Journal of
Kerman University of Medical Sciences

https://jkmu.kmu.ac.ir
10.34172/jkmu.3914
JKMU. 2025;32:3914

Case Report

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# Comorbidity of Wilson's Disease and Alkaptonuria in a 12-Year-Old Child: A Case Report

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**Abstract**

**Background:** Wilson's disease (WD) and alkaptonuria (AKU) are genetic diseases.

**Case Report:** A 12-year-old boy presented with tremors, dysarthric drooling, poor school performance, and dark urine. Neurologic examination showed ataxia and Kayser-Fleischer (KF) rings in the eye examination. Black pigment deposits were observed in the subconjunctival area and on the sclera. Brain magnetic resonance imaging (MRI) indicated high signal intensity in the basal ganglia and head of the caudate nucleus of both sides in T2WI serum ceruloplasmin. Pathogenic homozygous variants were reported in whole exome sequencing for WD and AKU.

**Discussion:** There is diagnostic complexity of overlapping metabolic disorders, including WD and AKU, in a pediatric patient with neurological and systemic symptoms. Genetic testing and biochemical analyses played a critical role in identifying pathogenic abnormalities.

**Conclusion:** Rare genetic diseases such as WD and AKU can happen simultaneously.

**Keywords:** Wilson's disease, Alkaptonuria, Magnetic resonance imaging, Dark urine

**Citation:** Talakesh H, Kasiri K. Comorbidity of wilson's disease and alkaptonuria in a 12-year-old child: a case report. *Journal of Kerman University of Medical Sciences*. 2025;32:3914. doi:10.34172/jkmu.3914

**Received**: March 17, 2024, **Accepted**: December 30, 2024, **ePublished**: January 19, 2025

## Introduction

Wilson's disease (WD) is an inherited autosomal recessive disorder causing impaired copper metabolism, in which copper pathologically accumulates in the liver and neurological system (1). The *ATP7B* gene mutation is responsible for copper accumulation in different body organs, including the liver and brain (2). Symptoms can appear anytime between the ages of 3 and 55 years. They can vary from no symptoms to hepatic or neurological symptoms. Liver disease primarily affects individuals below the age of 18 (3). Liver damage can vary from having no symptoms and experiencing only a rise in liver biochemistry indices, such as serum aminotransferases and bilirubin, to developing cirrhosis or facing acute liver failure. Some patients may have neurological symptoms. Neurological manifestations of WD include dysarthria, dopaminergic deficit, cerebellar ataxia, abnormal gait dystonia, decreased ceruloplasmin levels, tremor, Parkinsonism, copper deposits, and cognitive impairment (4). Kayser-Fleischer (KF) rings are seen in almost all patients with WD with neurological manifestations (5); potent chelators are used to remove copper.

Alkaptonuria (AKU; MIM# 203500) is an autosomal recessive disorder caused by decreased activity of homogentisic acid dioxygenase (HGD), leading homogentisic acid level to increase, leading to pigment deposition in the connective tissue of the body (ochronosis). Patients are usually asymptomatic in childhood (6). The patient's urine turns dark after standing in the environment or alkalinization. There are no confirmed treatments for AKU. However, in several studies, nitisinone decreased more than 95 percent of urinary and blood human granulocytic anaplasmosis levels (7).

In this case report, we present a 12-year-old boy diagnosed with both WD and AKU.

## Case report

The patient was a 12-year-old Iranian boy who presented with foot tremors, incomprehensive speaking, drooling, and weight loss that had started a month before the consult. His performance at school had also suffered. The child was born through consanguineous marriage; his parents were first-degree cousins. He was born at 38 weeks gestational age and by Normal Vaginal Delivery (NVD), and his birth history was uneventful. He weighed 2650 g at birth, which is in the 10th percentile. His body length measured 47 cm, also in the 10th percentile. His occipital-frontal circumference, according to Fenton's growth charts, was

34 cm, which is in the 50th percentile.

He had no history of hospitalization until before the diagnosis of his disease. His mother had breastfed him in his infancy. He had average developmental and neurodevelopmental growth. His performance at school was remarkable. His mother also mentioned urine discoloration from yellow to black over time. Upon physical examination, his weight was 35 kg, and his height was 160 cm. His gait was ataxic, he had a tandem gait, and his Romberg test was impaired. He could not talk fluently, and his speech was not comprehensive. He had not had nystagmus. Brain magnetic resonance imaging (MRI) was performed, and it revealed high signal intensity in T2WI in the basal ganglia and head of the caudate nucleus on both sides, which could be suggestive of systemic metabolic abnormalities (WD or Wernicke encephalopathy). A laboratory test was requested to rule out WD. The laboratory data revealed mildly increased transaminases: aspartate aminotransferase [AST] 69 U/L [RR: 10–45], alanine aminotransferase [ALT] 51 U/L [RR: 10–45]) and low ceruloplasmin (10 mg/dL; RR: 20–40) levels. Bilirubin and hepatic function were also normal (Bilirubin test = 0.6 mg/dL and INR = 1). Viral and autoimmune hepatitis markers were also negative.

