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(CASE REPORT)

Familial chronic cholestasis associated with renal insufficiency and a TTC21B Gene Mutation: A family case report

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Abstract

Introduction: Familial chronic cholestases associated with renal involvement are rare and may reveal a genetic disease such as a ciliopathy. The TTC21B gene, involved in intraflagellar transport, is mainly associated with tubulointerstitial and glomerulocystic nephropathies, although hepatobiliary manifestations have also been described.

Observation: We report the case of a 48-year-old female patient followed for chronic cholestatic liver disease, initially considered to be seronegative primary biliary cholangitis in view of the familial context. The course was marked by edematous-ascitic decompensation with refractory ascites, persistent cholestasis despite ursodeoxycholic acid, chronic pruritus, and chronic renal insufficiency followed in nephrology. Viral, autoimmune, overload, and biliary MRI investigations did not support a classic etiology. Family investigation found several relatives affected by chronic cholestasis and/or renal involvement. Familial genetic testing identified a recurrent mutation in exon 6 of the TTC21B gene in two sisters.

Discussion: This observation underlines the diagnostic difficulty in distinguishing seronegative primary biliary cholangitis from familial genetic cholestasis, particularly when hepatobiliary involvement is associated with renal insufficiency. The presence of a TTC21B mutation points toward a ciliopathy, an entity that may combine renal and extra-renal involvement.

Conclusion: In the presence of seronegative familial chronic cholestasis associated with renal insufficiency, a genetic origin should be investigated. Identification of a TTC21B mutation has diagnostic, prognostic, therapeutic, and familial implications.

Keywords: Familial cholestasis; Chronic renal insufficiency; TTC21B; Ciliopathy; Seronegative primary biliary cholangitis; Liver transplantation

1. Introduction

Chronic cholestases in adults are dominated by acquired cholangiopathic diseases, particularly primary biliary cholangitis (PBC) and primary sclerosing cholangitis. However, atypical presentations, especially familial and seronegative forms associated with renal involvement, should raise the possibility of a genetic etiology.

PBC is usually defined by the association of biochemical cholestasis, specific autoantibodies, and/or compatible histological lesions. International guidelines recall that, in AMA-negative forms, the presence of PBC-specific antibodies such as anti-gp210 or anti-sp100, or liver histology, can support the diagnosis [1,2,3].

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Ciliopathies are a heterogeneous group of genetic diseases related to abnormalities in the structure or function of primary cilia. They may involve several organs, particularly the kidney, liver, bile ducts, eye, and skeleton. The TTC21B gene, which encodes a protein of the intraflagellar transport complex, has been described in chronic nephropathy, nephronophthisis, glomerulopathy, and, more rarely, biliary cirrhosis [4,5].

We report a familial observation of chronic cholestasis associated with renal insufficiency in a patient carrying a TTC21B gene mutation, in order to discuss the contribution of genetics in seronegative familial cholestasis and the practical implications for patient management.

2. Case Report

The patient was a 48-year-old woman followed for long-standing epilepsy treated with sodium valproate, schizophrenia treated with neuroleptics, and hypothyroidism under replacement therapy. Since 2022, she had also been followed in nephrology for chronic renal insufficiency of undetermined etiology, with six-monthly monitoring.

The family history was particularly suggestive: a first sister, aged 58 years, had been followed since 2007 for PBC documented on clinical, biological, and histological arguments, and was receiving ursodeoxycholic acid; a second sister, aged 60 years, had undergone kidney transplantation in 2004 for nephropathy of undetermined etiology and had recently been diagnosed and treated for PBC; a third sister had died from gastric neoplasia with secondary localizations.

From a hepatic standpoint, the patient had been followed since February 2023 for chronic cholestatic liver disease, initially considered to be seronegative PBC in view of the familial context. She was treated with ursodeoxycholic acid at a dose of 750 mg/day, approximately 13 mg/kg/day, with reported good adherence. The course was complicated by edematous-ascitic decompensation with refractory ascites and pruritus requiring evacuative paracentesis combined with albumin therapy every two weeks. No neurological or hemorrhagic decompensation was reported.

