CASE REPORT

Sheehan's syndrome co-existing with Graves' disease

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Abstract

Sheehan's syndrome (SS), which is an important cause of hypopituitarism, is common in developing countries. The most common presentation is the absence of lactation and amenorrhea. Hypothyroidism rather than hyperthyroidism is the usual expected phenomenon in SS. Postpartum hyperthyroidism is also common and Graves' disease (GD) is an important cause of postpartum hyperthyroidism. Here we report a case of a 22-year-old female patient in our clinic presented symptoms of amenorrhea, lack of lactation, palpitations and sweating. Her physical examination revealed goiter, moist skin and proptosis. Her laboratory evaluation showed suppressed thyroid stimulating hormone, elevated levels of free thyroxine and free triiodothyronine. Thyroid antibodies were positive. Tec^{99m} thyroid scintigraphy results were gland hyperplasia and increased uptake consistent with GD. She gave birth 7 months ago; after delivery she had a history of prolonged bleeding, amenorrhea and inability to lactate. She had hypogonadotropic hypogonadism, hyperprolactinemia and growth hormone deficiency. Serum cortisol and adrenocorticotropic hormone levels were normal. Her magnetic resonance imaging was empty sella. Our diagnosis was GD co-existing with SS. GD with concomitant hypopituitarism is rare but has been described previously, but there are no reports of GD occurring with SS. In this case study, we report a patient with GD associated with SS.

Key words: Graves, hyperthyroidism, Sheehan's syndrome

Date of Acceptance: 10-Jan-2014

Introduction

Sheehan's syndrome (SS) results from ischemic pituitary necrosis caused by severe postpartum hemorrhage.[1] SS is a common problem in underdeveloped or developing countries where epidemiological studies have reported a high prevalence rate.[2,3] SS clinical spectrum varies from general symptoms, such as weakness and fatigue, to severe pituitary insufficiency that can lead to coma and even death.[4] Because prolactin (PRL) and growth hormone (GH) are the first two hormones to be lost in patients with SS, the most common presentation of SS is the absence of postpartum lactation and menstruation.[1,5]

Due to the susceptibility of the pituitary gland's vascular structure to ischemia in instances of prolonged arterial hypotension or venous congestion, the pathogenesis and the natural history of SS remain unclear.[6] During pregnancy, pituitary volume increases up to 36% of the average normal size due to lactotrophic hyperplasia; the most common cause is excess bleeding during delivery.[7] Diagnosis of SS is based on medical history, physical findings and pituitary hormone levels. Radiological findings in SS patients vary according to the stage of the disease; an enlarged pituitary gland is evident in the early stages, whereas pituitary atrophy and an empty sella due to arterial necrosis can be seen in the later stages.[8] The treatment goal for SS is a replacement of the absent hormones; glucocorticoid hormone replacement should be performed first, then thyroid hormone replacement and finally sex steroid administration until the time of menopause.[1]

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.141447

PMID: *******

Postpartum exacerbation is seen in several autoimmune diseases. Suggested reason is that suppressed immune system during pregnancy returns to normal after delivery; even beyond the normal showed a rebound. Postpartum thyrotoxicosis is the most common problem 3-4 months after delivery.[9] Graves' disease (GD) is an autoimmune disorder caused by activation of the thyrotropin receptor by thyroid receptor antibodies, leading to the production of thyroid hormones.[10] Hyperthyroidism, especially diffuse toxic goiter, is common in postpartum women. In rare cases of pituitary insufficiency, there may be difficulties in diagnosis, treatment and follow-up. Concomitant hypopituitarism with thyrotoxicosis is rare and has been described previously, but there have been no documented cases of concomitant GD and SS. Here, we present the first report of such a patient.

Case Report

This was a case of a 22-year-old female patient came to our clinic with amenorrhea, lack of lactation, palpitations and sweating. In her medical history, she had a birth 7 months ago, however she had excessive bleeding during the delivery and was unable to breastfeed and she had amenorrhea. She had been admitted to another center 3 months previously with these symptoms. Her laboratory tests revealed suppressed thyroid stimulating hormone (TSH), elevated free thyroid hormones, chronic thyroiditis at ultrasonography and high I^{131} uptake (43% and 63% after 4 and 24 h, respectively). It was considered that her symptoms were related to GD and she was administered propylthiouracil and propranolol, she received this medication for 3 months until admission to our clinic. However, she did not have any healing; she admitted our center with the same symptoms. Goiter, moist skin, proptosis were found in her physical examination. Laboratory testing also revealed low levels of serum TSH (<0.0001 mIU/mL; normal range 0.4-4.0 mIU/mL) and elevated levels of free thyroxine (FT4) (2.14 ng/dL; normal range 0.85-1.78 ng/dL), free triiodothyronine (FT3) (13.06 pg/mL; normal range 1.57-4.71 pg/mL), anti-thyroperoxidase (>1000 IU/mL; normal range < 5.6 IU/mL), anti-thyroglobulin (939 IU/mL; normal range < 4.11 IU/mL) and TSH receptor antibody: 6.56 U/L (normal range 0-1 U/L). Tec^{99m} thyroid scintigraphy results were in agreement with GD. Her physical examination revealed exophthalmos, with Hertel measurements of 21 mm (right eye) and 19 mm (left eye). Because she had excessive bleeding during the delivery of her baby 7 months previously and was unable to breastfeed, additional laboratory examinations were performed. Her serum estradiol levels were low (28 pg/mL; normal range 33-196 pg/mL), while the levels of other pituitary hormones were as follows: Luteinizing hormone (LH): 5.66 mIU/mL (normal range 0.5-16.9 mIU/mL), follicle stimulate hormone (FSH): 6.12mIU/mL(1.5-9.1mIU/mL),PRL3.48ng/mL(2.8-29.2ng/mL), GH: 0.031 ng/mL (0-5 ng/mL), insulin such as growth factor-1 (IGF-1): 97.9 ng/mL (109-284 ng/mL), cortisol 12.99 mcg/dL (5-18 mcg/mL) and adrenocorticotropic hormone (ACTH) 10.0 pg/mL (0-60 pg/mL). Due to the low basal serum cortisol level in the patient, 250 mcg Synacthen was administered intravenously and the resulting cortisol levels were found to be normal (>20 mcg/dL) after this stimulation. The serum calcium level was also normal (9.6 mg/dL). The patient presented hypogonadotropic hypogonadism and GH deficiency and pituitary magnetic resonance imaging (MRI) showed an empty sella. We continued to administer her anti-thyroid therapy by increased dose, in addition to them; we started cyclic estradiol valerate and norgestrel progesterone therapy. At 2 months later, she did not have any palpitation or sweeting. At 4 months later, her menstrual bleeding had been started.