A 24-hour urine sample was gathered, and the 24-hour urine copper level was also measured. The results showed an increase in copper in the urine (330 µg/24 h [RR = up to 70]).

Due to the history of dark urine, urinalysis was performed, and the results showed no hematuria or hemoglobinuria in the urine analysis. Only 5–6 calcium oxalate crystals were seen.

A core needle biopsy of the liver was performed. It showed chronic hepatitis Stage 5 (incomplete cirrhosis), moderate continuous piecemeal necrosis (3), centrilobular necrosis in some areas (2), one to four foci of apoptosis and inflammation (2), moderate inflammation of some portal tracts, (2) no cholestasis, no neoplastic involvement, and no metastatic lesion. In the liver needle biopsy, hepatic copper concentration was measured as 465.1 (µg/g). No thrombosis was observed in the abdominal color Doppler ultrasound. The diameter and flow direction of the portal vein and hepatic veins were average. There were no signs of portal hypertension. Esophagogastroduodenoscopy was performed to rule out esophageal varicose veins; the endoscopic view of the esophagus was normal, and varicose veins were not observed. An eye examination was also performed with a slit lamp, and black pigment deposits were observed in the subconjunctival area and on the sclera, which could confirm AKU, and a KF ring was seen on the cornea of the eye. The patient's peripheral whole blood sample was used to extract genomic DNA. Whole exome sequencing was performed on the Illumina HiSeq 4000 platform with 100 × depth of coverage and 101 bp paired-end reads. The raw sequence data was analyzed, which included base calling, demultiplexing, alignment to the hg1 human reference genome (Genome Reference Consortium GRCh37), and variant calling. The American College of Medical Genetics and Genomics (ACMG) has previously reported the pathogenic homozygous variant of NM_000053: c.C2363T: pT7881in the ATP7B gene.

Incidental findings in whole exome sequencing are indicated in Table 1.

Considering the urine discoloration and eye black pigment deposits, a metabolic disease was suspected, and panel A metabolic (organic acids and acyl glycines profile) was performed on the patient's blood sample, homogentisic acid (1925 mmol/mol, normal < 3) was increased. This result was compatible with the biochemical diagnosis of AKU. The treatment of AKU was done by managing symptoms and preventing complications. Therefore, to address dietary management, we suggested a low-protein diet and prescribed him vitamin C (1–4 g/d). Moreover, nitisinone (low dose) was administered at 0.5 mg/kg of body weight daily. Patient did not experience any pain that required pain management.

**Table 1.** Incidental findings in whole exome sequencing

| Gene | Variant | Zygosity | Disease (OMIM) | Inheritance | Pathogenicity | |
|---|---|---|---|---|---|---|
| | | | | | ACMG | ClinVar |
| HGD | NM_000187:exon3:c.175delA:p.S59Afs*52 | Hom | Alkaptonuria | AR | Pathogenic | Pathogenic |
| LRAT | NM_001301645: exon2:c.C487G:p.H163D | Het | Leber congenital amaurosis 14<br>Retinal dystrophy, early-onset severe.<br>Retinitis pigmentosa, juvenile | AR | Likely pathogenic | Pathogenic |
| SGCB | NM_000232:exon4:c.G499A:p.G167S | Het | Muscular dystrophy, limb-girdle | AR | Likely pathogenic | Uncertain significance |
| CYP24A1 | NM_000782:exon2:c.428_430del:p.E143del | Het | Hypercalcemia, infantile, 1 | AR | Pathogenic | Pathogenic |
| IGF1 | NM_000618:exon3:c.C292T:p.R98W | Het | Growth retardation with deafness and mental retardation due to IGF1 deficiency | AR | Likely pathogenic | Pathogenic |
| DPYS | NM_001385:exon5:c.G905A:p.R302Q | Het | Dihydropyrimidinuria | AR | Likely pathogenic | Likely pathogenic |

The patient was diagnosed with WD, and treatment with trientine zinc and vitamin E was started. In his follow-up, tremors, drooling, and ataxia had disappeared, his school performance had improved, and his appetite and weight had become normal again.

