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Illuminating and Instructive Clinical Case

Late-onset Cholestasis with Paucity of Portal Area Secondary to HNF1β Deficiency in Adulthood: A Case Report

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Abstract

Hepatocyte nuclear factor 1β (HNF1β) is essential for biliary development, while its genetic defect triggers the dysplasia of interlobular bile ducts, leading to life-threatening hepatitis and cholestasis. To date, this disorder has mainly been documented in neonates. Here, we report a case of cholestasis in an adult patient caused by a *de novo HNF1β* mutation. A liver biopsy revealed remarkable shrinkage of the portal area accompanied by a decrease or absence of interlobular bile ducts, veins, and arteries in the portal area. Our case showed that an *HNF1β* defect could induce late-onset cholestasis with paucity of the portal area in adulthood.

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Introduction

The hepatocyte nuclear factor 1β (HNF1β) is a key transcriptional regulator expressed in biliary epithelial cells. It plays an essential role in the developmental and functional regulation of the hepatobiliary system.[1,2] Several studies have demonstrated that HNF1β facilitates the differentiation of interlobular bile ducts and the morphogenesis of the biliary system.[2,3] Targeted knockout of *HNF1β* in mice was found to induce dysfunction of the intrahepatic bile ducts, leading to cholestasis and jaundice.[4] In clinical practice, pathogenic *HNF1β* mutations, including missense mutations, small insertions-deletions, or whole-gene deletions, have been reported to be associated with cholestatic disease with abnormally increased liver enzymes.[5,6] However, the incidence of cholestasis associated with *HNF1β* mutations is rare, and almost all reported cases have occurred in neonates. Here, we report a case of adult-onset cholestasis caused by *HNF1β* mutation, which exhibited paucity of the portal area in histopathological examination.

Case presentation

A 30-year-old man was admitted to the hepatology department for abnormal liver function, along with a 10-year history of liver aminotransferase anomalies, mainly exhibiting abnormal elevation of glutamine transferase (GGT) and alkaline phosphatase (ALP). The clinical examination results are shown in Table 1. Routine blood tests confirmed that the patient suffered from cholestasis, with serum GGT levels elevated to 798 U/L (upper limit of norm [ULN] 58 U/L) and the ALP level at 200 U/L (ULN 126 U/L). Routine screening was performed to identify the etiology of the cholestatic liver disease. Tests for autoimmune liver disease antibodies (antinuclear, antimitochondrial, anti-smooth muscle, anti-liver-kidney microsomal antigen-1, anti-liver cytosol-1) and serum immunoglobulins (gamma globulin and IgG) showed negative results, ruling out autoimmune hepatitis. Serological tests for hepatitis A, B, C, D, and E viruses, as well as cytomegalovirus, syphilis, rubella, toxoplasmosis, parvovirus, and human immunodeficiency virus, were negative, ruling out viral infections. Renal and coagulation functions were within the normal range. Physical examination was unremarkable. Spinal magnetic resonance, cardiac ultrasonography, and electrocardiogram showed normal results. Abdominal computed tomography revealed multiple bilateral renal cysts. The patient had no history of alcohol consumption or other drug abuse, no cholestasis in infancy or childhood, and no relevant family medical history.

Hematoxylin and eosin staining of the liver biopsy tissue (1.4 cm length × 0.1 cm diameter) obtained by puncture sampling showed partial destruction of hepatic lobules, edema and fatty degeneration around the central veins, and scattered necrotic focus in the lobules (Fig. 1A). Notably, eight central veins were detected versus only one complete portal tract in the sampling tissue, and only one bile duct and one vessel were found within the portal tracts, suggesting

Keywords: HNF1β; Cholestasis; Adult patient; Paucity of the portal area; Renal cysts; Case report.

Abbreviations: AGS, Alagille syndrome; ALP, alkaline phosphatase; GGT, glutamine transferase; HNF1β, hepatocyte nuclear factor 1β; MODY5, type 5 maturity-onset diabetes of the young; UDCA, ursodeoxycholic acid.

