

# Autoimmune thyroiditis and thyroid cancer in a child with lymphocytic infundibuloneurohypophysitis

**Mirjana Kocova, Daniela Pop Gjorcheva, Elena Kochova**

## ABSTRACT

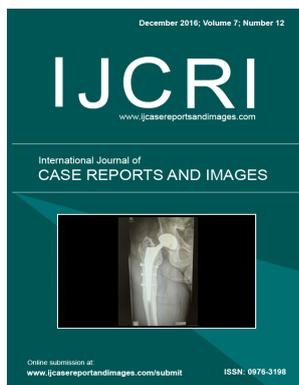
**Introduction:** Lymphocytic infundibuloneuro-hypophysitis (LINH) is a chronic autoimmune inflammation of the posterior pituitary and pituitary stalk which is found only exceptionally in children. Its long-term evolution and the association with other autoimmune diseases are largely unexplored.

**Case Report:** An 11-year-old girl who initially presented with diabetes insipidus was diagnosed with LINH based on the MRI findings. She was treated with desmopressin acetate spray. One year later autoimmune thyroiditis developed with increased thyroid peroxidase antibodies and typical ultrasonographic finding. Due to normal thyroid hormone levels, the girl was not treated with levothyroxine. A large thyroid nodule developed within two years. The standard diagnostic and therapeutic procedures and follow-up for both diseases were undertaken. The LINH had a favorable evolution with regression of the pituitary swelling on MRI, but with permanent diabetes insipidus, whereas the thyroid nodule progressed towards thyroid papillary/follicular carcinoma and was treated surgically with subsequent L-thyroxin substitution.

**Conclusion:** This thus-far unreported combination of a rare and a common autoimmune disease in a pediatric patient demonstrates the possible simultaneity and independent evolution of autoimmune thyroiditis and lymphocytic infundibuloneurohypophysitis.



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and was treated surgically with subsequent L-thyroxin substitution. **Conclusion:** This thus-far unreported combination of a rare and a common autoimmune disease in a pediatric patient demonstrates the possible simultaneity and independent evolution of autoimmune thyroiditis and lymphocytic infundibuloneurohypophysitis.

**Keywords:** Association, Autoimmune thyroiditis, Child, Disease progression, Lymphocytic infundibuloneurohypophysitis

### How to cite this article

Kocova M, Gjorcheva DP, Kochova E. Autoimmune thyroiditis and thyroid cancer in a child with lymphocytic infundibuloneurohypophysitis. Int J Case Rep Images 2016;7(12):853–857.

Article ID: Z01201612CR10739MK

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doi:10.5348/ijcri-2016151-CR-10739

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Received: 25 June 2016

Accepted: 20 September 2016

Published: 01 December 2016

## INTRODUCTION

Lymphocytic adenohypophysitis (LAH) is a chronic autoimmune inflammation of the anterior pituitary leading to its gradual destruction over years. The symptoms are mainly due to hypopituitarism, which in turn causes adrenal insufficiency, hypothyroidism and/or hypogonadism. It is well known that autoimmune hypophysitis occurs usually during pregnancy and in the postpartal period [1]. The posterior pituitary can also be affected, in isolation or in association with LAH, resulting

in diabetes insipidus—a condition known as lymphocytic infundibuloneurohypophysitis (LINH) [2]. In a comprehensive review of 370 articles published during 42 years including a total of 379 patients with primary lymphocytic hypophysitis, a prevalence of 1:9,000,000 adults was reported [1].

The LAH is distinguished from other forms of hypophysitis by several characteristics:

(1) it is considerably rare, (2) there is a female predominance, (3) it is commonly, but not necessarily associated with pregnancy and (4) it is associated with other well established autoimmune diseases, most frequently autoimmune thyroiditis, which appears in 7.4% of patients according to larger studies [1]. LAH and LINH have rarely been reported in children [3]. On the other hand, Hashimoto thyroiditis (HT) is a frequent cause of hypothyroidism in childhood [4]. In adults, the progression of autoimmune thyroiditis towards differentiated thyroid carcinoma is not rare and develops in approximately 30% of patients [5]. Pediatric data, however, are limited.

