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CASE REPORT

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# First report of Wilson disease and Bruton agammaglobulinemia in the same patient caused by new mutations in *ATP7B* and *BTK* genes

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**Abstract**
*Introduction*: Wilson disease is characterized by an alteration in copper metabolism that causes its accumulation in different tissues. Its diagnosis is established by the combination of clinical manifestations and paraclinical and genetic studies. Bruton agammaglobulinemia is an X-linked recessive hereditary disease belonging to the group of primary immunodeficiencies and is produced by mutation in the *Bruton tyrosine kinase* (*BTK*) gene.
*Case report*: A 14-year-old Colombian patient with clinical characteristics of Bruton agammaglobulinemia presented with liver disease and clinically and molecularly diagnosed with Wilson disease.
*Discussion*: Bruton agammaglobulinemia and Wilson disease are considered rare diseases because of their low prevalence. We report for the first time a pediatric patient from southwestern Colombia presenting with both entities, and diagnosed clinically and molecularly, an association so far not reported in the literature.


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## Introduction

Wilson disease (WD) (Online Mendelian Inheritance in Man [OMIM]: 277900) is characterized by an alteration in copper metabolism that causes its accumulation in different tissues, mainly the liver, basal nuclei, and cornea. A disease with wider phenotypic and genotypic variability, WD causes multiple clinical manifestations.[1] WD has an autosomal recessive pattern of inheritance, and more than 300 mutations of the gene *ATP7B* have been identified.[2] It has a prevalence of 1 per 50,000 inhabitants.[3] Its diagnosis is established by a combination of clinical manifestations, laboratory investigations, and genetic studies; laboratory examinations include elevated transaminases, plasma ceruloplasmin < 30 mg/dL, serum copper < 60 µg/dl, urine copper > 100 µg/dL, and hepatic copper > 250 µg/g of dry weight.[4,5]

Bruton agammaglobulinemia (BA) (OMIM: 300300) is an X-linked recessive hereditary disease and is a part of the group of primary immunodeficiencies.[6] BA leads to recurrent infections when maternal antibodies disappear and has a prevalence of 1 per 379,000 inhabitants.[7,8] It is produced by the deletion of or mutation in the *Bruton tyrosine kinase* (*BTK*) gene.[9] BA is characterized by low levels of serum immunglobulins and almost undetectable levels of B cells.[10,11]

We report a patient from southwestern Colombia with clinical and molecular diagnosis of both WD and BA. To our knowledge, this is the first case reported in the literature with both WD and BA, and with no previously reported mutations in *ATP7B* and *BTK* genes.

## Case Report

The patient was a 14-year-old boy born full-term with adequate weight for gestational age, without immediate complications after birth. The family had no relevant antecedents, and there was no consanguinity. Clinical manifestations began at the age of 15 days, with repeated infections. The patient also presented with right hemiparesis 15 days after the administration of oral polio vaccine. He was admitted to the pediatric intensive care unit for severe gastrointestinal and respiratory infections, and experienced several episodes of septic arthritis. Paraclinical tests at the time demonstrated hypogammaglobulinemia of all isotypes, and the patient was being managed as though he had a primary humoral immunodeficiency. At the age of 3, he had 0.2% B cells with normal T cells in the ratio of 4:1. He was started intravenous immunoglobulin (IVIG) replacement, with lessening of infectious manifestations. At the age of 9, sequencing of *BTK* gene was performed, revealing an unreported deletion mutation of exons 13 to 17 (BTK:c.1178_1908del, p.Gly393-Glu636del), thereby confirming the diagnosis of X-linked BA.

At the age of 9, the patient presented with intermittently elevated liver function tests. Initially, this elevation was considered secondary to IVIG infusion, but because of the persistence of alteration, he was referred to hepatology. Autoimmunity and infectious causes were ruled out, and as the elevated transaminases persisted, studies were expanded, which established low levels of ceruloplasmin (3.87 mg/dL) and serum copper (13.7 µg/dL) and an elevated level of urine copper (83 µg/dL). Liver biopsy depicted evidence of 60% microsteatosis and negative orcein staining, with high suspicion of WD. For this reason, treatment was started with high-dose zinc for being a cupriuresis agent, resulting in marked attenuation in transaminase levels. Given the suspicion of a copper metabolism disorder of genetic origin, exome sequencing was performed, which revealed two mutations in *ATP7B* gene: c.2332C>T mutation (p.Leu778Phe, missense variant),[12] a variant classified as potentially pathogenic and reported previously,[13] and c.229G>T mutation (p.Glu77Ter, nonsense variant),[12] a variant classified as pathogenic but unreported, confirming the diagnostic suspicion of WD. Brain magnetic resonance imaging (MRI) was performed without any evidence of copper deposition in the basal ganglia and alteration in the cornea.

Currently, the patient is being managed with monthly IVIG replacement and zinc therapy for WD, and he is stable with adequate clinical and paraclinical progression.

## Discussion

Wilson disease and BA are two entities classified as rare diseases because of their low prevalence. No case studies or reports that identify an association between these two diseases are found in the literature; however, based on their prevalence, a probability of coexistence of both entities in 1 per 18,950,000,000 inhabitants is accounted, which indicates that it is an infrequent condition. It was not possible to find predisposing factors that could favor this association, such as consanguinity between parents, which suggests that this genetic association is secondary to chance.

Currently, the management of immunodeficiencies is based on immunoglobulin replacement therapy, as being provided to this patient. Studies on gene therapy are currently being accomplished, and early recognition and treatment of infections and complications is the key to reducing morbidity and mortality in such patients. In addition, education and lifestyle changes and regular follow-up by specialized professionals who thoroughly understand these pathologies are necessary.[7,8]

Multiple treatments for patients with WD have been described, including dietary restriction and inhibition of intestinal copper absorption, for which the use of zinc as a cupriuresis agent is endorsed,[2] as exercised to the present patient. This has resulted in significant improvement in patient's condition. There are also other therapeutic options, such as the use of copper chelators – among which the use of penicillamine stands out – and liver transplant in severe cases presenting with fulminant liver failure.[2]

## Conclusion

This case report broadens the clinical spectrum of both genetic conditions. It establishes that a patient with an established diagnosis may present a different entity and that not all clinical manifestations are attributable to the underlying disease. Instead, they could be associated with other entities that, in turn, could be classified within the

group of rare diseases that merit study and concomitant management, as in this patient. This association was random but usually is not be associated. approximately 3% of patients with a rare disease can have another condition. Finally, identifying two new mutations makes it necessary to research poorly studied populations, such as the Colombian population.

## Data Availability

The data used to support the findings of this study are restricted by the Ethics Committee of Fundación Valle del Lili in order to protect patient's privacy. Data are available from Dr. Manuela Olaya-Hernández for researchers who meet the criteria to access confidential data.

## Disclosure

There was no sponsorship, and the study was conducted by the own dedication of the authors. The manuscript was submitted solely to this journal and is not published or submitted elsewhere.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

## Consent

The planning, conduct, and reporting of this human research was in accordance with the Helsinki Declaration as revised in 2013. The study was approved by the Ethics Committee of Fundación Valle del Lili. Patient-informed consent was obtained and retained by the authors, and is available to researchers only on request who meet the criteria to access confidential data.

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