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Table 1. Demographic information and clinical examination results of the patient

Demographic characteristics	Factor	Value
	Sex	Male
	Age in years	30
	Weight in kg	74
	Height in cm	178
	Underlying disease	/

	Parameter	Value	Normal range
Liver function			
	Bilirubin total in mg/dL	16	0–23
	Conjugated bilirubin total in mg/dL	12.2	0–21
	AST in U/L	35	25–40
	ALT in U/L	26	9–50
	ALP in U/L	200	45–125
	GGT in U/L	798	10–60
	Albumin in g/dL	38	40–55
Kidney function			
	Serum creatinine in μmol/L	63	57–111
	eGFR in mL/(min*1.73m^2)	135	>90
	Uric acid in μmol/L	400	208–428
Autoimmune liver disease antibodies			
	Antinuclear	(−)	N/A
	Antimitochondrial	(−)	N/A
	Anti-smooth muscle	(−)	N/A
	Anti-liver-kidney microsomal antigen-1	(−)	N/A
	Anti-liver cytosol-1	(−)	N/A
	Gamma globulin	(−)	N/A
	IgG in g/L	7.92	7.2–16.9
Virological indicators			
	Hepatitis A virus	(−)	N/A
	Hepatitis B virus	(−)	N/A
	Hepatitis C virus	(−)	N/A
	Hepatitis D virus	(−)	N/A
	Hepatitis E virus	(−)	N/A
	Cytomegalovirus	(−)	N/A
	Syphilis	(−)	N/A
	Rubella	(−)	N/A
	Toxoplasmosis	(−)	N/A
	Parvovirus	(−)	N/A
	Human immunodeficiency virus	(−)	N/A
Coagulation functions			
	Prothrombin time in s	10.8	10.4–12.7
	INR	0.9	0.85–1.15
Imaging examination			
	Spinal magnetic resonance	Normal	N/A
	Cardiac ultrasonography	Normal	N/A
	Electrocardiogram	Normal	N/A
	Abdomen computed tomography	Renal cysts	N/A

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, glu-tamine transferase; INR, international normalized ratio; N/A, not applicable.

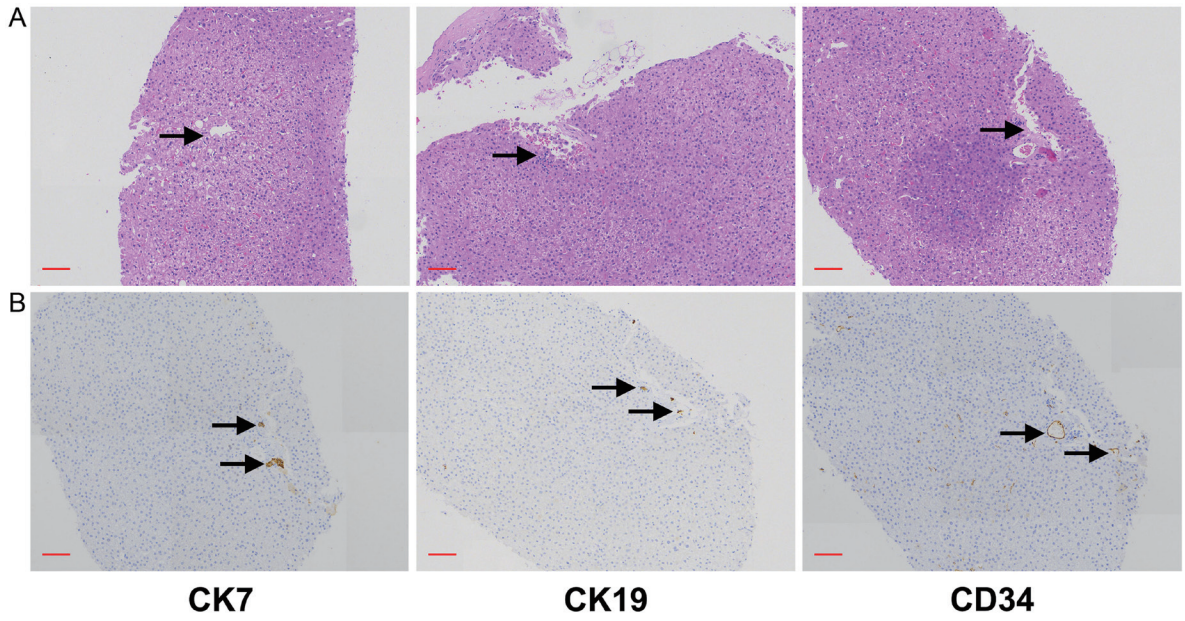

Fig. 1. Pathohistological analysis and immunohistochemistry of liver biopsy. (A) Hematoxylin and eosin staining of mounted tissue showed pathological impairment of hepatic lobules accompanied by shrinkage of portal area, as indicated by arrow (200×). (B) Immunohistochemical staining showed decreased expression of CK7 and CK19, corresponding to the loss of bile ducts indicated by arrow, and decreased expression of CD34, corresponding to the absence of small vessels indicated by arrow (200×).

