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Case Report: Werner Syndrome with Non-Alcoholic Fatty Liver Disease and Elevated Liver Function Tests in a 17-Year-Old Male

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Abstract

Background: Werner syndrome (WS) is a rare autosomal recessive disorder characterized by premature aging and various metabolic complications. Non-Alcoholic Fatty Liver Disease (NAFLD) is primarily associated with metabolic syndrome, but its occurrence in young patients with WS is rarely reported. We describe the case of a 17-year-old male diagnosed with Werner syndrome who presented with grade 2 NAFLD and elevated liver function tests (LFTs).

Case Presentation: A 17-year-old male, born to consanguineous parents, presented with clinical features suggestive of premature aging. Genetic testing confirmed a mutation in the WRN gene, establishing a diagnosis of Werner syndrome. Liver ultrasound revealed grade 2 fatty liver, and liver biopsy confirmed moderate steatohepatitis (activity grade 6, stage 2). Elevated liver enzymes were observed, although other metabolic parameters were within normal limits.

Conclusion: This case highlights the importance of recognizing liver involvement in patients with Werner syndrome and underscores the need for routine monitoring and a multidisciplinary approach to management. Genetic counseling is essential for families with consanguineous backgrounds to reduce the risk of autosomal recessive conditions like WS.

Key Words: Autosomal recessive disorder, Non-Alcoholic Fatty Liver Disease, Werner syndrome, WRN gene.

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1- INTRODUCTION

Werner syndrome (WS), also known as adult progeria, is a rare autosomal recessive disorder caused by mutations in the WRN gene, which encodes a DNA helicase involved in maintaining genomic stability (1). The syndrome is characterized by premature aging, starting in adolescence or early adulthood, and is associated with an increased risk of several age-related diseases such as diabetes mellitus, osteoporosis, cardiovascular disease, and various malignancies (2, 3). The global prevalence of WS is estimated to be less than 1 in 1,000,000, but it is more common in populations with high rates of consanguinity, such as in Japan, Italy, and certain Middle Eastern countries (4).

The clinical features of WS can be broadly classified into dermatologic, metabolic, musculoskeletal, and ophthalmologic manifestations. Typical dermatologic findings include sclerodermatous skin changes, atrophic skin, and hyperkeratosis over the extremities (5).

Musculoskeletal abnormalities such as short stature, premature osteoporosis, and calcification of soft tissues are commonly observed (5). Bilateral cataracts are a hallmark feature of WS, usually presenting before the age of 30. Metabolic complications, including insulin resistance, dyslipidemia, and an increased risk of myocardial infarction, are prominent features of the disease (6).

Liver involvement in WS is not well-documented compared to other complications. Although the liver plays a central role in metabolic regulation, few reports are linking WS to hepatic disorders such as Non-Alcoholic Fatty Liver Disease (NAFLD) (7). NAFLD is a spectrum of liver diseases that includes simple hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. It is commonly associated with metabolic syndrome, obesity, and type 2 diabetes mellitus (8). In younger populations, NAFLD is relatively uncommon unless secondary to genetic disorders, lipodystrophies, or metabolic syndromes (9).

In the context of WS, the mechanisms underlying liver disease may differ from those in the general population. Mitochondrial dysfunction, impaired DNA repair, chronic inflammation, and insulin resistance are potential contributors to liver pathology in WS (10). Given the limited number of reported cases of NAFLD in patients with WS, clinicians must remain alert to the possibility of liver disease in this population. Early recognition and management are essential to prevent progression to cirrhosis and its associated complications (11).

This report presents a unique case of a 17-year-old male diagnosed with Werner syndrome who was found to have grade 2 NAFLD with elevated liver enzymes. This case highlights the need for regular liver monitoring in patients with WS, even in the absence of classical risk factors for NAFLD, and emphasizes the role of a multidisciplinary approach in managing such complex cases.

2- CASE PRESENTATION

2-1. Patient History

A 17-year-old male, the second child of consanguineous parents, presented with early graying of hair, short stature, fatigue, and growth retardation. There was no significant family history of genetic disorders.

2-2. Clinical Examination

The patient had a progeroid appearance, with short stature (height: 155 cm) and atrophic skin changes, including sclerodermatous skin over the extremities.

2-3. Investigations

- Genetic Testing: A mutation in the WRN gene confirmed the diagnosis of Werner syndrome (12).
- Liver Function Tests (LFTs): Elevated ALT (142 U/L), AST (67 U/L), and GGT (123 U/L).
- Lipid Profile: Within normal limits.
- Hepatitis Panel: Negative for hepatitis B and C infections.
- Liver Biopsy: Moderate steatohepatitis (activity grade 6, stage 2), consistent with NAFLD (13).
- Abdominal Ultrasound: Revealed grade 2 fatty liver (13).

2-4. Diagnosis

The patient was diagnosed with Werner syndrome complicated by grade 2 NAFLD and elevated LFTs.

2-5. Management

The patient was advised to adopt lifestyle modifications, including a low-fat diet and increased physical activity. He was referred to a hepatologist for further management. On follow-up after three months, there was partial improvement in liver enzyme levels.