Here we present a girl with LINH and diabetes insipidus appearing at the age of 11 years, later associated with autoimmune thyroiditis with a fast evolution towards papillofollicular thyroid microcarcinoma.

## CASE REPORT

An 11-year-old girl was admitted due to polyuria of >6 l/d and polydipsia. Her height and weight were within the normal range. The urine and plasma osmolality were 34 and 264 mmol/l, respectively. The urea and creatinine levels were within the normal range. Both kidneys were of normal size and structure on ultrasound. MRI of the pituitary region showed a thickened pituitary stalk, a missing bright signal of the posterior pituitary and a normal-sized pituitary fossa (Figure 1A). Central diabetes insipidus was diagnosed; desmopressin spray therapy (5.5 mg/kg/day) normalized the diuresis. The growth hormone (GH), follicular stimulating hormone (FSH), luteinizing hormone (LH), and estrogen levels were within the normal range and the girl reached the expected final height. Her pubertal development was normal with menarche at 12.5 years and a regular menstrual cycle at 40-day intervals. Follow-up MRI at yearly intervals showed normalization of the pituitary stalk and a continuously missing bright signal of the neurohypophysis (Figure 1B). Upon consulting experts in France, the diagnosis of lymphocytic infundibuloneurohypophysitis (LINH) was confirmed after histiocytosis and hypothalamic hamartoma were excluded as the possible underlying cause. Pituitary antibody levels were not evaluated, only follow-up was recommended.

Sixteen months after the onset of diabetes insipidus, at the age of 12.3 years a diffuse enlargement of the thyroid gland was noticed. The TSH, T4 and thyroglobulin

levels were within the normal range (3.25 mIU/ml, 11 ng/ml and 22.2 IU/ml, respectively), but the anti-thyroid peroxidase (aTPO) antibody levels were above 3000 IU/ml. The ultrasound findings indicated typical Hashimoto autoimmune thyroiditis in both lobes of the thyroid gland (Figure 2A). The recommended l-thyroxine therapy (considering the goiter, ultrasound finding and significantly elevated aTPO antibody levels) was postponed by the endocrinologists in France. The follow-up showed fluctuations of the TSH levels (highest 4.43 mIU/ml, lowest 1.84 mIU/ml), whereas the gland enlargement advanced, especially in the right lobe (40x23x50 mm), where a hyperechogenic nodule (29x17x49 mm) with cystic degeneration appeared (Figure 2B). Fine needle aspiration biopsy led to evacuation of 3.5 ml of hemorrhagic liquid content and histological examination revealed cystic degeneration of a nodular goiter. Two months later, the previously cystic structure developed into a solid nodule measuring 17x14x10 mm which grew during the following six months up to 29x14x14 mm (Figure 2C–D). <sup>99m</sup>TcO<sub>4</sub> scintigraphy showed slightly reduced overall uptake and a “cold” non-functional nodule (Figure 3).

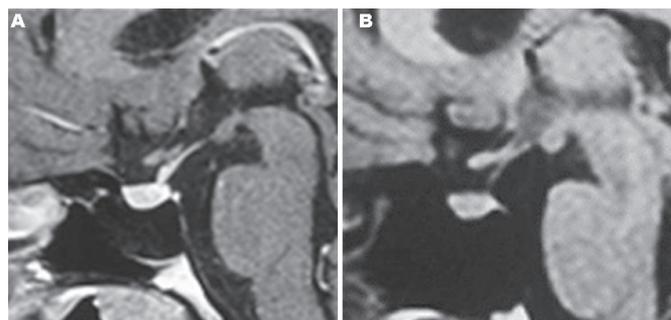


Figure 1: MRI of the pituitary region showing (A) thickening of the pituitary stalk and no bright signal of the posterior pituitary and (B) normalization of the pituitary stalk size and a continuously absent bright signal of the neurohypophysis.

