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Uncommon cause of cirrhosis—A case of Werner syndrome with a novel WRN mutation

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Abstract

Werner syndrome is a rare progeroid syndrome caused by the WRN gene mutation. It is characterized by a general appearance of premature aging, diabetes mellitus, and atherosclerosis, and an increased risk of malignancies. We report a patient who presented with hematemesis due to cirrhosis of liver and was subsequently diagnosed with Werner syndrome. Further genetic analysis showed a novel mutation in the WRN gene which has not previously been reported. Werner syndrome should be considered for the cases of liver cirrhosis when accompanied by the features of accelerated aging.

Keywords

Cirrhosis; Werner syndrome; WRN

Introduction

Werner syndrome (WS) is a rare autosomal recessive disorder with multiple symptoms suggestive of accelerate aging [1]. It is caused by the biallelic mutations of the *WRN* gene, which encodes a multifunctional nuclear helicase [2]. Two major causes of death are cancer and myocardial infarction in their 50s. WS cases have been reported from all over the world including India, although it is likely underdiagnosed because of the relatively low awareness of the disorder as well as the complexity of the features [3, 4].

Case report

A 35-year-old male was admitted to our hospital with hematemesis. He had undergone bilateral cataract surgeries at 13 years of age and was diagnosed with hypothyroidism at age 15 and diabetes mellitus at age 16. On examination, he had short stature (height 126 cm), gray hair, pinched nose, goiter, thin limbs, and non-healing ulcers over the Achilles tendons (Fig. 1a, b). X-rays showed calcification of Achilles tendons, a highly characteristic feature of WS (Fig. 1d, e). He was born of consanguineous marriage, and there was no similar

illness in other family members. Based on his physical features and past history of cataract surgeries, he was clinically diagnosed to have WS.

Abdominal CT scan showed the enlarged nodular liver (span of 20 cm) and spleen (18 cm in diameter) (Fig. 1c). In addition to hepatosplenomegaly, it also showed calcification of coronary arteries and the aortic valve. The upper gastrointestinal endoscopy showed grade 3 varices in esophagus. Liver function tests were within normal range. Work up for viral, autoimmune hepatitis, Wilson disease, and hemochromatosis were all negative. Liver biopsy was not performed in view of pancytopenia due to hypersplenism. DEXA scan showed severe osteoporosis.

Methods

Blood sample was collected from the patient and his mother, after taking informed consent. Genomic DNA isolation from peripheral blood samples was done using the Puregene BloodCore Kit B (QIAGEN Sciences, MD, USA), and lymphoblastoid cell lines (LCLs) were established with Epstein-Barr virus [5]. Sanger sequencing, polymerase chain reaction (PCR), and reverse transcription PCR (RT-PCR) were performed at the International Registry of Werner Syndrome, Seattle, WA, USA, as described before [2, 3]. Western blotting analysis was done as previously described [5], using the mouse monoclonal antibody against aa 1074–1432 of human WRN protein (W0393, clone 195C, 1:2000 dilution; Sigma-Aldrich, St. Louis, MO) and a biotinylated anti-mouse antibody (BA9200, 1:500 dilution; Vector laboratories, Burlingame, CA) [2].

Results

Sanger sequencing of *WRN* coding exons of the patient revealed a homozygous variation at c.1720+5G>A in the intron 14 (Fig. 2a). This variant has not been in previous publications or publicly available databases. The RT-PCR sequencing spanning exon 12 to exon 17 show the homozygous deletion of 68 nucleotides corresponding to the exon 14 (Fig. 2b). Western blotting analysis using the antibody against C-terminal region of human WRN protein confirmed the absence of wild type WRN protein in the patient. The mother was heterozygous for the c.1720+5G>A mutation, and the cells derived from the mother were expressing the reduced amount of WRN protein, consistent with the obligatory heterozygous status. These data confirmed the molecular diagnosis of Werner syndrome.

Based on the above findings, the patient was diagnosed with Werner syndrome with cirrhosis and multiple endocrine deficiencies. The patient was started on propranolol for esophageal varices, thyroxine for hypothyroidism and metformin for diabetes mellitus. He also received zoledronate for osteoporosis.

Discussion

WS is a premature aging syndrome with multisystem involvement. The genetic basis for classical WS has been attributed to the *WRN* gene which encodes a DNA helicase [2]. Enzymatic functions of the WRN protein include unwinding of DNA and strand separation of DNA during various DNA transactions such as replication, repair, and recombination.

Two mutations in three pedigrees with genetically confirmed WS have been reported earlier from India [3]. Our case had yet another novel *WRN* mutation which was found only in patients with Indian origin.

Unique features of our patient are his relatively early onset of cataracts and hepatic involvement. Median age of cataract surgery in WS patients is reported to be around 31 years, although there have been cases in which cataract surgery was performed during teens similar to our patient [1]. Hepatic involvement is not uncommon in WS. Liver diseases reported in WS range from non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis, and metastasis from other sites [6–8]. Studies on mouse models of WS have shown that the liver sinusoids undergo morphological changes of aging termed as “pseudocapillarization”. This refers to loss of sinusoidal fenestrations and deposition of extracellular matrix leading to defective transport of nutrients across the sinusoids [9].

Our patient is likely to have had NASH, since no other cause could be found for the cirrhosis. Mechanistic causes of NASH include hyperlipidemia, diabetes mellitus, insulin resistance, truncal obesity, and free radicals, all aggravated by accelerated aging process [7, 10]. A recent report suggests reversal of NASH in WS by astaxanthin, an antioxidant [10]. In conclusion, WS is a multisystem disease with protean manifestations. NASH may be an important cause of morbidity in some of the patients.

Acknowledgments

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Fig. 1. Profiles and radiographical studies of the patient. **a** Facial feature of the patient. Notice the pinched nose. **b** Skin ulcer over Achilles tendon. **c** Abdominal CT scan showing nodular liver and ascites. **d** and **e** Calcification of Achilles tendon (*red circles*)

Fig. 2.

Molecular studies of the *WRN* gene. **a** Sanger sequencing of exon 14 and intron 14 boundary showing a homozygous c.1720+5G>A mutation in patient and the heterozygous mutation in the mother. Normal sequence of this region and the mutation is shown on *top* and sequence results at *bottom*. **b** RT-PCR sequencing of the region. Comparing wild-type sequence, the patient's sequence shows a 68 nucleotide deletion of exon 14. RT-PCR sequencing results are shown along with amino acid sequences and junctions on *top*. GenBank accession number AF091214 was used as a reference. **c** Western blot analysis of WRN protein. WRN+/+ and WRN-/- indicate control individuals with known genotypes. Nonspecific bands show equal loadings. Molecular weight markers are shown on the *right*