3- DISCUSSION

WS is a rare autosomal recessive disorder caused by mutations in the WRN gene, which encodes a RecQ DNA helicase involved in maintaining genomic stability, telomere maintenance, and DNA repair (1). The loss of WRN gene function results in accelerated cellular senescence and premature aging. WS typically presents in late adolescence or early adulthood, and clinical manifestations often include early graying of hair, short stature, bilateral cataracts, sclerodermatous skin changes, diabetes mellitus, osteoporosis, and an increased risk of malignancy (14). Most patients are diagnosed in their 20s or 30s; however, the diagnosis in this 17-year-old patient highlights the importance of recognizing early signs of WS.

In this case, the patient presented with clinical features characteristic of WS, including short stature, atrophic skin, early graying of hair, and a progeroid appearance. Genetic testing confirmed the diagnosis with a mutation in the WRN gene. An important and unusual finding in this case was the presence of grade 2 NAFLD with elevated liver enzymes, an uncommon complication in young patients with WS (4) . While metabolic complications such as diabetes, dyslipidemia, and insulin resistance are well-recognized features of WS, liver involvement has been rarely reported (15).

NAFLD is a spectrum of liver disorders characterized by hepatic steatosis in the absence of significant alcohol consumption. It ranges from simple steatosis to NASH, which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (16). NAFLD is typically associated with obesity, insulin resistance, and metabolic syndrome, which were not prominent features in this patient. The absence of obesity or hyperlipidemia suggests that the development of NAFLD in WS may be related to underlying genetic and mitochondrial dysfunction rather than classical metabolic risk factors (17).

The pathophysiology of NAFLD in WS is likely multifactorial. Insulin resistance is a central feature of WS and may contribute to hepatic steatosis. In addition, chronic inflammation and mitochondrial dysfunction—both of which have been implicated in the progression of liver disease—are commonly seen in WS patients (18). Dysfunction in the WRN gene may impair mitochondrial DNA stability, leading to oxidative stress and lipid accumulation in hepatocytes (19).

Furthermore, the premature aging process and chronic inflammation in WS could exacerbate the progression from simple steatosis to NASH (20).

Liver biopsy in this patient revealed moderate steatohepatitis with an activity grade of 6 and stage 2 fibrosis, indicating significant liver involvement. These findings underscore the importance of early detection and monitoring of liver function in patients with WS, as untreated NAFLD can progress to advanced liver disease, including cirrhosis and hepatocellular carcinoma (13). Regular screening for liver complications is crucial for patients with WS, even in the absence of overt metabolic syndrome, as they may develop atypical presentations of NAFLD (21).

From a clinical management perspective, a multidisciplinary approach is essential for optimizing patient care. The involvement of hepatologists, geneticists, endocrinologists, and dietitians is crucial in providing comprehensive management for patients with WS and associated liver disease (22). Lifestyle modifications, including a low-fat diet and regular physical activity, remain the cornerstone of NAFLD management in these patients. Given the underlying genetic etiology, pharmacologic options targeting insulin resistance and inflammation may also be considered in future treatment protocols (23).

3-1. Genetic Considerations and Consanguinity

The role of consanguinity in autosomal recessive disorders such as WS cannot be overlooked. The patient in this case was born to consanguineous parents, which likely increased his risk of inheriting this rare genetic condition. Consanguinity is a well-known risk factor for rare genetic disorders, particularly in populations with high rates of intermarriage (1). Genetic counseling should be offered to families with consanguineous marriages to help reduce the risk of genetic disorders in future generations. Awareness and education about genetic risks in communities with high consanguinity are essential for early diagnosis and prevention.

3-2. The Need for Further Research

This case also highlights the need for further research to better understand the link between WS and NAFLD. While insulin resistance and chronic inflammation are likely contributors, the exact mechanisms leading to hepatic steatosis in WS remain unclear. Studies exploring mitochondrial dysfunction and the role of the WRN gene in liver disease could provide valuable insights into the pathogenesis of NAFLD in these patients. Moreover, the establishment of guidelines for regular liver function screening and management in WS patients is essential to reduce morbidity and improve long-term outcomes.

3-3. Clinical Implications

Clinicians should maintain a high index of suspicion for liver complications in patients with WS.

Given the increased risk of progressive liver disease, early diagnosis and intervention are crucial. Regular monitoring of liver enzymes, imaging studies, and lifestyle interventions should be a routine part of the care plan for these patients.

4- CONCLUSION

This case highlights a rare presentation of Werner syndrome in a 17-year-old male complicated by grade 2 NAFLD and elevated liver enzymes. Clinicians should be vigilant for liver involvement in patients with WS, even in the absence of classical risk factors for liver disease. Regular monitoring and a multidisciplinary approach are essential for preventing long-term complications.

Genetic counseling should be offered to families with consanguineous marriages to reduce the risk of autosomal recessive conditions. Further research is needed to establish guidelines for managing hepatic complications in WS.

5-ETHICS CONSIDERATION

Informed consent was obtained from the patient and his legal guardians for the publication of this case report. All procedures were performed according to ethical standards and the Declaration of Helsinki. No identifying information has been disclosed to maintain confidentiality.

6-CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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