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CASE-BASED UPDATE

Lymphocytic hypophysitis in the pediatric population

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Abstract
Background Lymphocytic hypophysitis (LYH) is a rare inflammatory disease of the pituitary gland that usually affects women in their ante- or immediate postpartum period; males are affected less frequently than females. An autoimmune pathogenesis is suggested. Symptoms comprise anterior and/or posterior pituitary insufficiency of varying degrees. So far, specific characteristics of this rare disease in childhood are not well described.
Case history We report the case of a 12-year-and-11-month-old boy with histologically confirmed LYH clinically presenting with diabetes insipidus. A high-dose steroid therapy was administered, in which the therapeutic effect was uncertain. His 6-year follow-up is presented.
Discussion The literature is reviewed for children presenting with LYH; their characteristics, pituitary involvement, and clinical follow-up are listed and discussed.
Conclusion Even though magnetic resonance imaging can be highly suspicious for LYH, only surgical exploration can confirm the diagnosis. The efficacy of medical treatment is still controversial; a close follow-up is necessary to control and correct the endocrinological function, if required.

Keywords Lymphocytic hypophysitis · Lymphocytic infundibulo-hypophysitis · Diabetes insipidus · Pediatric

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Background

Introduction

What we know about lymphocytic hypophysitis (LYH) is largely based upon case reports and small case series, which are summarized in some extensive literature reviews together with a research update. So far, however, there has been little attention paid to the occurrence of LYH in the pediatric group. This paper reviews the literature concerning the reports of LYH in children and adolescents and adds to this list an additional case of LYH in a 12-year-old boy.

Classification and definition

Primary LYH is a rare inflammatory disease of the pituitary gland. Depending on the involved inflammatory process, LYH can be classified morphologically as lymphocytic adenohypophysitis (LAH; anterior pituitary lobe), lymphocytic infundibulo-neurohypophysitis (LINH; posterior pituitary lobe and infundibulum), and lymphocytic infundibulo-hypophysitis (anterior and posterior lobe, and infundibulum) [1, 6, 10, 22, 26, 28, 29, 32, 33, 35, 36, 40, 42, 43]. LINH demonstrates inflammatory changes involving the posterior lobe as well as the pituitary stalk [3, 6, 10, 18, 20, 21, 36]. LYH was first described by Goudie and Pinkerton in 1962 [14], and LINH was first described by Saito et al. in 1970 [37].

Pathogenesis and epidemiology

To the current knowledge, LYH is grouped into disorders of autoimmune origin [3, 6, 10, 12, 18, 19, 36, 38, 43]. This opinion is supported by the highly infiltration of lympho-

plasmacytic cells, the inconstant occurrence of anti-pituitary antibodies, and the coexistence of other endocrine or non-endocrine autoimmune conditions [1, 6, 25, 35, 45]. LAH occurs mainly in women with a strong correlation to pregnancy and the postpartum period [10]. About 57% of all cases are reported to be related to pregnancy [10]. LINH seems to show no sex predilection [10, 36]. The mean age at the onset of the disease is estimated at 34.5 years for women and 44.7 years for men [6].

Clinical presentation and outcome

Presenting signs and symptoms are related to a space occupying lesion and/or various degrees of pituitary anterior and/or posterior lobe dysfunctions depending on the pituitary portion that is more affected. The main symptom of LINH is diabetes insipidus and in most patients, the function of the anterior lobe is not affected [3, 6, 18, 20, 21, 36]. The clinical course of LYH includes possible spontaneous remission with or without sequelae up to a rapid deterioration resulting in panhypopituitarism and/or death [6, 10, 36]. The inflammatory process can progress to fibrosis possibly by the mechanism of destroying the vascular supply and resulting in a decrease of blood flow in the pituitary gland. This phenomenon was observed in dynamic magnetic resonance imaging (MRI) follow-up studies [18, 38].