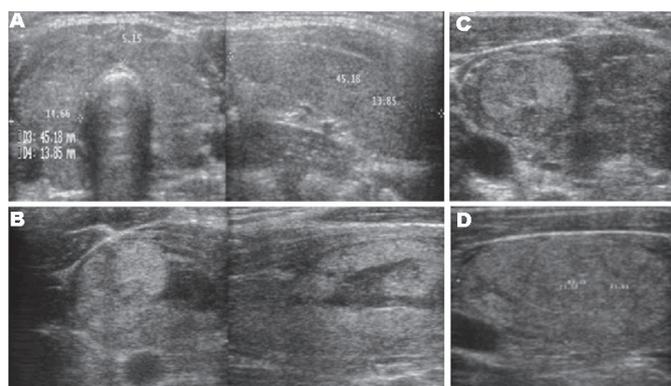


Figure 2: Evolution of the thyroid disease as seen on ultrasound. (A) Hypoechoicity and anisoechoicity (typical Hashimoto thyroiditis) at the age of 12.5 years. (B) Appearance of a cystic nodule at 14 years; fine needle biopsy revealed hemorrhagic content. (C) Solid evolution of the nodule at 15 years; metaplasia was confirmed on biopsy (D) Nodular growth at 16 years. Hemithyroidectomy was performed with pathohistologically confirmed mixed papillofollicular microcarcinoma.

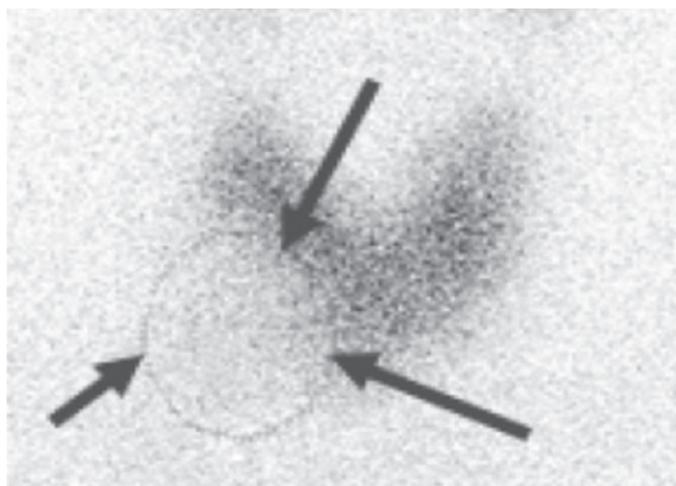


Figure 3:  $^{99m}\text{TcO}_4$  scintigraphy of the thyroid gland. Diffusely reduced thyroid uptake with a “cold”, non-functional nodule in the right lobe.

Repeated aspiration biopsy revealed a group of thyrocytes with oncocytic metaplasia and diffusely dispersed inflammatory infiltration. After surgical removal of the right lobe and isthmus, we obtained a histological confirmation of a hyperplastic follicular nodule with malignant transformation. Within the nodule two encapsulated foci of mixed papillofollicular multicentric microcarcinoma were detected, with a diameter measuring 7 mm and 2 mm, respectively; they were clearly delineated from the surrounding thyroid tissue and surgical excision line and did not invade the blood vessels or lymph nodes.

The girl is currently on continuous replacement therapy with l-thyroxine at 1.5 mg/kg/day. Her yearly follow-up showed normal values of T4 and TSH value in the range 1–2 mIU/ml) and stabilized levels of thyroglobulin (up to 30 ng/ml). There were no clinical or ultrasound indications of disease progression during the two-year follow-up after surgery.

## DISCUSSION

We have described a patient with LINH resulting in permanent diabetes insipidus associated with autoimmune thyroiditis evolving towards malignancy. There are few reports of LINH in literature, mostly in pregnant and postpartum women and usually accompanied by LAH [1]. In the study of Imura et al., 9 out of 17 adult patients with diabetes insipidus had a typical enlargement of the pituitary stalk and/or neurohypophysis with a missing bright signal [2]. Many of these patients had impaired growth hormone secretion.

