                     -
| Persistent hypopituitarism or DI* | 6          | 25          | 2          | 33                     +
| Death*           | 2           | 5           | 2          | 9                      -

*References 1–12, 14–20, 25–37
*Total or partial
*Increased intracranial pressure with or without visual field defects
*Pernicious anemia
*Anti-smooth muscle antibody
*Some received both steroids and surgery
*Excluding replacement for ACTH deficiency
*Due to surgery and/or lymphocytic hypophysitis
*In 3 patients unspecified, others due to cardiovascular collapse probably as a result of adrenal insufficiency

stalk and/or neurohypophysis with the inflammatory process causing destruction of hypothalamic pathways which transport vasoressin to the posterior pituitary. In our case, biopsy documented the presence of the inflammatory lesion in the pituitary stalk, suggesting the latter process as a cause of her DI.

As with our patient, most cases of lymphocytic hypophysitis are diagnosed by histological examination of pituitary gland tissue [1–5, 7, 10, 11, 13–39]. Pituitary adenoma is the most common misdiagnosis because of similar imaging characteristics: i.e. an enlarged pituitary that is T1-sointense with homogenous gadolinium enhancement [1, 5, 36]. These were the signal characteristics of the infundibular/hypothalamic mass in our patient. However, its location primarily in the stalk virtually ruled out an adenoma before biopsy, although other neoplasms were still a consideration. The loss of the normal posterior pituitary T1 hyperintensity has been described in lymphocytic hypophysitis [5, 36] and may have been a clue to the diagnosis before biopsy in this case.

Conservative management is generally recommended unless there are signs of optic nerve compression or increased ICP [2, 10, 11, 27, 28, 30–32, 34]. Spontaneous disappearance has been observed occasionally [6, 7, 11, 18, 30, 36]. Anti-inflammatory therapy with oral steroids has been tried with either no effect or temporary improvement with relapse after discontinuation of the medication [2, 28, 31, 32, 34, 36].
References

1. Abe T, Matsumoto K, Sanno N, Osamura Y (1995) Lympho-
syndrome of diabetes insipidus and hypopituitarism. J Clin
Endocrinol Metab 76:1499-1504
Lymphocytic Hypophysitis of pregnancy resulting in hypo-
95:166-171
enohypophysitis of pregnancy simulating a pituitary adenoma:
a distinct clinicopathologic entity. Report of two cases. J Neurosurg
56:148-153
5. Beresti N, Cohen R, Beresi JP, Dumas JL, Legrand M, Ibá-
zzen MT, Modigliani E (1994) Pseudotumoral lymphocytic
Reversible adenocorticotropin deficiency due to probable au-
toimmune hypophysitis in a woman with postpartum thy-
oriditis. J Clin Endocrinol Metab 74:548-552
The course of lymphocytic hypophysitis. Surg Neurol 36:40-43
8. Bode HH, Crawford JD, Danon M (1996) Disorders of anti-
diuretic hormone homeostasis. In: Lifszit F (eds) Pediatric en-
docrinology. Marcel Dekker, New York, pp 731-751
cytic hypophysitis. Report of 3 new cases and review of the
literature. Medicine 68 (4):240-256
Lymphocytic adenohypophysitis: a pituitary mass lesion occur-
in endocrine disorders of pregnancy and influence in the cause
of maternal autoimmune disease. Endocrinol Metab Clin North
Am 24 (1):187-205
hypophysitis in a patient with hypoglycemic episodes. Arch
Pathol Lab Med 102:46-48
14. Goudie RB, Pinkelton PH (1962) Anterior hypophysitis and
Hashimoto's disease in a young woman. J Pathol Bacteriol
83:584-585
15. Hayashi H, Yamada K, Kuroki T, Katayama M, Shigemori M,
Kuramoto S, Nonaka K (1991) Lymphocytic hypophysitis and
16. Hume R, Roberts GH (1967) Hypophysitis and hypopituitar-
hypophysitis as a cause of central diabetes insipidus. N Engl J
Med 329:683-689
Besser GM, Wais JAH (1995) Lymphocytic hypophysitis Un-
usual features of a rare disorder. Clin Endocrinol 42:529-534
19. Jensen MD, Handwerger BS, Scheithauer BW, Carpenter PC,
Mirakian R, Banks P (1986) Lymphocytic hypophysitis with
20. Koshiyama H, Sato H, Yorita S, Koh T, Kanatsuna T,
Nishimura K, Hayakawa K, Takahashi J, Hashimoto N
(1994) Lymphocytic hypophysitis presenting with diabetes
insipidus: Case report and literature review. Endocrine Journal
41:93-97
21. Lack EE (1975) Lymphoid "Hypophysitis" with end organ
22. Mayfield RK, Levine JH, Gordon L, Powers J, Galbraith RM,
Raw SE (1980) Lymphocytic Hypophysitis presenting as a
23. Mazzone T, Kelly W, Ensink J (1983) Lymphocytic hypo-
physitis associated with antiparallel cell antibodies and vitamin
B12 deficiency. Arch Intern Med 143:1794-1795
25. Mc Grail KM, Beyerl BD, Black PM, Klhanski A, Zervas NT
(1987) Lymphocytic Hypophysitis of pregnancy with complete
recovery. Neurosurg 20:791-793
cytic adenohypophysitis causing pituitary mass. Neurology
37:158-161
phocytic hypophysitis with massive fibrosis and the role of
surgical intervention. Surg Neurol 42:74-78
hypophysitis with involvement of the cavernous sinus and hy-
pothalamus. Neurosurg 28:440-444
30. Ozawa Y, Shishiba Y (1993) Recovery from Lymphocytic hy-
pophysitis associated with painless thyroiditis: Clinical impli-
cations of circulating antipituitary antibodies. Acta Endocr
128:493-498
31. Pestell RG, Best JD, Alford FP (1990) Lymphocytic hy-
pophysitis. The clinical spectrum of the disorder and evidence
for an autoimmune pathogenesis. Clin Endocrinol 33 (4):457-
466
32. Reusch JEB, Kleinschmidt-DeMasters BK, Lillehei KO, Rapp
D, Gutierrez-Hartmann A (1992) Preoperative diagnosis of
lymphocytic hypophysitis (adenohypophysitis) unresponsive to
short course dexamethasone: case report. Neurosurgery 30:268-
272
hypophysitis with selective adenocorticotropic hormone defi-
cency. Arch Intern Med 140:1243-1245
34. Scully RE, Mark EJ, McNeely WF, McNeely BU (1995) Case
records of the Massachusetts General Hospital, Case 25-1995.
35. Sobrinho-Simoes M, Brandao A, Paiva ME, Vilela B, Fernandes
E, Carneiro-Chaves F (1985) Lymphocytic hypophysitis in a
patient with lymphoid thyroiditis, lymphoid adenitis, and
idiopathic retroperitoneal fibrosis. Arch Pathol Lab Med
109:230-233
36. Thodou E, Al S, Kontogeorgos G, Kovacs K, Horvath E,
Ezrat S (1995) Clinical case seminar: lymphocytic hypophysitis:
clinicopathological findings. J Clin Endocrinol Metab 80:2302-
2311
Surg Neurol 28:145-149
38. Wild RA, Kepley M (1986) Lymphocytic hypophysitis in a
patient with amenorrhoea and hyperprolactinemia. A case re-
disease: Lymphocytic hypophysitis, in hamsters by recombinant
rubella virus glycoprotein and prevention of disease by neonatal