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# Early Onset Werner Syndrome

## Erken Başlangıçlı Werner Sendromu

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### Abstract

Werner syndrome (WS) is a rare autosomal recessive adult-onset progeroid disorder characterized by the early onset of aged-appearance and age-related metabolic disorders. Symptoms of premature aging usually first develop in the second-third decades of life. We report a 27-year-old female who was admitted to our clinic at the age of eighteen with hyperglycemia. She was diagnosed with diabetes and type 4 dyslipidemia at the age of seven. In her family history, her parents were first cousins and she had three healthy brothers. On her first physical examination; she had bird-like face appearance, global hair loss, beaked nose, short stature and she was overweight. She had global hair loss with gray and thin hair. Hoarseness of voice and hyperkeratosis of skin were observed. She had bilateral cataracts and moderate sensorineural hearing loss. On psychiatric examination, borderline mental retardation was detected. She had severe insulin resistance and hypertriglyceridemia despite levothyroxine, gemfibrozil, omega-3 and intensive insulin treatment. Routine lipid apheresis was performed to lower the triglyceride levels reaching 5256 mg/dL. She also had focal segmental glomerulosclerosis, hepatosteatosis, osteoporosis and epilepsy. Disease was accompanied by several congenital deformities, such as Rathke's cleft cyst, angiomyolipoma and femoral neck hypoplasia. WS is a rare genetic disorder characterized by multiple endocrine manifestations as well as soft tissue changes. We present a case of early disturbances that were diagnosed before typical clinical signs and symptoms. We propose that WS should be kept in mind when type 2 diabetes and hyperlipidemia are diagnosed early in childhood. *Turk Jem 2015; 19: 99-104*

**Key words:** Werner syndrome, type 2 diabetes, dyslipidemia, hypertriglyceridemia, congenital syndrome

### Özet

Werner sendromu (WS) erken başlangıçlı yaşlı görünüm ve yaş ilişkili metabolik bozukluklarla karakterize, erişkin başlangıçlı, otozomal resesif kalıtılan nadir bir hastalıktır. Erken yaşlanma bulguları genellikle yaşamın ikinci-üçüncü dekadlarında ortaya çıkar. Kliniğimize 18 yaşında hiperglisemi nedeniyle başvuran, 27 yaşında kadın hastayı sunmaktayız. Hastaya diyabet ve tip 4 hiperlipidemi tanıları 7 yaşında konulmuştu. Aile hikayesinde; ebeveynleri 1. derece akrabaydı ve üç sağlıklı erkek kardeşi vardı. İlk fizik muayenesinde; gaga burun, yaygın saç dökülmesi, boy kısalığı mevcuttu ve kiloluydu. Sesi kalındı ve dermatolojik muayenede hiperkeratoz saptandı. Bilateral kataraktı ve orta derecede sensörinöral işitme kaybı vardı. Psikiyatrik muayenede sınırda zeka geriliği saptandı. Levotiroksin, gemfibrozil, omega-3 ve intensif insülin tedavilerine rağmen ciddi insülin direnci ve hipertrigliseridemisi mevcuttu. Rutin lipid aferezi, 5256 mg/dL'ye ulaşan trigliserit düzeylerini düşürülmesi amacıyla uygulandı. Olgunun fokal segmental glomerüloskleroz, hepatosteatoz, osteoporoz ve epilepsisi de mevcuttu. Rathke kleft kisti, anjiomiyolipoma ve femur boynu hipoplazisi gibi çok sayıda konjenital deformite hastalığa eşlik etmekteydi. WS yumuşak doku değişiklikleri ile birlikte çok sayıda endokrinolojik bozukluğun görüldüğü nadir bir genetik hastalıktır. Sunduğumuz olguda metabolik bozukluklar, klinik belirti ve bulgulardan önce ortaya çıkmıştır. Erken çocuklukta tip 2 diyabet ve hiperlipidemi saptanması halinde WS göz önünde bulundurulmalıdır. *Turk Jem 2015; 19: 99-104*