Diagnosis

Clinical presentation, endocrinological assessment, presence of serum anti-pituitary antibodies, and characteristic MRI findings may be highly suspicious for the adequate diagnosis of LYH, but histopathology of the surgical specimen provides confirmation [6, 10, 36]. The pathological endocrinological changes correlate in most cases with the pituitary mass lesion detected by MRI. Histopathologic evaluations show a typical dense lymphocytic infiltration of the pituitary gland without formation of granulomas.

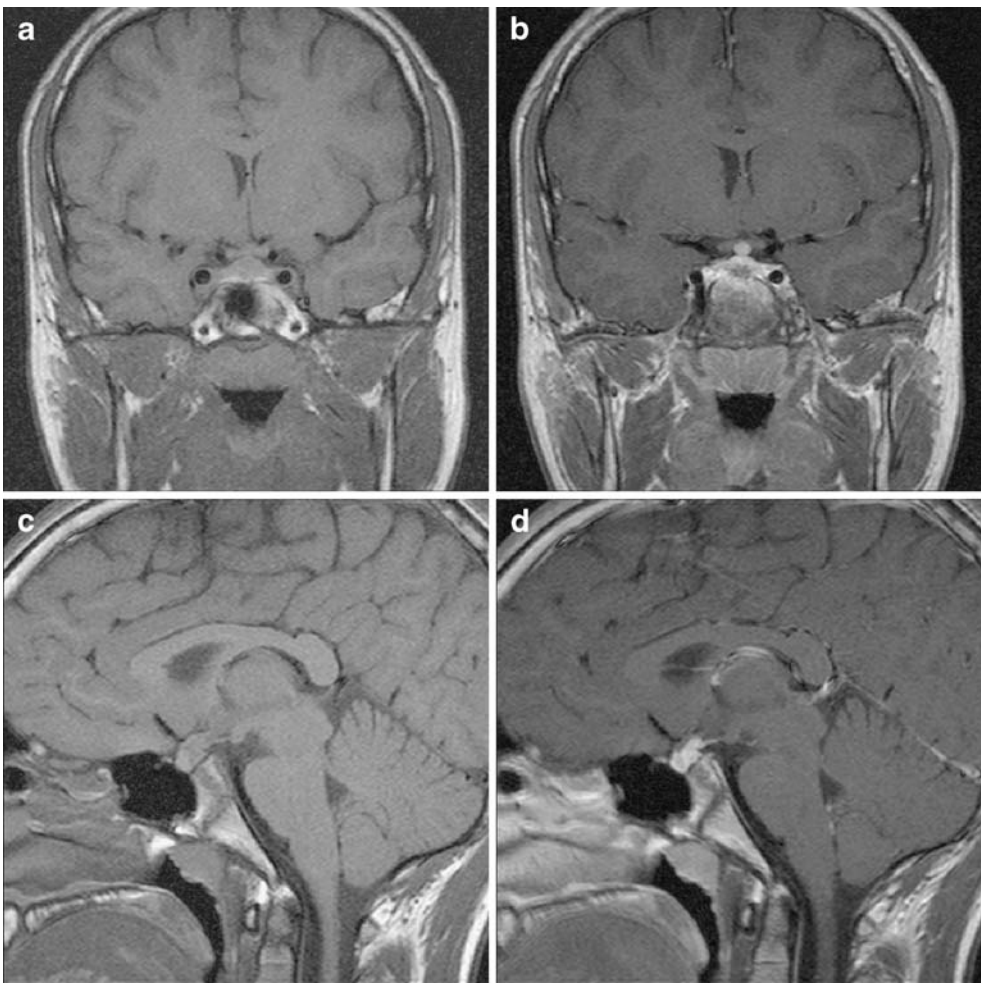

Fig. 1 **a** Coronal T1-weighted MRI performed preoperatively demonstrating pituitary enlargement with suprasellar extension. **b** Contrast enhanced MRI, coronal view, showing a homogeneous enhancing thickened stalk. **c** Sagittal unenhanced T1-weighted MRI obtained preoperatively, revealing an isointense mass lesion of the pituitary stalk, an enlarged pituitary gland, and lack of the hyperintense signal of the posterior lobe. **d** Sagittal gadolinium-enhanced T1-weighted MRI demonstrating homogeneous enhancement of the mass