Discussion

SS results from excessive postpartum hemorrhage are an important cause of postpartum hypopituitarism.[1,4] SS is a common problem in underdeveloped or developing countries. In epidemiological studies prevalence of SS in India is higher than Iceland.[2,3] Its clinic is highly variable; it may range only amenorrhea and lack of lactation to coma, eventually death. All of the anterior pituitary hormones may be decreased.[1,5] In our case hypogonadism, hypoprolactinemia and GH deficiency were seen. Smaller anatomic size of sella, disseminated intravascular coagulation and autoimmunity are predisposition factors for SS. This syndrome has a slow clinical progression in terms of pituitary dysfunction, often occurring several years after delivery. Anti-pituitary and anti-hypothalamic antibodies may be present in some patients with SS and autoimmune pituitary response could also play a role in SS.[11] We did not find any predisposable factors in our case. The mean duration between the date of the last delivery and the time of diagnosis varies between 2 and 40 years.[12] Our patient was diagnosed 7 months after delivery.

Diagnosis of SS is based on medical history, physical findings and pituitary hormone levels. Thus, basal hormone levels, including those of PRL, FT3, FT4 and TSH, cortisol, ACTH, FSH, LH, estradiol and IGF-1 should be measured for proper diagnosis. After laboratory evaluation pituitary MRI is necessary for differential diagnosis. A spectrum of differential diagnosis of SS includes pituitary apoplexy, lymphocytic hypophysitis and primary empty sella syndrome. Lymphocytic hypophysitis is an autoimmune disorder characterized by lymphocytic infiltration and destruction of pituitary glands. It is more common in female than male and causes to pituitary deficiency. It usually manifests during pregnancy and the postpartum period.[13] First hormone being lost is ACTH. PRL level is high. Diabetes insipidus

is common. Diagnosis is pathological, but MRI is useful in diagnosis showing diffuse thickening of the pituitary stalk.[13] In our case, PRL level was low and MRI was compatible with empty sella.

Some autoimmune diseases have exacerbation in the postpartum period due to normalization of the immune system. Postpartum hyperthyroidism is a common problem. The most common etiologies are postpartum thyroiditis (PPT) and GD. Hyperthyroid phase of PPT may be confused with GD. In PPT uptake is low, in GD uptake is high. GD has goiter and ophtalmopathy.[9] In our case, patient had goiter and proptosis. Her uptake was high and thyroid receptor antibody was positive.

The measurement of TSH levels is one of the best indicators used for thyroid disorder diagnoses and treatment monitoring. But with certain conditions, such as central hypothyroidism, TSH-secreting adenomas, pregnancy and thyroid hormone resistance, TSH is not the appropriate test for diagnosing thyroid disease. GD is common in postpartum women, as is SS in developing countries. Our case illustrates the development of autoimmune thyrotoxicosis with undiagnosed SS. Although cases of concomitant hypopituitarism and thyrotoxicosis are rare, it has been described previously. Lewandowski *et al*.[14] reported a similar case in a patient with previous panhypopituitarism and hyperthyroidism (GD).

Moulik *et al*.[15] described a patient with post-operative hypopituitarism who was administered thyroid hormone and steroid replacement therapy following transsphenoidal resection. The therapy induced weight loss and sweating in the subject and the results of thyroid function tests revealed thyrotoxicosis. After ceasing thyroid replacement, Tc^{99m} pertechnetate thyroid uptake measurements were in accordance with those of GD. Furthermore, the patient was positive for thyroid stimulating hormone receptor antibodies. In another case report, a 24-year-old male patient presenting with hypercalcemia and hypernatremia was diagnosed with hypopituitarism, diabetes insipidus and GD.[16]

More recently, the potential coexistence of TSH-secreting pituitary adenomas and autoimmune hypothyroidism,[17] GD and macroprolactinoma[18] and GD and lymphocytic hypophysitis has been reported.[19,20] In cases of acromegaly, the presence of goiter is 59.2%; however, overt hyperthyroidism develops in 8.6% of patients.[21] In contrast, some studies have shown that in patients with autoimmune thyroid disease, the frequency of antipituitary antibodies is higher than that in both non-autoimmune thyroid disease patients and control groups, including Hashimoto's thyroiditis patients. Yet, in these cases, anterior pituitary hormone deficiencies were not detected.[22-24]

Conclusion

Concomitant pituitary deficiency and GD is seldom reported. TSH levels are typically low with pituitary deficiency; however, serum TSH measurements alone are insufficient for accurate diagnosis and free hormone levels should also be considered.

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How to cite this article: Arpaci D, Cuhaci N, Saglam F, Ersoy R, Cakir B. Sheehan's syndrome co-existing with Graves' disease. Niger J Clin Pract 2014;17:662-5.

Source of Support: Nil, **Conflict of Interest:** None declared.