**Anahtar kelimeler:** Werner sendromu, tip 2 diyabet, dislipidemi, hipertrigliseridemi, konjenital sendrom

## Introduction

Werner syndrome (WS) is a rare autosomal recessive adult-onset progeroid disorder characterized by the early onset of aged-appearance and age-related metabolic disorders caused by homologous mutations at the WRN helicase locus (1). The features of the syndrome were first described as scleroderma-like skin changes, short stature, gray hair and genital hypoplasia (2). Later, other endocrinological manifestations, including osteoporosis and glucose metabolism abnormalities have been shown to be the components of this syndrome. Generally, the first manifestation of the disease is absence of growth spurt (3). The incidence of WS is one per million. It is known that the frequency of this syndrome is higher in Japan as 75% of patients were reported from Japan between 1904 and 2008 (4). Case reports from Turkey are extremely rare (5,6,7,8).

Symptoms of premature aging usually first develop in the third decade of life (3). Herein, we present an atypical case of WS with early onset of premature aging-related metabolic disorders.

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## Case Report

We report a 27-year-old female who presented to our clinic at the age of eighteen with hyperglycemia. She was diagnosed with type 2 diabetes mellitus (DM), primary hypothyroidism and type 4 dyslipidemia at the age of seven. In her family history, her parents were first cousins and she had three healthy brothers. In her medical history, she experienced loss and thinning of hair, voice and skin changes after the age of eleven. Her growth nearly stopped after age of eleven and her height was stable for the last three years. Age of menarche was twelve and her menses were regular.

On her first physical examination, when she was eighteen years old, she was overweight (height: 141 cm, weight: 53 kg; waist circumference 90 cm; and body mass index (BMI): 26.6 kg/m$^2$) and had bird-like face appearance, beaked nose, and short stature. Hair loss, thin hair, hoarseness of voice and hyperkeratosis of skin were observed (Figure 1). She had bilateral posterior subcapsular cataracts, bilateral optic atrophy and moderate sensorineural hearing loss. Genitourinary examination was normal.

On laboratory examination; she had hyperglycemia (fasting plasma glucose: 270 mg/dL-N: 70-100 mg/dL) and HbA1c: 10.2% (N: <6.5%), impaired renal function tests (serum creatinine: 1.7 mg/dL-N: 0.5-0.9 mg/dL, and blood urea nitrogen: 42 mg/dL-N: 7-20 mg/dL), hypertriglyceridemia (serum triglyceride: 1127 mg/dL-N: <150 mg/dL), and high VLDL cholesterol level (VLDL: 225 mg/dL-N: 2-30 mg/dL). LDL and HDL cholesterol levels were within normal range. Glutamic acid decarboxylase antibody was negative. Her complete blood cell count was normal. Under levothyroxine replacement therapy, her TSH level was 2.82 mIU/L. Thyroid peroxidase and thyroglobulin antibodies were negative. She had severe insulin resistance and hypertriglyceridemia despite intensive therapy with 220 IU/day insulin, levothyroxine, gemfibrozil, niacin and omega-3. Lipid apheresis was performed two times a month to lower the triglyceride levels reaching 5256 mg/dL.

**Figure 1.** The appearance of patient in 2011, at the age of twenty-three; beaked nose, truncal obesity, relatively thin extremities

In her medical history, she had metabolic acidosis and overt proteinuria (4200 mg/24 hours) at the age of fourteen. Dimercaptosuccinic acid (DMSA) scan showed a mild left pelvicalyceal stasis and glomerular filtration rates of 35.5 ml/min for the right and 26.0 ml/min for the left kidney measured with diethylenetriamine pentaacetic acid (DTPA). Abdominal ultrasonography revealed hepatomegaly and hepatosteatosis, an increased renal parenchymal echogenicity and a mass appearance of 9 cm maximal diameter in the right kidney, which was considered as an angiomyolipoma. Pathological examination of the renal biopsy specimen showed focal segmental glomerulosclerosis and tubulointerstitial injury. Even though a surgical intervention was offered by urology consultation to remove the angiomyolipoma, the patient denied any interventional or surgical procedures.