Management

Apart from hormone replacement, if required, treatment options for LYH are symptomatic with the intended effect of mass reduction. The administration of glucocorticoids or other immunosuppressive agents alternatively such as azathioprine, methotrexate, and cyclosporin A has described to be effective[6, 10, 36]. Surgery either by the transsphenoidal or transcranial route, depending on the target, may reduce tumor volume as well as confirm the diagnosis. In particular cases, stereotactic radiosurgery was used successfully to treat LYH [39].

Illustrative case

A 12-year-and-11-month-old boy presented with headaches, polyuria, and polydipsia, drinking about 11 l of water per day for the past 1.5 months. His past medical history revealed only a Quinke-edema 6 years earlier. The medical history of his family was unremarkable except for his mother who presented a struma nodosa without affecting her general health. Clinical examination of the boy showed normal physical, mental, and sexual development for his age. Fundoscopy, visual fields, and visual acuity were normal on neuro-ophthalmological exploration. The routine blood parameters were within normal range except for the protein level which was slightly increased with 8.6 g/dl (reference value, 6.4–8.2 g/dl). The urinary volume collected over a 22-h period was 10 l and had an osmolarity of 91 mosmol/l. A renal sonography was performed and revealed a diffused parenchymal hyperechogenicity and an ampullary renal pelvis, most likely as a result of polyuria. Conservative treatment with 10 μg vasopressin nose spray was started twice a day and showed immediate effect with improvement of polydipsia and polyuria. A detailed endocrinological examination showed a basal vasopressin of 10 pg/ml (0.0–6.8 pg/ml), free thyroxin 13.6 pmol/l (9–26 pmol/l), and free trijodthyronin 5.9 (2–8 pmol/l). Provocative tests of anterior pituitary functions were also performed and showed good stimulation ability of the pituitary gland with normal levels of follicle-stimulating hormone (FSH), humane growth hormone (HGH), insulin-like-growth-factor-binding protein (IGFBP)-1, IGFBP-3, luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and somatomedin-C. The cortisol level was also within normal range.

A skeletal scintigraphy showed signal intensification in the pituitary gland due to increased storage of the isotopes without any other focal pathological changes in the skeleton.

MRI of the sellar region revealed an 8×8 mm homogeneously enhancing mass lesion in the pituitary stalk and the posterior pituitary gland with lack of the hyper intensity signal of the posterior lobe on unenhanced T1-wheighted images. Enlargement of the whole pituitary gland with symmetrical suprasellar expansion was observed demonstrating slightly inhomogeneous enhancement (Fig. 1a–d).

Surgical treatment

Based on clinical, endocrinological, and neuroradiological findings, the boy underwent a biopsy via a right-sided pterional craniotomy. Macroscopically, the pituitary gland was enlarged; the surface anterior to the pituitary stalk was nodular bulged out considering small abscess-like formations. After opening the diaphragm, the tissue was melting away, and yellowish viscous fluid appeared. Specimens for pathological examination were collected, operative procedure was terminated, and wound closure was uneventful.

