Case Report
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Williams-Beuren Syndrome Associated with Parathyroid Adenoma: A Case Report

Williams-Beuren Sendromu'nun Paratiroid Adenoma ile İlişkisi: Olgu Sunumu

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Abstract
Williams-Beuren syndrome (WBS), a rare familial multisystem disorder, is characterized by congenital heart defects, skeletal and renal anomalies, cognitive disorders, social personality disorder, dysmorphic facies, and hypercalcemia. Herein, we report a case of WBS with parathyroid adenoma (PA). In a 32-year-old women who was admitted to the endocrinology clinic for hypercalcemia. We diagnosed PA with neck ultrasonography and parathyroid scintigraphy. Very few cases of WBS have been documented worldwide. To the best of our knowledge, this is the first report on WBS associated with PA.
Keywords: Williams-Beuren syndrome; parathyroid adenoma

Özet
Williams-Beuren sendromu (WBS), ender görülen ailesel bir multisistem bozukluktur. Sendrom konjenital kalp defektleri, iskelet ve böbrek anomalileri, bilişsel bozukluklar, sosyal karakter bozuklukları, dismorfik yüz ve hiperkalsemi ile karakterizedir. Bu çalışmada, paratiroid adenomu (PA) olan WBS'li bir hasta incelenmiştir. Otuz iki yaşındaki kadın hasta, hiperkalsemi nedeni ile endokrinoloji kliniğine başvurmuş, boyun ultrasonu ve paratiroid sintigrafisi ile PA tanısı almıştır. Tüm dünyada rapor edilen WBS sayısı sınırlıdır. Bu çalışmada PA ilişkili bir WBS hastası tartışılmıştır. Bilgimiz dâhilinde bugüne kadar rapor edilmiş ilk hastadır.
Anahtar kelimeler: Wiiliams beuren sendromu; paratiroid adenom

Introduction

Williams-Beuren syndrome (WBS) is a rare disease that is seen in 1 in 20,000 births. Approximately 90% of patients with WBS have deleted 7q11.23 chromosome, which can be detected with fluorescent in situ hybridization (FISH) (1). In addition, the mutation of the elastin gene leads to phenotypic changes in patients (2). WBS is characterized by congenital heart defects (CHDs; supravalvular aortic stenosis and/or supravalvular pulmonary stenosis, and mitral valve anomaly are seen in less than 30%) (3, 4), neonatal hypercalcemia, nephrocalcinosis, skeletal and renal anomalies, auditory anomalies, dental anomalies, hypertension, cognitive disorder, social personality disorder, hypothyroidism, and dysmorphic facies (5, 6). The neurocognitive profile of patients with WBS mainly includes mild mental retardation. The patients have similar facial features that become more noticeable with age (7-9). No cure exists for WBS and patients diagnosed with this disease need to be treated and followed-up for symptoms for their entire life (10).

Patients with WBS have higher serum calcium concentration than the general population (11). The degree of hypercalcemia is usually mild to moderate and typically non-symptomatic. In some cases, the episodes of hypercalcemia may be present with the loss of appetite, anorexia, nausea, polyuria, polydipsia, and constipation (12). Hypercalciuria is often seen during the episodes of hypercalcemia and rarely results in nephrocalcinosis. It is diagnosed in approximately 5% to 10% of the patients undergoing renal ultrasonography. Hypercalciuria is not commonly observed in patients with WBS after the first year of their life (11, 12).

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As WBS is known a childhood disease accompanied by cardiac and cognitive problems, the endocrinological disorders and management of adult patients are not well known (9).

Case Presentation

A 32 year-old-female patient was diagnosed with WBS at the age of 5 during an examination for hypothyroidism and on genetic evaluation. The karyotype determined by FISH was 46 XX (7q11.23). The patient's medical history revealed that she was under treatment for hypothyroidism and taking L-thyroxin (50 mcg) once daily. Furthermore, the thyroid hormone levels were within the normal range. The patient was admitted to the endocrinology clinic because of mild hypercalcemia-11.7 mgr/dL (8.6-10.0 mg/dL), calcium ionized-5.94 mg/dL (4.64-5.68 mg/dL), and constipation. In addition, the patient had a typical face with a bulged forehead (Figure 1). Cardiac examination of the patient revealed that she only had mild mitral valve regurgitation and the blood pressure was within the normal range (110/70 mm/Hg). Whole-body dual energy X-ray absorptiometry scan revealed a bone density of 0.614 g/cm2. This value translated to a T-score of –2.1 (<–1) at the left femur neck, indicating osteopenia. The 25-OHD3 vitamin level: 49 ng/mL (25-80 ng/mL), 1,25(OH)2D3 vitamin level: 77.5 pg/mL (26.1-95 pg/mL), phosphorus (P): 3.34 mg/dL (2.7-4.5 mg/dL), calcitonin: <2.00 ng/mL (0-5 ng/mL), urinary calcium extraction: 150 mg/day (<250 mg/day), TSH: 2.25 uIU/mL (0.27-4.2 uIU/mL), FT4:15.85 pmol/L (12.0-22.0 pmol/L), and parathyroid hormone level: 113 pg/mL (15-65 pg/mL) of the patient were high (Table 1). In addition, renal ultrasonography findings were normal. We diagnosed the right inferior parathyroid adenoma with neck ultrasonography and parathyroid scintigraphy (Figure 2) during the examination for hypercalcemia. PA of 3-cm diameter on the right inferior side was removed. The pathological study of the specimen revealed PA as preoperatively suspected (Figure 3). The postoperative course of the patient was satisfactory, with normal calcium and parathormone levels within one-year follow-up. The patient had no symptoms or recurrences during the follow-up period.