Osteoporosis of the femur neck (Z score: -2.8) and osteopenia of the lumbar spine (Z score: -2.2) were demonstrated by the measurement of bone mineral density (BMD) at the age of twenty one. Computed tomography (CT) of the hip was performed because of left hip pain. CT revealed shortening and hypoplasia of the femur neck and subcortical cyst formation.

At the age of twenty-two, liver function tests have started to elevate. Anti-nuclear, anti-mitochondrial, anti-smooth muscle, anti-liver kidney microsomal, and anti-neutrophil cytoplasm antibodies, hepatitis B surface antigen, anti-HBc IgM, anti-HAV IgM, anti-HCV Ab, anti-toxoplasma IgM, anti-CMV IgM and anti-Rubella IgM were all negative. Serum ferritin, ceruloplasmin and copper levels in 24-hour urine were within the normal ranges. At follow-up visit, a liver biopsy was performed. Histopathological examinations revealed a mild portal and lobular inflammation, periportal fibrosis, mild sinusoidal fibrosis, and macrovesicular steatosis at 10% of hepatocytes and, the final diagnosis of grade 1 steatohepatitis was established. During psychiatric examination, borderline mental retardation was detected. Due to severe headache, eyelid twitching, visual loss that continued for ten minutes and relapsed two or three times in a day, cranial magnetic resonance imaging (MRI) was performed. It was normal except for large cerebellar folias. Paroxysmal sharp and slow waves in the right hemisphere were detected by electroencephalography. Lamotrigine therapy was started with the diagnosis of petit-mal epilepsy. In addition, pituitary MRI showed an 8 mm lesion which was reported to be either an adenoma or Rathke's cleft cyst.

Anterior pituitary hormone levels were all within the reference ranges (Table 1). The pituitary lesion was considered to be a Rathke's cleft cyst after neurosurgery consultation.

At the last visit in 2013, when she was 25 years old, HbA1c level was 7.2% with 220 units/day intensive insulin regimen. Other laboratory findings are summarized in (Table 1). Her medical treatment included levothyroxine 100 mcg/day, fenofibrate 267 mg/day, niacin 1000 mg/day, calcitriol 0.25 mcg/day, lamotrigine 300 mg/three times a day, omega-3 500 mg/day and sodium bicarbonate 500 mg three times a day. Her menses were regular with 28-32 days periods. Echocardiographic examination was normal. Abdominopelvic ultrasonography revealed hepatosteatosis, a right renal mass of 14 cm maximal diameter and bilateral ovarian cysts with the largest one 1 cm in diameter. An abdominal CT was performed to evaluate the renal mass and it was again reported as the appearance of renal angiomyolipoma with unchanged dimensions. Her seizures were persisting one or two times a week with eyelid twitching and vacant stare. Cranial imaging techniques did not show any additional findings other than cerebral and cerebellar atrophy. Valproic acid was added to her medical treatment. Pituitary MRI revealed a stable Rathke's cleft cyst with unchanged diameters. LMNA (lamin A/C) and WFS (wolframin) whole gene analysis (including exons, promoter and exon-intron junctions) were performed for differential diagnosis of progeria syndromes including atypical WS, Hutchinson-Gilford progeria syndrome and Wolfram syndrome. No mutations were found in both genes.

