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INFANTILE-ONSET WERNER'S SYNDROME PRESENTING WITH CHOLESTASIS AND HYPERCHOLESTEROLEMIA: A RARE PHENOTYPIC VARIANT

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SUMMARY

Werner's syndrome also known as progeria Adultorum, is a rare autosomal recessive disorder that accelerates the aging process due to mutation of the WRN gene which is involved in DNA repair. Patients with Werners syndrome typically develop normally until adolescence, by their middle age they begin to show signs of premature aging. We report a child who presented with cholestatic jaundice whose whole exome sequencing revealed presence of Werners Syndrome .This case is being reported due to rarity of the presentation of Werners syndrome at such a early age and also due to its rarity in its presentation as cholestatic jaundice .

BACKGROUND

Werner's syndrome also known as progeria Adultorum, is a rare autosomal recessive disorder that accelerates the aging process, beginning shortly after puberty [1]. This condition results from mutations in the WRN gene, which encodes a member of the RECQ family of DNA helicases involved in DNA repair [2]. WS is marked by genomic instability and early onset of various age-related diseases such as a senile appearance, ocular cataracts, dyslipidemia, diabetes mellitus, osteoporosis, arteriosclerosis, and malignancies.Patients with WS typically develop normally until adolescence, when they experience a lack of growth spurt and remain relatively short in stature as adults. By their middle age they begin to show signs of premature aging, including skin atrophy, loss of subcutaneous fat, cataract ,graying and loss of hair(1)

CASE PRESENTATION

A 1 year 3 months old child born to a 2nd degree consanguineous marriage with significant family history of familial cholestatic syndrome was brought with complaints of fever ,vomiting ,passage of dark yellow urine and yellowish discoloration of eyes. Child had mild gross motor delay .Family history revealed history of cholestatic jaundice in sibling who presented with the same complaints since 8 months of age whose clinical exome sequencing report revealed presence of PEX12 mutation (homozygous) –Zellweger syndrome . Whole exome sequencing of both parents revealed heterozygous mutation of PEX12 gene

Head to toe examination of the child revealed features like high forehead ,deep seated eyes ,icterus ,hypopigmented lesions (likely xanthomas)over the bilateral upper and lower limb .Systemic examination revealed presence of hepatomegaly ,liverwas palpable 6 cm under the right costal margin and was firm.

INVESTIGATIONS

Blood investigations revealed normal complete blood count,negative C Reactive protein

LIVER FUNCTION TESTS REVEALED aTotal bilirubin 2.08 mg/dl,direct bilirubin -1.5 mg/dl ,SGOT–2040 U/L ,SGPT -576 U/L,GGT-163 U/L ,Albumin -3.7 g/dl

PT,INR,APTTwas in normal range , Urine for bile salts was present

Child also had hypercholesterolemia -Total cholesterol-546 mg/dl ,LDL-410 mg/dl TG-311 mg/dl,HDL-53 mg/dl

DIFFERENTIAL DIAGNOSIS

Considering the presentation initial diagnosis which was considered was viral hepatitis , all viral markers sent were negative .Other infectious etiology was ruled out .In view of significant family history of cholestatic jaundice consanguinoeus marriage and heterozygous PEX 12 mutation in parents diagnosis of Zellwegers syndrome was considered .possibility of progressive familial intrahepatic cholestasis was also considered.In view of significant family history we decided to go with whole exome sequencing which revealed presence of mutation

TREATMENT

In view of cholestatic jaundice,exhaustion of fat soluble vitamins was suspected ,hence it was supplemented .UDCA supplementation was also given .Child was started on vitamin A supplementation at a dose of 25000 IU per day in the form of capsule .Vitamin D3 supplementation was given at a dose of 400 IU per day,Vitamin E at a dose of 400 IU per day and Vitamin K was given in the form of tablet at a dose of 5 mg twice weekly .