Discussion

This report aims to present a case of concomitant presence of WBS and PA in a 32-year-old female patient who was operated for PA. So far there have been many mechanisms suggested to explain hypercalcemia for WBS, such as increased Vitamin D sensitivity, primary hyperparathyroidism and osteoclasts increasing bone reabsorption. However, none has been found to be linked with hypercalcemia for WBS (8, 11–13). Although PA is one of the reasons to explain hypercalcemia for WBS, no previous study exists on WBS associated with PA.

Garabedian et al. (13) suggested that hypercalcemia may be the consequence of abnormal synthesis or degradation of 1,25-(OH)2D in children with WBS. The 1-25 OH D3 vitamin level of the patient was normal (1-25-OH D3 vitamin: 77.5 pg/mL). Culler et al. (14) claimed that a deficiency of calcitonin may explain the abnormalities of calcium metabolism seen in these patients. In this case report, the calcitonin level of the patient was normal (Calcitonin: <200 pg/mL; Table 1).

Figure 1: Patient's image.

Table 1. Patient laborotory results.

	Results	Reference values
Calcium	11.7 mg/dl	8.6 10.0 mg/dl
Calcium Ionized	5.94 mg/dl	4.64-5.68 mg/dl
25-OH D3	49 ng/ml	25-80 ng/ml
1-25-OH D3	77.5 pg/ml	26.1-95 pg/ml
P	3.34 mg/dl	2.7-4.5 mg/dl
UCE	150 mg/24 hour	<250 mg/day
Calcitonin	<2.00 ng/ml	0-5 ng/ml
PTH	113 pg/ml	15-65 pg/ml
TSH	2.25 uIU/ml	0.27-4.2 uIU/ml
FT4	15.85 pmol/L	12.0-22.0 pmol/L

UCE: Urinary calcium extraction; PTH: Parathyroid hormone; TSH: Thyroid stimulating hormone; P: Phosphorus.

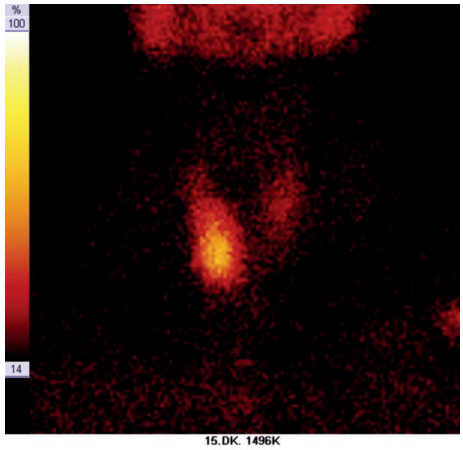

Figure 2: Parathyroid scintigrafi imaging.

Hypercalcemia in primary hyperparathyroidism is caused by parathyroid hormone-mediated activation of osteoclasts leading to increased bone resorption and elevated intestinal calcium ab-

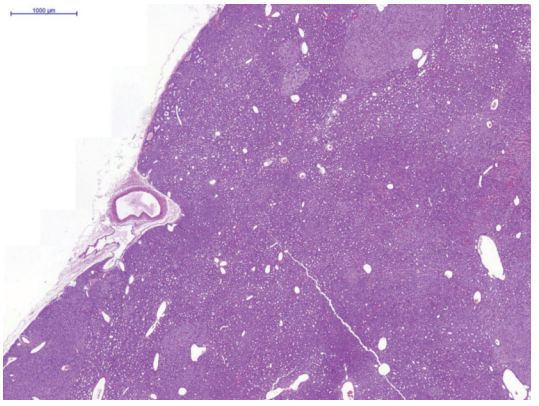

Figure 3: Microscopic imaging of parathyroid adenoma.

sorption (15, 16). Primary hyperparathyroidism is mainly caused by a PA (17). Patients typically have slight elevations in serum calcium concentrations (less than 11 mg/dL or 2.75 mmol/L), and several patients have intermittent hypercalcemia (17, 18).

Patients with PA may have increased bone resorption and decreased bone mineral density (BMD), particularly in more cortical sites (forearm and hip) when compared with more trabecular sites (spine) (19). However, a slight reduction in BMD was observed in the patient. The degree of bone loss reflects the severity of hyperparathyroidism and the presence of PA. A definitive treatment for PA and hypercalcemia should be applied to prevention of the morbidity and mortality related to osteopenia and osteoporosis. The only definitive treatment for the primary hyperparathyroidism is curative parathyroidectomy, which is defined by normocalcemia after surgery (20).

This case study reveals that PA may facilitate in explaining hypercalcemia in patients diagnosed with WBS. This sentence removed; Besides this, we did not find any other reason of hypercalcemia. However, further studies are required to establish the association between WBS and PA.

Author Contributions

Concept: Müjdat Kara, Design: Müjdat Kara, Data Collection or Processing: Müjdat Kara, Analysis or Interpretation: Müjdat Kara, Nurten Türkel, Literature Search: Müjdat Kara, İbrahim Sun, Writing: Müjdat Kara, Erkan Vardarelli.

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