**Table 1. Laboratory findings of patient at the last visit in 2013**

| | Patient's Value | Reference Levels |
|---|---|---|
| FPG (mg/dL) | 150 | 74-100 |
| HbA1c (%) | 7.2 | <5.9 |
| HDL-C (mg/dL) | 44 | 40-60 |
| LDL-C (mg/dL) | 123 | <100 |
| Triglyceride (mg/dL) | 1146 | <150 |
| Total Cholesterol (mg/dL) | 406 | <200 |
| Creatinine (mg/dL) | 2.0 | 0.5-0.9 |
| Sodium (mEq/L) | 139 | 136-145 |
| Potassium (mEq/L) | 4.5 | 3.5-5.1 |
| ALT (U/L) | 51 | <34 |
| AST (U/L) | 34 | <28 |
| TSH (mIU/ml) | 2.82 | 0.34-5.6 |
| Free T3 (pmol/L) | 4.25 | 3.5-5.5 |
| Free T4 (pmol/L) | 10.84 | 7-16 |
| FSH (IU/L) | 4.27 | 2.5-10.2 |
| LH (mIU/ml) | 2.41 | 1.5-9.3 |
| Prolactin (ng/ml) | 16.2 | 3.2-20 |
| ACTH (pg/ml) | 25.33 | 5-27 |
| Cortisol a.m (µg/dL) | 19.93 | 5-21 |
| Estradiol (pg/ml) | 45 | 39-375 |
| C-peptide (fasting) (ng/ml) | 6.6 | 0.8-3.1 |

## Discussion

Progeroid syndromes are a group of rare genetic disorders characterized by various clinical features mimicking physiological aging at an early age. These syndromes include clinically and genetically heterogeneous diseases, such as ataxia-telangiectasia, Bloom syndrome, Cockayne syndrome, Fanconi anemia, Hutchinson-Gilford syndrome, Rothmund-Thomson syndrome, trichothiodystrophy, xeroderma pigmentosum, and WS (9).

Hutchinson-Gilford syndrome and WS are two of the best characterized human progeroid diseases. While clinical features of Hutchinson-Gilford syndrome appear during the first years of life, WS represents one of the most studied diseases of premature aging in adulthood. WS is frequently caused by an autosomal recessive WRN gene mutation, which is a member of the RecQ family of DNA helicases. WRN is a multifunctional nuclear protein that maintains genome stability via DNA replication, DNA recombination, telomere maintenance, apoptosis, and DNA repair (10). More than 70 WRN gene mutations, including nonsense mutations, missense mutations, insertion/deletions and substitutions at splice junctions have been demonstrated in WS (10,11). Potential founder mutations have been reported for Japanese (c.3139-1G>C), Dutch (c.3590delA, p.N1197fs), Turkish (c.3460-2A>G, exon 30 deletion), and Moroccan (c.2179dupT, p.C727fs) patients (10,12). Other progeroid syndromes are also caused by mutations in different genes encoding DNA repair proteins (13).

In recent years, a group of progeroid syndromes were also linked to LMNA mutations encoding the nuclear proteins lamins A/C (14). Lamins are nuclear intermediate filament proteins and are the major components of nuclear lamina. More than ten diseases have been reported to be associated with LMNA mutations, including progeroid and non-progeroid disorders (The UMD-LMNA mutations database. http://www.umd.be/LMNA).

Diseases caused by LMNA mutations may be categorized into four groups according to the affected tissues. Disorders characterized by muscular atrophy, leading to muscle or cardiac involvement, are the most frequent subgroup of laminopathies (15). Emery-Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy (LGMD1B) and dilated cardiomyopathy (DCM) are the striated muscle laminopathies. Charcot-Marie tooth disorder type 2 (CMT2) is a peripheral nervous system laminopathy. Adipose tissue may also be involved in laminopathies. Familial partial lipodystrophy, generalized lipodystrophy type 2 and mandibuloacral dysplasia (MAD) type A are adipose tissue laminopathies. Progeroid laminopathies are autosomal dominant atypical WS, classical Hutchinson-Gilford syndrome, atypical Hutchinson-Gilford syndrome and restrictive dermopathy (16). WS is caused by mutations in the LMNA gene in 20% of cases and atypical WS patients with mutations in LMNA have a more severe phenotype compared with WRN mutant patients (14). The link between LMNA mutations and premature ageing is not well established yet due to the rarity of these syndromes, death at an early age and distinct symptoms in animal models (17). However, molecular studies have indicated a decreased cell proliferation and altered DNA-damage responses in progeroid laminopathies just as in other progeroid disorders (18).