OUTCOME AND FOLLOW-UP

There was gradual resolutions of symptoms .In the follow up of the child detailed liver functions and lipid profile analysis was done which showed a gradual reduction of transamnitis and direct hyperbilirubinemia .child has registered with a developmental paediatrician for regular follow up of development

DISCUSSION

Werner's syndrome was initially described by Werner′s in 1904.The syndrome is due to an autosomal recessive gene with a gene frequency of 1-5 per 1000 population(5).Mutations in the WRN gene, which codes for a protein in the RECQ family of DNA helicases, lead to the condition. This protein plays an essential role in DNA repair processes.(3).The WRN gene is situated on the short arm of human chromosome 8 at position 8p12 and contains 34 coding exons spread across 140 kilobases.(3)During transcription, replication, recombination, and repair, the complementary strands of the DNA double helix need to be separated. As a result, nucleic acid unwinding enzymes, known as helicases, play crucial roles in nearly all DNA metabolic processes(4).Around 86 distinct mutations in the WRN gene have been identified. This gene plays a crucial role in maintaining genomic stability and facilitating DNA repair.hence patients with werners syndrome present with early onset of age related diseases (1)

Patients with WS typically exhibit a range of clinical features such as short stature, a senile appearance, early onset of cataracts, premature arteriosclerosis, skin changes resembling scleroderma, and premature graying or loss of hair. Additionally, there is an elevated risk of age-related diseases such as diabetes, osteoporosis, and malignancies. Patients are diagnosed as per the diagnostic criteria mentioned on the international registry of wernerssyndrome .(2)

Recent case reports highlight the diverse clinical manifestations of WS across different populations. For instance, one case from India identified a novel mutation in the WRN gene, presenting with classical WS symptoms, including sclerodermatous skin, bilateral cataracts, and early signs of arteriosclerosis(1). Another case from China described a patient with an uncommon presentation of early-onset diabetes at 18 years of age, accompanied by low body mass index, insulin resistance, and early cataracts, alongside a unique mutation in the WRN gene.

In our case child presented in infancy with cholestatic Jaundice which has not been reported before .

Aging is associated with cumulative genetic and epigenetic damage that progressively impairs organ function, including the liver. Although Werner’s syndrome typically presents later in life, its progeroid nature mimics premature aging processes. Experimental studies have shown age-related hepatic changes such as mitochondrial dysfunction, lipid accumulation, and reduced regenerative capacity. These alterations can impair bile production and flow, potentially contributing to cholestasis(6). The early manifestation of such liver changes in our patient may reflect the accelerated cellular senescence characteristic of Werner’s syndrome.Early detection of Werners syndrome will help in early detection of age related disease like diabetes ,atherosclerosis and for early detection of malignancies .in our case child was also found to hevae hyperlipidemia with a total cholesterol of 546.Mori et al. conducted a study on the abnormalities of lipoprotein metabolism in 10 patients with Werner's syndrome (WS). They found that seven of the patients had hypercholesterolemia (serum cholesterol levels exceeding 250 mg/dL).Furthermore, low-density lipoprotein (LDL) receptor activity in peripheral lymphocytes of five patients with hypercholesterolemia ($P < 0.001$) compared to controls.This could be explained by WRN gene impairing normal lipid metabolism, mitochondrial function, and oxidative stress regulation(5).This case report highlights the diversity of clinical presentation in werner’s syndrome

LEARNING POINTS

- Regular follow up is essential for cases of Werners syndrome for early detection of age related diseases

- Werners syndrome has a diverse presentation.. Recognizing these diverse presentations is crucial for early diagnosis and appropriate management of the syndrome.

- The diagnosis of Werner Syndrome (WS) can be established clinically using the criteria proposed by the International Registry of Werner Syndrome. However, genetic sequencing is advised to identify correlations between specific clinical manifestations or organ involvement and genetic mutations

Additionally, genetic sequencing can provide deeper insights into the role of different elements of the WRN gene in the aging process.

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FIGURE/VIDEO CAPTIONS

Genetic report

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
WRN (NM_000553.6)	Exon 6	c.561A>G	Homozygous	Pathogenic	Werner syndrome	Autosomal recessive

Page 1 of 6