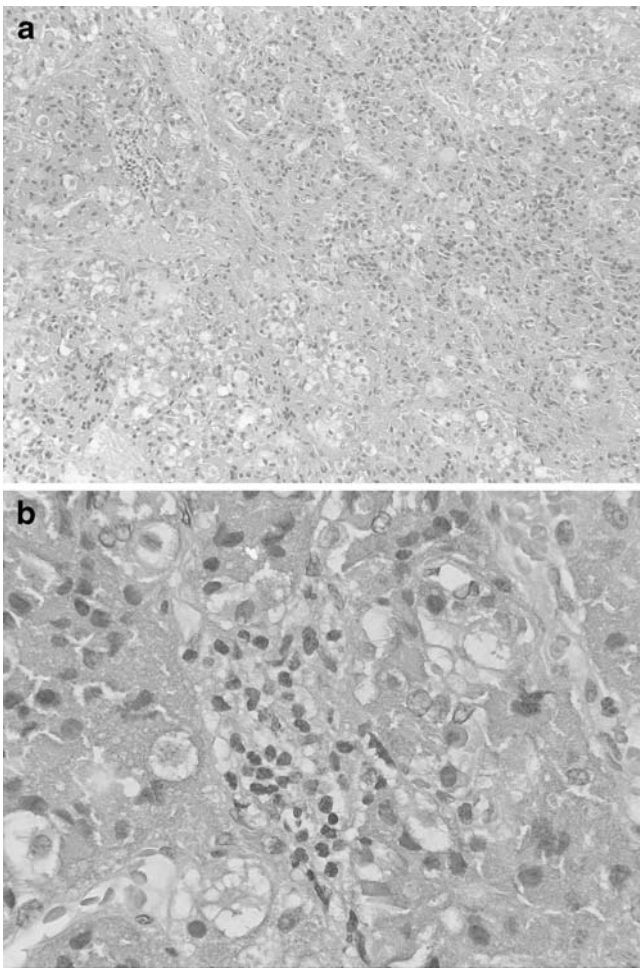

Fig. 2 **a** Photomicrograph of the pituitary specimen showing an overview of the pituitary gland with scattered lymphocytic infiltrates (HE, 200×). **b** In higher magnification, beside the acidophilic cell hyperplasia a diffuse, sometimes focally enhanced infiltration of lymphocytes can be noticed (HE, 400×)

Table 1 Chronological summary of reported children and adolescents with lymphocytic hypophysitis

First author	Year	Age	Sex	Related to pregnancy	Diagnostic method	Histology	Involvement AH/NH or both	Treatment	Follow-up years	Secondary to germinoma	Treatment response
Zeller JR et al. [47]	1982	18	F	Yes	Clinics and imaging	–	AH	Hormone replacement, Glucocorticoids	0.5	No	Significant regression
Levine SN et al. [23]	1988	18	F	Yes	Surgery (resection)	Lymphocytic	AH	Mass reduction[a], hormone replacement	–	No	Not recorded
Brandes JC et al. [9]	1989	17	F	Yes	Clinics and imaging	–	AH	Hormone replacement, glucocorticoids	10	No	Empty sella
Hoshimaru M et al. [16]	1992	6	M	–	Surgery	Lymphocytic	NH	Mass reduction, hormone replacement	–	No	Regression
Ahmadi J et al. [2]	1995	15	F	No	Surgery (biopsy)	Lymphocytic	AH	Mass reduction, Glucocorticoids	–	No	Not recorded
Ogawa R et al. [34]	1995	14	M	–	Clinics and imaging	–	Both	Hormone replacement	–	No	Not recorded
Mizokami T et al. [29]	1996	16	M	–	Clinics and imaging	–	Both	Hormone replacement, Glucocorticoids	6	No	Empty sella
Bastida Eizaguirre M et al. [5]	1996	8	F	No	Clinics and imaging	–	Both	Hormone replacement, Glucocorticoids	2	No	Empty sella
Cemeroglu AP et al. [11]	1997	13	F	No	Surgery (biopsy)	Lymphocytic	NH	Mass reduction, hormone replacement	1.5	No	Unchanged
Honegger J et al. [15]	1997	18	F	No	Surgery (resection)	Lymphocytic	Both	Mass reduction, further therapy not specified	1.5	No	No residual lesion
Weimann E et al. [44]	1997	18	F	No	Clinics and imaging	–	Both	Hormone replacement	–	No	Not recorded
Mootha SL et al. [30]	1997	11	M	–	Surgery (biopsy)	Lymphocytic	Both	Mass reduction, hormone replacement	0.5	No	Regression
Maghnie M et al. [24]	1998	8	F	No	Surgery (biopsy)	Lymphocytic	Both	Mass reduction, hormone replacement, glucocorticoids	7	No	Regression
Sato N et al. [38]	1998	14	M	–	Clinics and imaging	–	Both	Hormone replacement	4	No	Regression
Sato N et al. [38]	1998	9	F	No	Clinics and imaging	–	Both	Hormone replacement	5	No	Total regression
Atkins D et al. [4]	1999	9	M	–	Surgery	Lymphocytic	NH	Mass reduction, hormone replacement	9	No	Regression
Atkins D et al. [4]	1999	4	M	–	Clinics and imaging	–	NH	Hormone replacement	4	No	Significant regression
Fehn M et al. [13]	1999	8	F	No	Surgery (biopsy 2×)	Lymphocytic	Both	Mass reduction, hormone replacement, glucocorticoids	1.5	Yes	Not recorded
Bettendorf M et al. [8]	1999	8	F	No	Surgery (biopsy 2×)	Lymphocytic	Both	Mass reduction, hormone replacement, glucocorticoids, stereotactic radiosurgery, chemotherapy	6.5	Yes	No tumor recurrence