Differential diagnosis of WS consists of other progeroid disorders, including progeroid laminopathies and systemic sclerosis. Individuals with Hutchinson-Gilford progeria syndrome grow normally only during the first year of life and then growth retardation, loss of subcutaneous fat and hair, scleroderma-like changes of face occur (19). MAD may also be caused by LMNA mutations, but our patient had hyperpigmented skin, beaked nose, short fingers and bilateral cataracts, which were not components of MAD (20). In addition to distinct clinical features and severity of the disease, LMNA mutation analysis was also found as negative in our case.

**Table 2. Clinical diagnostic criteria for Werner syndrome and positive findings of our patient***

| Major signs and symptoms (onset over 10 years old) | Signs and symptoms of our patient |
|---|---|
| Cataracts (bilateral) | Present |
| Characteristic dermatological pathology (tight skin, atrophic skin, pigmentary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy) and characteristic facies ('bird-like' face) | Present |
| Short stature | Present |
| Parental consanguinity (3rd cousin or greater) or affected sibling | Present |
| Premature greying and/or thinning of scalp hair | Present |
| Additional signs and symptoms | |
| Type 2 diabetes mellitus | Present |
| Hypogonadism (secondary sexual underdevelopment, diminished fertility, testicular or ovarian atrophy) | - |
| Osteoporosis | Present |
| Osteosclerosis of distal phalanges of fingers and/or toes (X-ray diagnosis) | - |
| Soft tissue calcification | - |
| Evidence of premature atherosclerosis (e.g., history of myocardial infarction) | - |
| Neoplasms: mesenchymal (i.e., sarcomas), rare (unusual), or multiple | Present |
| Abnormal voice (high-pitched, squeaky, or hoarse) | Present |
| Flat feet | - |
| Definite diagnosis | Present |
| All the major signs and two additional signs | |
| Probable diagnosis | |
| The first three major signs and any two others | |
| Possible diagnosis | |
| Either cataracts or dermatological alterations and any four others | |
| Exclusion of diagnosis | |
| Onset of signs and symptoms before adolescence (except short stature) | |

*Werner syndrome signs and symptoms are from the diagnostic criteria established by the International Registry of Werner syndrome: www.wernersyndrome.org/registry/ diagnostic.html.

Additionally, scleroderma-like skin changes and extremity ulcers are present in both WS and systemic sclerosis. Previous reports from our country have showed that Turkish WS patients had scleroderma-like skin changes prominently and some of them were misdiagnosed as scleroderma (5,6). Otherwise, progeria, premature cataract, DM, sensorineural hearing loss, premature atherosclerosis and dyslipidemia in WS may be helpful for the differential diagnosis (21). Besides, absence of anti-scleroderma antibodies can prompt to WS.

We excluded ataxia-telangiectasia, Bloom syndrome, Cockayne syndrome, trichothiodystrophy, xeroderma pigmentosum and Fanconi anemia due to their distinct clinical characteristics. Rothmund-Thomson syndrome is also caused by mutations in RecQ helicase genes and characterized by short stature, telangiectasias, cataracts, pigmentation of skin and abnormalities of the teeth, nails and bones whereas the latter clinical features were not components of our case (22). We could not demonstrate the WRN mutation in our patient as this genetic test is not available in our country. However, an update from the International Registry of WS reported that 23% of WS patients do not have neither WRN nor LMNA mutations (10). Besides, WS diagnosis depends on clinical signs of the disease. Nakura et al. have described diagnostic criteria for WS which includes major and additional signs and symptoms (23). A recent guideline for the diagnosis of WS has been proposed by the International Registry of WS (http://www.wernersyndrome.org/registry/diagnostic.html). Definite diagnosis is based on the four major signs and symptoms. Our patient had four major and three minor signs that enough for the diagnosis of WS. Diagnostic criteria for WS and clinical features of our patient are summarized in (Table 2).