Laboratory testing showed anicteric cholestasis, hypoalbuminemia, and renal insufficiency without proteinuria, with preserved prothrombin time and factor V. Ascitic fluid analysis found a sterile transudate. Abdominal imaging showed chronic liver disease with irregular contours and large-volume ascites, with no evidence of abdominal vascular thrombosis.

The etiological work-up was negative: viral serologies were negative; autoimmune testing was negative, including antinuclear antibodies, anti-smooth muscle antibodies, anti-LC1, anti-SLA, anti-LKM1, anti-mitochondrial M2, anti-gp210, and anti-sp100 antibodies; overload testing was normal, including ferritin, transferrin saturation coefficient, ceruloplasmin, and urinary copper. No metabolic syndrome was identified. Biliary MRI showed chronic liver disease without evidence of primary sclerosing cholangitis. Liver biopsy was not performed because of refractory ascites and renal insufficiency under diuretic therapy.

The case was discussed in a multidisciplinary meeting, which concluded that probable seronegative PBC should be retained in view of the family history, with an indication to continue ursodeoxycholic acid and to perform genetic evaluation. Initially, no specific genetic syndrome had been retained by the genetics institute. Nevertheless, the familial course and the association with renal involvement prompted subsequent familial genetic analysis.

Under treatment, the patient maintained persistent cholestasis. The available data showed alkaline phosphatase increasing from 576 IU/L in March 2023 to 596 IU/L in July 2025, and GGT decreasing from 413 IU/L to 189 IU/L over the same period, with only mildly elevated transaminases.

At the latest available assessment, normochromic normocytic anemia at 8.8 g/dL, platelets at 146,000/mm3, prothrombin time at 100%, AFP at 4.7, creatinine at 22 mg/L, urea at 0.67 g/L, total bilirubin at 4 mg/L, and albumin at 29 g/L were also noted. Clinically, the patient still had large-volume ascites and pruritus without jaundice, with no hepatic encephalopathy or externalized gastrointestinal bleeding.

Because of pruritus, the patient was started on cholestyramine. Therapeutic discussion focused on adding a second-line treatment, particularly a fibrate, but the course was marked by persistent cholestasis and unavailability of the second-line treatment. Familial genetic testing ultimately revealed a recurrent mutation in exon 6 of the TTC21B gene in two sisters. According to the available report, the identified variant was c.626C>T, p.Pro209Leu. The patient was considered a candidate for liver transplantation because of ascitic decompensation and the absence of an effective available therapeutic alternative.

Table 1 Chronological Summary of Clinical and Paraclinical Data

Period	Clinical or Paraclinical Element	Interpretation
2004	Kidney transplantation in a sister for nephropathy of undetermined etiology.	Family argument in favor of possible genetic renal involvement.
2007	Diagnosis of PBC in a sister, treated with UDCA.	Familial context of chronic cholestasis.
2022	Nephrology follow-up of the patient for chronic renal insufficiency.	Renal involvement associated with cholestasis.
February 2023	Hospitalization for edematous-ascitic syndrome and pruritus; anicteric cholestasis; sterile transudative ascites.	Revelation of decompensated chronic cholestatic liver disease.
2023-2025	Persistence of cholestasis despite UDCA; refractory ascites requiring evacuative paracentesis and albumin therapy.	Unfavorable course under first-line treatment.
Familial genetic analysis	Recurrent mutation in exon 6 of the TTC21B gene in two sisters.	Orientation toward familial hepatorenal ciliopathy.
Recent course	Discussion of second-line treatment; candidacy for liver transplantation.	Need for specialized and multidisciplinary management.

3. Discussion

This observation illustrates a complex diagnostic situation: familial chronic cholestasis, initially considered to be seronegative PBC, associated with chronic renal insufficiency and a TTC21B gene mutation. The main interest of the case lies in the coexistence of familial hepatobiliary involvement, renal involvement, and a negative conventional etiological work-up.