## Discussion

WD is an autosomal recessive disorder resulting in copper deposits in multiple organs like the brain and liver. Primarily, liver involvement is observed in young patients, and neurological symptoms are mostly seen in adults, although both liver and neurological manifestations may occur at an early or late age (8). Therefore, the treatment of WD primarily focuses on attenuating copper levels in the body. Chelating agents like penicillamine and trientine bind to copper and promote its excretion, while zinc salts reduce copper absorption from the gastrointestinal tract. Despite these effective options, challenges remain in managing treatment adherence, monitoring copper levels, and addressing potential side effects (9). Here, we report a young patient with neurological signs and symptoms (tremors, drooling, ataxia, and dysarthria). Dysarthria is a common symptom. Ataxia is typically not clinically relevant, and frank limb ataxia is uncommon (10). An eye examination with a slit lamp showed a KF ring. KF rings are seen in almost all patients with WD who present with neurological signs and symptoms (5). The patient also had a brain MRI. In the brain MRI, the basal ganglia and head of the caudate nucleus on both sides revealed high signal intensity in T2WI, and WD was suspected. An MRI of the brain in WD may show structural abnormalities in the basal ganglia or striatal and thalamic atrophy, such as increased density on T2-weighted basal ganglia (11). We also checked liver transaminase levels, serum ceruloplasmin, and 24-hour urine copper to rule out WD. The results showed low ceruloplasmin levels and high 24-hour urine copper. WD is diagnosed when the copper concentration in the liver is higher than 250 mcg/g dry weight (4 μmol/g dry weight) (12). Our patient's hepatic copper concentration was 465.1 (μg/g). Another interesting finding in our patient was urine discoloration. A urine analysis was performed, and it was normal. Suspecting AKU, a metabolic analysis was also performed, and the results showed increased homogentisic acid in urine, confirming the diagnosis of AKU.

AKU is an autosomal recessive disorder. HGD activity deficiency results in increased levels of homogentisic acid in the urine, causing urine to turn dark after standing in the environment (13). Whole exome sequencing was performed to determine the genetic connection between WD and AKU. Primary findings showed a pathogenic homozygous variant of NM_000053: c.C2363T: p. T7881in ATP7B gene and a pathogenic homozygous variant NM_000187: exon3: c.175delA: p.S59Afs*52, confirming the diagnosis of AKU.

Despite the various complications of AKU in affected patients, there is no FDA-approved treatment. Treatment commonly relies on symptom management. However, emerging therapies like nitisinone have shown promising effects in clinical studies. Nitisinone reduces homogentisic acid levels by inhibiting a key enzyme in the tyrosine degradation pathway, potentially slowing disease progression (14). The long-term safety and accessibility of nitisinone remain unclear (15).

## Conclusion

In conclusion, our case showed that rare genetic diseases can happen simultaneously, probably due to consanguineous marriage. Following the diagnostic processes for WD and AKU is crucial, as both conditions can present with overlapping symptoms, necessitating thorough clinical evaluation and diagnostic testing. The simultaneous occurrence of WD and AKU, in this case, highlights the complexity and variability of ultra-rare genetic disorders. This comorbidity emphasizes the need for comprehensive diagnostic approaches considering multiple genetic mutations and abnormalities, mainly when clinical manifestations are atypical or involve overlapping symptoms. The case underscores the importance of integrating advanced genetic testing, such as whole exome sequencing, into routine clinical practice to effectively diagnose and manage comorbid genetic disorders. Furthermore, this case could direct further research into the genetic and molecular mechanisms underlying the concurrence of rare diseases, potentially leading to improved diagnostic criteria, personalized treatment strategies, and a deeper understanding of genetic interactions in rare and complex cases.

### Authors' Contribution

**Conceptualization:** Hassan Talakesh and Karamali Kasiri.
**Investigation:** Karamali Kasiri.
**Methodology:** Hassan Talakesh.
**Project administration:** Hassan Talakesh.
**Resources:** Karamali Kasiri.
**Writing–original draft:** Hassan Talakesh and Karamali Kasiri.
**Writing–review & editing:** Hassan Talakesh and Karamali Kasiri.

### Competing Interests

The authors declare that they do not have any conflict of interest.

### Ethical Approval

The study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1402.154).

### Funding

This work has been funded by Shahrekord University of Medical Sciences, Shahrekord, Iran (grant No. 4047 ).

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