The first clinical sign of WS is lack of growth spurt. Our patient's height and weight measurements were consistent with the previous reports (4). She had typical short stature, truncal obesity with relatively thin extremities. However, the onset of progeroid and metabolic features of the disease were atypically earlier as they usually develop in the second or third decade of life. The average age for onset of type 2 DM is usually third decade in WS (4). Previously, Sert et al. (7) have reported two siblings with early-onset WS. However, their cases were 16 and 20 years old at initial diagnosis.

Additionally, oral antidiabetic drugs are usually enough for the treatment of DM. A previous report has showed that only 20% of diabetic WS patients require more than 200 IU of insulin for glycemic regulation (24). Our patient had very severe insulin resistance that HbA1c level was still high with 220 IU/day insulin doses.

Kidney and liver diseases are rarely reported in WS and the present case had also those infrequent components of WS. Recently, Hashizume et al. have described three patients with WS and histologically proven non-alcoholic steatohepatitis

(NASH) for the first time (25). Severe insulin resistance, visceral fat accumulation and hyperlipidemia were suggested to be the reasons of NASH in WS. Our patient had an early diagnosis of histopathologically proven steatohepatitis. She also had focal segmental glomerulosclerosis and tubulointerstitial injury detected by renal biopsy. Renal disorders are extremely rare in WS. A previous report from Turkey presented a 26-year-old male patient with 'possible WS' and end-stage renal disease (8). Our patient had primary hypothyroidism without thyroid autoimmunity. Thyroid dysfunction is another rare endocrine manifestation of this syndrome. Additionally, she had borderline mental retardation and petit-mal epilepsy. Mental impairment has been reported in 9% of Japanese patients and, brain atrophy was a remarkable radiologic feature of the disease (24). To the best of our knowledge, the present case is the first WS case with petit-mal epilepsy.

Atherosclerosis and malignancy are the major causes of mortality in WS. Myocardial infarction, cardiac failure and cerebrovascular events cause mortality in 50% of patients (26). Premature atherosclerosis in WS is suggested to be a result of either abnormal lipid metabolism, or inflammation (4). Our patient has no evidence of atherosclerotic features yet, although she had multiple risk factors.

Both epithelial and non-epithelial malignancies are frequent in WS. The reported malignancy incidence is 23 to 40% in WS (3,4). A recent review of the literature has showed that thyroid neoplasms (mainly follicular thyroid carcinoma), malignant melanoma, meningioma, soft tissue sarcomas, leukemia, and osteosarcoma/bone neoplasms accounted for 67% of all neoplasms (27). Otherwise, multiple tumors were prevalent in this population. Our patient had a right renal mass radiologically evaluated as an angiomyolipoma and stable in diameter for the last seven years.

There is no effective treatment for WS. It has been reported that p38 MAPK activation causes stress-induced premature senescence (SIPS) and p38 selective inhibitor molecule SB203580 may increase the growth and life span of fibroblasts (28,29). This data suggest that further studies are necessary to identify new targets for the treatment of premature aging. Therapeutic approaches for components of the disease, such as endocrine manifestations, skin ulcers, cataracts, and atherosclerosis and, if present, malignancies must be considered separately.

## Conclusion

WS is a rare genetic disorder characterized by multiple endocrine manifestations as well as soft tissue alterations. We present a patient with early metabolic disturbances that was diagnosed before other clinical signs and symptoms. We propose that WS should be kept in mind when type 2 DM and dyslipidemia are diagnosed early in childhood.

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