

Pathogenesis of Marked Pituitary Enlargement and Increased Serum Thyroid-Stimulating Hormone in Primary Hypothyroidism

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Dear Editor:

Longstanding untreated primary hypothyroidism may lead to pituitary enlargement on account of thyrotroph hyperplasia (1). Imaging has a low specificity to differentiate pituitary hyperplasia from an adenoma. An accurate diagnosis is of the utmost importance, as hyperplasia will resolve with thyroid hormone supplementation, while thyroid-stimulating hormone (TSH)-secreting adenomas usually require surgical intervention. We present a case of postpartum autoimmune hypothyroidism associated with pituitary gland enlargement and a TSH level of almost 1400 μ IU/mL, which is the highest level reported in an adult with autoimmune hypothyroidism.

A previously healthy 23-year-old Caucasian woman noticed weight gain, cold intolerance, hair loss, and fatigue 3 months postpartum. She subsequently developed headaches, blurred vision, and cessation of her menstrual cycles. Family history was remarkable for hypothyroidism. She was evaluated 10 months postpartum and did not have a goiter, myxedema, or other endocrine stigmata. A formal visual field exam showed bitemporal hemianopsia. Laboratory data showed a markedly elevated TSH of 1398 μ IU/mL (repeated 1362, normal: 0.34–5.6), low free thyroxine (T4; 2.83 pM/L, normal: 6.44–20.59), low free triiodothyronine (T3; 1.54 pM/L, normal: 3.7–6.47), and mildly elevated prolactin (1,260.8 pM/L, normal: 43.5–1,043.5). Pituitary magnetic resonance imaging (MRI) showed a uniformly enlarged pituitary gland with homogeneous contrast enhancement, suprasellar extension, impingement on the anterior aspect of the optic chiasm, and no involvement of the cavernous sinuses (see Supplementary Data, available online at www.liebertonline.com/thy). The patient was initiated on 88 mcg of oral levothyroxine (LT4) daily (1.6 mcg/kg). Two weeks later, TSH was 123 μ IU/mL, with normal free T4 (10.3 pM/L) and free T3 (3.7 pM/L). Heterophile antibodies against TSH (scantibodies heterophile blocking reagent) were negative, and thyroid microsomal antibodies were elevated (254 units/L, normal <35). Alpha-subunit was normal (1.4 μ g/L, normal: <3.7) and the alpha-subunit/TSH molar

ratio was <1. Serum cortisol and adrenocorticotropic hormone were normal, and insulin-like growth factor 1 level was low (14 nM/L, normal: 17–64). A few weeks after LT4 initiation, headaches and visual defects resolved, energy improved, and menstrual cycles returned. Three months after LT4 initiation, TSH was 6.51 μ IU/L, with normal free T4, free T3, and prolactin (see Supplementary Data). A follow-up MRI showed a decrease by >60% of the pituitary size. The dose of LT4 was increased to 100 mcg (1.9 mcg/kg). Nine months after the diagnosis, TSH normalized at 1.93 μ IU/mL and MRI demonstrated a normal pituitary gland (see Supplementary Data).

The differential diagnosis of elevated TSH includes primary hypothyroidism, TSH-secreting pituitary adenoma, lab interference due to antibodies directed against TSH, and thyroid hormone resistance. Our patient had primary autoimmune hypothyroidism as shown by decreased T3 and T4, elevated microsomal antibodies, normal alpha-subunit ratio to TSH, and absence of heterophile antibodies against TSH. Even more, the patient experienced resolution of symptoms, visual field defects, laboratory abnormalities, and pituitary enlargement after LT4 replacement. As imaging cannot reliably distinguish a TSH-secreting pituitary adenoma from pituitary enlargement due to primary hypothyroidism, a thorough clinical and biochemical evaluation and repeated pituitary imaging are required to make the diagnosis and to avoid unnecessary surgical intervention.

Pituitary enlargement as a result of untreated primary hypothyroidism was reported initially in 1851 by B. Niepce, but its pathogenesis remains uncertain. In humans, histology studies showed thyrotroph cell hyperplasia (large, oval cells with eccentric nucleus, abundant cytoplasm, and prominent Golgi complexes are called “thyroidectomy cells”) and multifocal lactotroph hyperplasia (1). The thyrotroph cell hyperplasia is attributed to a loss of thyroxine feedback inhibition at the hypothalamic level and subsequent overproduction of thyrotropin-releasing hormone (TRH). However, the relative contribution of these factors is unclear. *In vitro* experiments with TRH perfusion of pituitary cultures caused a greater

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TSH stimulation in thyroidectomized versus euthyroid rats. The response persisted despite adding T3 to the hypothyroid rat culture media, although it was of lower amplitude (2), suggesting that TRH has an independent role in thyrotroph stimulation. Different results emerged from experiments on athyroid Pax8^{-/-} double-knockout mice that lacked both the functional thyroid gland and pituitary TRH transducing receptor-1. Despite the lack of TRH effect, these animals exhibited severe thyrotroph hyperplasia and increased expression of Dio2 mRNA enzyme (converts T4 to T3 and regulates TSH mRNA expression), supporting a direct effect of the athyroidism (3). Finally, Long-Evans rats receiving methimazole exhibited thyrotroph hyperplasia, increased TRH receptor immunoreactivity, decreased somatotroph cell population, and colocalization of growth hormone and TSH in the rough endoplasmic cisternae of some thyroidectomy cells. This suggests that thyrotroph hyperplasia may be partly due to transdifferentiation of somatotrophs into thyrotrophs (4). In summary, further studies are necessary to clarify the mechanism of pituitary hyperplasia caused by primary hypothyroidism.

Disclosure Statement

No competing financial interests exist.

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