LAH and LINH are rare in children. Some reports of isolated LINH are published in the medical literature. It usually presents as central diabetes insipidus and the function of the anterior lobe is usually preserved [2]. In a series of 21 children and adolescents diagnosed during

a period of 24 years, six had isolated neurohypophysis and four of them had a pituitary mass that was removed [3]. Our patient presented with isolated central diabetes insipidus and was effectively treated with desmopressin replacement therapy only.

Most of the LINH patients reviewed in literature are diagnosed based on the typical clinical presentation, avoiding aggressive diagnostic procedures when possible. However, the diagnostic approach differs between centers [6]. The significance of determining the concentration and type of anti-pituitary antibodies is a subject of large debate since the available methods provide limited sensitivity and specificity, which precludes the establishment of standard reference levels [1, 6, 7]. MRI is an important tool in the diagnosis of LINH since the pituitary stalk thickening and a missing posterior pituitary bright signal are considered characteristic radiological signs. Both these findings were present in our patient. Some authors consider pituitary stalk biopsy as mandatory, however, it has not been performed in most of the published cases with LINH [6]. The autoimmune process is usually self-limited and therefore biopsy should be performed with caution, especially in children [7].

Different approaches towards the management of LINH have been proposed and it remains controversial. Most authors suggest conservative treatment [8]. Some authors recommend corticotherapy, hormonal replacement and newer therapeutic options such as azathioprine or radiation, however, when a larger pituitary mass is detected, the best treatment approach is unclear [7]. Possible evolutions of the disease include spontaneous remission with or without sequelae, rapid deterioration towards panhypopituitarism or delayed fibrosis of the affected part of the pituitary. Our patient underwent spontaneous remission with normalization of the pituitary stalk and consequent permanent diabetes insipidus. However, long-term follow-up is warranted.

As an autoimmune disease, LINH can be associated with other autoimmune diseases, but most evidence comes from studies of adult patients [1]. To our knowledge, no data on these associations are available for children. Hashimoto thyroiditis in our patient appeared with typical findings. The evolution towards a thyroid nodule with central liquefaction, followed by the histological finding of a mixed papillofollicular microcarcinoma along with LINH is a unique evolution of two independent autoimmune diseases. In different studies progression towards malignancy in children with Hashimoto thyroiditis is low and varies between 0.67% and 10% [9]. However, fine needle aspiration is recommended in all patients with Hashimoto thyroiditis and single nodules with a diameter greater than 1 cm [6].

The patient had high aTPO antibody titers during the entire follow-up. Although there is evidence that early treatment of autoimmune thyroiditis with l-thyroxine decreases aTPO antibodies and thyroid gland volume, the treatment approach remains controversial [10]. European guidelines recommend treatment when TSH

is above 5.5 mU/ml. The question whether early therapy with l-thyroxin in our patient might have prevented the evolution towards carcinoma will remain unanswered. As in adults, the treatment of differentiated thyroid carcinoma is a combination of surgery, radioiodine ablation of the thyroid remnant and metastases and hormone replacement/suppressive therapy with l-thyroxine. According to the cytological findings in our patient (classification group I), there were no arguments in favor of a total thyroidectomy, radioiodine ablation and/or application of suppressive l-thyroxine doses. Our patient is continuously treated with 1.5 µg/kg/day l-thyroxine per day, which maintains the levels of TSH below 1 mIU/ml and TG below 30 IU/ml, in the presence of the left thyroid lobe.

## CONCLUSION

Lymphocytic infundibuloneurohypophysitis (LINH) can appear in childhood and can occasionally be accompanied by autoimmune thyroiditis. The evolution of both diseases is independent. The diagnostic and therapeutic approach should be tailored to each case separately, avoiding unnecessary invasive procedures when possible, but including a thorough follow-up when a single thyroid nodule appears.

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## Author Contributions

Mirjana Kocova – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Daniela Pop Gjorcheva – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Elena Kochova – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

Authors declare no conflict of interest.

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