Table 1 (continued)

First author	Year	Age	Sex	Related to pregnancy	Diagnostic method	Histology	Involvement AH/NH or both	Treatment	Follow-up years	Secondary to germinoma	Treatment response
Younes JS et al. [46]	2002	8	F	No	Clinics and imaging	–	AH	Hormone replacement	2	No	Not recorded
Terao T et al. [41]	2003	13	M	–	Clinics and imaging	–	NH	Hormone replacement	1.5	No	Unchanged
Houdouin L et al. [17]	2003	13	M	–	Surgery	Lymphocytic	Not recorded	Mass reduction, chemotherapy	1.5	Yes	Not recorded
Beni-Adani L et al. [7]	2005	8	M	–	Surgery (biopsy)	Lymphocytic	NH	Mass reduction, hormone replacement	1	No	Not recorded
Mikami-Terao Y et al. [27]	2006	13	F	No	Surgery (biopsy 2×)	Lymphocytic	Both	Mass reduction, hormone replacement, glucocorticoids, chemotherapy	1.5	Yes	No tumor recurrence

m Male, *f* female, *AH* adenohypophysis, *NH* neurohypophysis

[a] The term "mass reduction" is used in each surgically treated case, even when only a biopsy was performed, because removal of tissue results anyway in a volume reduction of variable degree

Pathological examination

The quick section pathological evaluation of the hematoxylin and eosin (H & E) stained frozen tissue probe revealed a highly malignant lymphoma. The detailed histopathologic examination of the specimen, however, showed a chronic unspecific inflammatory process with hyperplasia of acidophilic cells (Fig. 2a,b). Inflammation consisted predominantly of lymphocytes, plasma cells, granulocytes, and monocytes. There were no signs for either a monoclonal cell proliferation or a neoplastic process. However, the tissue showed secretion of LH and also a positive antibody reaction against FSH and α-human chorionic gonadotropin (HCG). The antibody fusion with TSH and prolactin (PRL) was weaker. There were no reactions seen with antibodies against β-HCG, HGH, adrenocorticotrop hormone (ACTH), parathomone (PTH) or neurofilament (NF). The antibody reaction to pan-cytokeratines, however, was strongly positive. Tests of organ-specific autoantibodies showed normal values for anti-glutamic acid decarboxylase (GAD) 2. Histopathologic findings were consistent with the diagnosis of LYH. Tissue specimens sent to the European reference center at the "Katholisches Marienkrankenhaus" in Hamburg, Germany, confirmed the diagnosis.

