Werner Syndrome: A Case Report

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INTRODUCTION

Progeroid syndromes are fatal and rare genetic disorders which are characterized by physiological premature ageing and present with various clinical features.\(^1\)

The term Werner syndrome is coined after the German scientist Otto Werner. In 1904, he observed the concept of premature aging in four siblings, which he explored as the subject of his dissertation. It is also known as progeria adultorum and pangeria.\(^2\) The authors describe a case of Werner syndrome, which was diagnosed in a 39-year-old unmarried woman with diabetes.

CASE PRESENTATION

A 39-year-old unmarried woman presented with the complaints of frequent episodes of giddiness, palpitations, and generalized weakness for the past one month. Her past medical history revealed that she had undergone bilateral cataract surgery in 1999. She attained menarche at the age of 16 years. She had regular menstrual cycles until the age of 30 years. She attained precocious menopause at the age of 31 years. During the evaluation for hair loss over her scalp, she was diagnosed to have diabetes mellitus in 2001. She was on oral antidiabetic medication for 10 years and later started on insulin. She is on treatment for systemic hypertension for the past 5 years. She had a history of chikungunya in 2009. She had undergone partial amputation of right great toe in 2011.

On physical examination, the patient was short in stature (142 cm) and emaciated with a body weight of 27.4 kg (body mass index: 13.6 kg/m\(^2\)) (Fig. 1). She had a hoarse voice, a peculiar face with prominent eyes pointed
Fig. 1: Emaciation with lipodystrophy in the upper limbs and lower limbs
(For color version see Plate 4)

Fig. 2: Premature graying of the hair along with hair loss (For color version see Plate 4)

chin, beak-like nose, taut lips, and micrognathia. Her scalp hair was diffusely thin and gray (Fig. 2); eyelashes were gray in color, and pupils were irregular in both the eyes (Fig. 3); the skin presented extensive signs of xerosis. Her extremities were thin, without subcutaneous fat, and she had markedly reduced muscle mass. The breast tissue was atrophied. The skin of the limbs was sclerosed with thin tapering digits. The patient had features of hypogonadism with scanty axillary and pubic hair. Eye examination revealed presence of intraocular lens in both the eyes and evidence of vitreous degeneration.

Hemogram and liver function test were normal. Renal function test showed mild proteinuria. Ultrasound abdomen showed grade 1 fatty liver. She also had evidence of small sized kidneys and bilateral renal calculi. Chest
Fig. 3: Distorted pupil in the right eye and gray eyelashes (For color version see Plate 4)

X-ray showed atheromatous aorta. Electrocardiogram showed left ventricular hypertrophy with strain pattern and two-dimensional echocardiogram showed concentric left ventricular hypertrophy, normal left ventricular systolic function, and mild mitral regurgitation. Thyroid function test showed subclinical hypothyroidism. Biothesiometry showed sensory neuropathy in both the lower limbs. Carotid Doppler showed focal calcific plaque in the right carotid bulb.

**DISCUSSION**

Werner syndrome is inherited as an autosomal recessive or a sporadic disease, which is due to mutation in the WRN gene. This gene is located on chromosome 8p12, which codes for a 165 KDa multifunctional nuclear protein (WRN), a homolog of *Escherichia coli* RecQ deoxyribonucleic acid (DNA) helicase. 4,5 Hence, it is named as *RECQL2* or *WRN* gene. It is involved in DNA transcription, replication, repair, and telomere maintenance. 6–10 The defect in this function leads to genomic instability. The global incidence rate is less than 1 in 100,000 live births.1 Werner syndrome is more prevalent in Japan and the Italian island of Sardinia than any other part of the world.1 About 1,000 cases have been reported worldwide, more than 800 of which are from Japan. Both the sexes are affected equally.

Werner syndrome can be diagnosed based on six cardinal symptoms, which are: (i) premature graying of the hair or hair loss, (ii) sclerodermalike skin changes, (iii) sharp facial features, (iv) presence of bilateral cataracts, (v) soft tissue calcification, and (vi) an abnormal, high-pitched voice.11
Development of ocular cataracts in the early 30s is seen in majority of the cases with WRN mutations, which require surgical intervention. The most common causes of death in Werner syndrome patients are myocardial infarction due to atherosclerosis and malignancy with the median age of death being 56 years.\textsuperscript{12}

Werner syndrome is caused by null mutations at the WRN locus,\textsuperscript{13} which codes for a member of the RecQ family of DNA helicases. The disease is connected with excessive synthesis of collagen types I and III, which is dependent on elevated messenger RNA (mRNA) levels. More than 70 disease-causing mutations have been described, the majority being stop codon mutations, splice mutations, or small ins/del-producing truncations of the protein and/or nonsense-mediated decay of mutant mRNA.\textsuperscript{14} Two novel WRN mutations were described in patients of South Asian ancestry.\textsuperscript{15} There is no specific treatment for Werner syndrome. Symptomatic treatment of related complications is recommended. A 2010 study on WRN mutant mice showed that vitamin C supplementation rescued the shorter mean life span and reversed several age-related abnormalities in adipose tissues and liver endothelial defenestration, genomic integrity, and inflammatory status. Hence, it has been suggested that vitamin C supplementation will be beneficial for patients with Werner syndrome.\textsuperscript{16}

In our patient, the diagnosis of Werner syndrome was made based on the clinical findings like short stature, premature graying of hair and hair loss, peculiar facial features like beaked nose, micrognathia and pointed chin, high pitched voice, scleroderma-like skin changes, hypogonadism (uterine and ovarian atrophy), soft tissue calcification, atherosclerosis, abnormal fat distribution (enlarged fatty liver with subcutaneous atrophy), and osteoporosis.

The differential diagnosis of Werner syndrome includes progeria, acrogeria, and Rothmund-Thomson syndrome.

Progeria, also known as Hutchinson-Gilford progeria syndrome, is a progressive and rare genetic disorder that causes children to age rapidly. It begins in the first 2 years of life. The probable cause is a mutation in the lamin located in the nuclear matrix.\textsuperscript{17} Most kids with progeria do not live past the age of 13. The disease affects both sexes and all races equally. It affects about 1 in every 4 million births worldwide.

Acrogeria is a progeroid syndrome of premature aging of the skin without the involvement of internal organs seen in progeria. It is seen mainly in females and in the form of sporadic cases.

Rothmund-Thomson syndrome is a hereditary and familial disease characterized by short stature, cataracts, pigmentation of skin, baldness, and abnormalities of bones, nails, and teeth.
REFERENCES


5. Rossi ML, Ghosh AK, Bohr VA. Roles of Werner syndrome protein in protection of genome integrity. DNA Repair (Amst). 2010;9:331-44.