The diagnosis of seronegative PBC classically relies on the presence of persistent biochemical cholestasis, PBC-specific autoantibodies when anti-mitochondrial antibodies are negative, or compatible histological lesions [1,2,3]. In our observation, the absence of anti-mitochondrial M2, anti-gp210, and anti-sp100 antibodies, the impossibility of performing liver biopsy, and the association with chronic renal insufficiency make the diagnosis of seronegative PBC less certain and require discussion of a familial genetic cholangiopathy.

The TTC21B gene encodes a protein involved in retrograde intraflagellar transport within primary cilia. Primary cilia play a central role in the development and homeostasis of several organs, notably the kidney and bile ducts. TTC21B abnormalities have been associated with a broad spectrum of ciliopathies, with variable phenotypes ranging from tubulointerstitial or glomerular renal involvement to extra-renal manifestations [4,6,7].

From a renal perspective, biallelic TTC21B mutations have been described in nephronophthisis, tubulointerstitial fibrosis, certain forms of focal segmental glomerulosclerosis, early-onset hypertension, and chronic renal insufficiency [6,8]. The existence of a sister who underwent kidney transplantation for an undetermined cause strengthens, in our observation, the hypothesis of a familial genetic disease preferentially affecting the kidney and bile ducts.

From a hepatobiliary perspective, the association between TTC21B and cholangiopathy is rare but has already been reported. The case described by Gambino et al. is particularly close: a patient carrying the homozygous c.626C>T, p.Pro209Leu variant of the TTC21B gene presented with end-stage renal insufficiency associated with biliary cirrhosis, requiring combined liver-kidney transplantation [5]. This observation supports the plausibility of a link between the TTC21B variant identified in our family and the observed hepatorenal phenotype.

Biliary involvement in ciliopathies may be explained by the role of primary cilia of cholangiocytes in sensing bile flow and regulating ductular proliferation and repair. Ciliary dysfunction may promote abnormalities in development or remodeling of the bile ducts, which can progress to chronic cholestasis, portal fibrosis, or biliary cirrhosis. This pathophysiology helps explain why some ciliopathies can mimic acquired cholangiopathies such as PBC or primary sclerosing cholangitis.

Therapeutic management remains difficult. Ursodeoxycholic acid is the first-line treatment for PBC [2,3], but its efficacy is uncertain when cholestasis is related to a genetic abnormality of ciliary structure or function. In our observation, persistent cholestasis despite treatment at an appropriate dose, combined with refractory ascites, suggests advanced disease and a risk of progression toward liver failure.

Transplantation is a central issue. In this patient, ascitic decompensation and persistent cholestasis justify evaluation for liver transplantation. However, given chronic renal insufficiency and the familial context of kidney transplantation, the indication should be discussed in an expert center in order to assess the appropriateness of isolated liver transplantation or combined liver-kidney transplantation according to renal function, glomerular filtration rate, proteinuria, renal imaging, and nephrological course.

This observation also emphasizes the importance of family screening and genetic counseling. Identification of a recurrent mutation in two sisters requires a broader family investigation, characterization of the mode of inheritance, assessment of carrier status in at-risk relatives, systematic renal and hepatic evaluation, and discussion of genetic counseling, particularly in descendants.

The main limitations of this observation are the absence of liver biopsy and the absence of renal histological description. Nevertheless, the association of familial cholestasis, renal involvement, and a TTC21B variant constitutes a strong body of evidence in favor of hepatorenal ciliopathy.

4. Conclusion

This observation reports familial chronic cholestasis associated with chronic renal insufficiency and a TTC21B gene mutation. It highlights the need to go beyond the diagnosis of seronegative PBC when cholestasis is familial, when specific autoantibodies are negative, and when renal involvement is associated.

In this context, genetic analysis has major diagnostic and prognostic value. It helps orient the diagnosis toward hepatorenal ciliopathy, organize family screening, and adapt the therapeutic strategy, particularly when liver transplantation or combined liver-kidney transplantation is being discussed.

The main message of this case is that any unexplained chronic cholestasis, whether familial or associated with renal insufficiency, should raise suspicion of a genetic disease, particularly TTC21B-related ciliopathy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study."

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