Postoperative course and follow-up

A postoperative endocrinological investigation showed a cortisol level of 258 ng/ml, FSH basal 5.49 mE/ml (0.7–11.1), HGH basal 0.1 ng/ml (0.0–10.0), LH 2.68 mE/ml (0.8–7.6), PRL 92.1 (53–360), insulin-like-growth factor (IGF) 1 630.6 ng/ml, somatostatin 27.0 pg/ml (0.0–26). Under replacement therapy, the vasopressin level was 2.2 pg/ml (0.0–6.8). The daytime cortisol levels were normal with 198.0 ng/ml at 8.00 (70–250), 156.0 ng/ml at 12.00 (50–180) and 86.8 ng/ml at 17.00 (30–120). Medical treatment with high-dose prednisolone (60 mg/m^2) was started and administered for 4 weeks and then slowly reduced over a period of 3 months.

Postoperatively, frequency and intensity of headaches decreased and diabetes insipidus was continued to be treated with vasopressin. At 3 months follow-up, the boy demonstrated steroid-induced side effects, such as severe steroid acne and an iatrogenic Cushing's syndrome. An endocrinologic blood test showed a cortisol level of 91 ng/ml under prednisolone therapy. The levels of FSH, LH, and thyroid hormones were normal. Hormonal blood test results showed a normal HGH peak (14.7 ng/ml) after application of Arginin. IGFBP-3 and IGF 1 were within normal range. After 7 months, the cortison therapy was stopped completely and consequently, side effects resolved.

Six years after initial presentation, a substitution therapy with vasopressin was still necessary but well tolerated to control the diabetes insipidus; no other

replacement of hormone therapy was necessary. At this time, follow-up MRI demonstrated a residual and, over the years, stable 5 mm nodular lesion in the cranio-rostral aspect of the anterior pituitary lobe without contrast enhancement.

Literature review

PubMed searches and the bibliography from the John Hopkins Hypophysitis Research Center which includes 379 patients with LYH were used for this review [10]; a total of 24 patients with this disease up to the age of 18 years at the time of presentation could be detected (Table 1) [2, 4, 5, 7–9, 11. 13, 15–17, 23, 24, 27, 29, 30, 34, 38, 41, 46, 47]. Including our case, 25 children were available for evaluation. There was a slight female preponderance with 56% (14/25); the mean age at diagnosis was 12 years. Twelve percent (3/25) were related to pregnancy. Diagnosis was based on surgical specimens in 56% (14/25); in the remaining children, LYH was concluded from clinical characteristics and typical MRI findings. There were no deaths and no reported morbidity associated with the surgical approaches. Follow-up ranged from several months to 10 years. Involvement of both the adeno- and the neurohypophysis was present in 52% (13/25); all except one presenting with posterior lobe involvement (6/25) were male. In four children (16%), LYH was classified as a secondary form in the presence of germinomas. Steroids were administered, so recorded, in seven patients (three of whom the diagnosis was proven by biopsy), mass reduction was achieved in four (three resulted in an empty sella), one remained unchanged and one could not be evaluated. Fourteen (14/25) children received no steroids, five of whom demonstrated a spontaneous regression; in two, the lesion remained unchanged, five were not recorded, and two showed a normal hypophysis at the last follow-up.

Discussion

Clinically, our patient presented with diabetes insipidus without any other signs of anterior lobe dysfunction, thus, suggesting LINH. Interpretation of the initial MRI may conclude that the enhancing mass obviously originated from the posterior lobe of the pituitary gland. This is consistent with radiological descriptions by Sato et al. [38]. However, intraoperative findings and histological specimens showed that the anterior lobe was extremely altered. The pituitary enlargement with suprasellar expansion on neuroimaging may also favor the affection of the anterior lobe. Despite the fact that there were no anterior lobe hormone deficiencies, macroscopic, histological, and radiological findings support the diagnosis of a lymphocytic infundibulo-hypophysitis assuming the involvement of the adenohypophysis without causing endocrine dysfunction. The present review has found that around 50% of all children with LYH showed both anterior and posterior lobe involvement.

MRI appearance and clinical presentation ruled out the diagnosis of a pituitary adenoma in our patient. Differential diagnoses for the rare non-adenomatous hypophyseal lesions include LYH, idiopathic giant cell hypophysitis, and granulomatous hypophysitis caused by conditions such as tuberculosis, sarcoidosis, syphilis, histiocytosis X, and mycotic infections [6, 11, 19, 25, 36, 40]. Biopsy via a transsphenoidal or pterional approach, depending on where the main mass is located, still remains the gold standard for diagnosing LYH, although MRI has advanced the diagnostic accuracy for LYH in differentiating this disease especially from pituitary adenomas [6, 10, 32, 36, 40]. Surgery may also be therapy to relieve signs and symptoms of marked compression. Referring to the reviewed pediatric group, confirmation of the diagnosis by histopathology was present in 56%. In particular, the possibility of secondary forms to germinomas and the lack of reported surgical morbidity may argue additionally for surgical exploration [7, 8, 10, 13, 17, 27]. The intraoperative aspect of the lesion resembling a yellowish abscess-like formation in the cranial portion of the anterior pituitary lobe seems to be different from other reported findings. Jabre et al. [19] described a gelatinous yellowish fluid with firm tissue which could only be excised by tedious curettage. Furthermore, Abe et al. [1] found a firm yellowish-white mass in the region of the sellar floor after incision of the dura. The first frozen sections of tissue stained during surgery in our patient revealed a uniform picture of the pituitary tissue with dense infiltrations of lymphocytes suggesting a malignant lymphoma. The final histopathologic examination of the specimen including immunohistochemical investigations was able to finally demonstrate the typical signs of LYH.

So far, there is no well-defined concept for medical treatment available; steroids and immunosuppressive agents are proposed without strong evidence of their efficacy [6, 10, 36]. The endocrinological deficit has to be treated by adequate replacement hormone therapy. In most cases, steroid therapy does not improve the symptoms of diabetes insipidus, but some report improvement of their headaches [3, 20, 29, 32]. Neuroradiologically, this treatment may result in a visible reduction of the mass lesion [3, 20]. In our patient, the steroid treatment neither changed the radiological appearance of the residual postoperative lesion nor did it improve diabetes insipidus but caused the well-known side effects which, however, resolved after medication was stopped. The current review indicates that treatment strategies for LYH in childhood may differ

significantly and steroids were administered in only 28%. However, no patient showed a progression of the inflammatory process; all with recorded outcome showed either a documented regression of the lesion or at least an unchanged status. Therefore, no standardized treatment guidelines can be derived from this review.

Six years after the diagnosis of LYH, diabetes insipidus is still present but stable under therapy. On neuroimaging, the lesion remained essentially unchanged in size compared with the immediate postoperative images but demonstrated a slow decrease of contrast enhancement over the years. The lack of the hyperintensive signal of the posterior lobe persisted. This may represent the natural course of the disease, suggesting a correspondence between the decrease of the inflammatory process and the decrease of contrast enhancement on MRI. Residual fibrosis may be responsible for the persistent endocrinological deficit.

Conclusion

LYH is very rare in the pediatric population with 25 identified cases in the literature but has to be recognized as a differential diagnosis of pituitary lesions. Not all involved portions of the pituitary or infundibular system seem to become necessarily symptomatic regarding the endocrinological function. Even though MRI can be highly suspicious for the diagnosis of LYH due to the typical morphology, surgery can confirm the diagnosis and eventually remove mass-effect symptoms if required. An effective medical treatment to control the inflammatory process is still under debate. A close follow-up is mandatory to provide a stable endocrinological status and a good quality of life and gives us the possibility to learn more about the natural course of this disease.

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