shrinkage of the portal area. Immunohistochemical staining revealed a significantly decreased expression of CK7, CK19, and CD34, further confirming the loss of interlobular bile ducts and interlobular vessels (Fig. 1B). Negative results of *JAG1* and *NOTCH2* mutations in genetic tests excluded Alagille syndrome (AGS) as a diagnosis. Whole-exome sequencing analysis revealed a deletion mutation in the *HFN1β* gene. Copy number variation sequencing verified the pathogenic deficiency of the *HFN1β* gene, characterized by a copy number heterozygous deletion variation in the region of 17q12q12, confirming the etiology of cholestasis in our case (Fig. 2A and B). The absence of an abnormal gene-related proband in his family indicated that the patient was a carrier of a *de novo* *HNF1β* mutation (Fig. 2C and D). During hospitalization, the patient was treated with ursodeoxycholic acid (UDCA) at a dose of 14 mg/kg/day, in accordance with clinical practice guidelines.[7] Consequently, his GGT and ALP levels, which are indicators of cholestasis, effectively decreased and fell in the normal range at the end of the therapy (Fig. 3).

Discussion

Cholestasis related to *HNF1β* mutation is a rare genetic disease of bile metabolic dysfunction.[8] To the best of our knowledge, only six cases of cholestasis associated with *HNF1β* mutations have been reported thus far, and noticeably, all of them have occurred in neonates.[6] Herein, we have presented a case of late-onset diagnosis in an adult patient, thereby contributing to the understanding of this rare disease.

A notable clinical characteristic in our case of cholestasis associated with *HNF1β* mutation was the co-occurrence of renal cysts. In fact, *HNF1β* mutations were first recognized in a small group of patients with type 5 maturity-onset diabetes of the young (MODY5), and the first instance of *HNF1β*-related neonatal cholestasis was diagnosed in a patient with MODY5.[9,10] The typical symptoms of MODY5 include diabetes due to impaired insulin secretion and insulin resistance, and non-diabetic renal disease, manifesting as cysts.[11,12] These findings suggest the association of the *HNF1β* gene with the functional regulation of the pancreas and the kidneys, evidenced by the expression of *HNF1β* in pancreatic β cells and renal epithelial cells.[11]

In this context, renal involvement may be an important indicator of an *HNF1β* defect, and our patient also showed bilateral renal cysts. Thus, the presence of renal cysts would be a useful indicator for the diagnosis of cholestasis caused by *HNF1β* mutations. Besides its roles in the kidney, liver, and pancreas, HNF1β also acts as a broad transcription factor that regulates the development of other organs such as the urogenital tract, brain, and parathyroid gland by controlling diverse developmental genes. Therefore, diseases related to *HNF1β* defects present as multifaceted syndromes, characterized by pathological profiles affecting multiple organs.[13] In male patients with *HNF1β* mutations, clinical observations have reported genital defects such as testicular abnormalities, hypospadias, and prostatic hypoplasia.[14] However, such pathological variations were not found in our case.

Another pathological characteristic observed in our patient was the paucity of the portal area, marked by the decrease or lack of interlobular bile ducts, veins, and arteries. A similar paucity of interlobular bile ducts was also observed in another genetic cholestatic disease, AGS, caused by the mutation in *JAG1* or *NOTCH2* genes.[15] However, besides the paucity of interlobular bile ducts, our patient with *HNF1β* mutation also exhibited the absence of interlobular veins and arteries, unlike patients with AGS. Despite the underlying mechanism being unclear, this observation suggested the importance of HNF1β in maintaining the integrity of the hepatobiliary duct system. Moreover, studies using mouse models have shown that liver-targeted *HNF1β* deletion could lead to a significant reduction in intrahepatic bile ducts and interlobular arteries,[16] which is consistent with the histopathological finding in our patient. These results reinforce the function of *HNF1β* in facilitating the development of the hepatobiliary and vas-

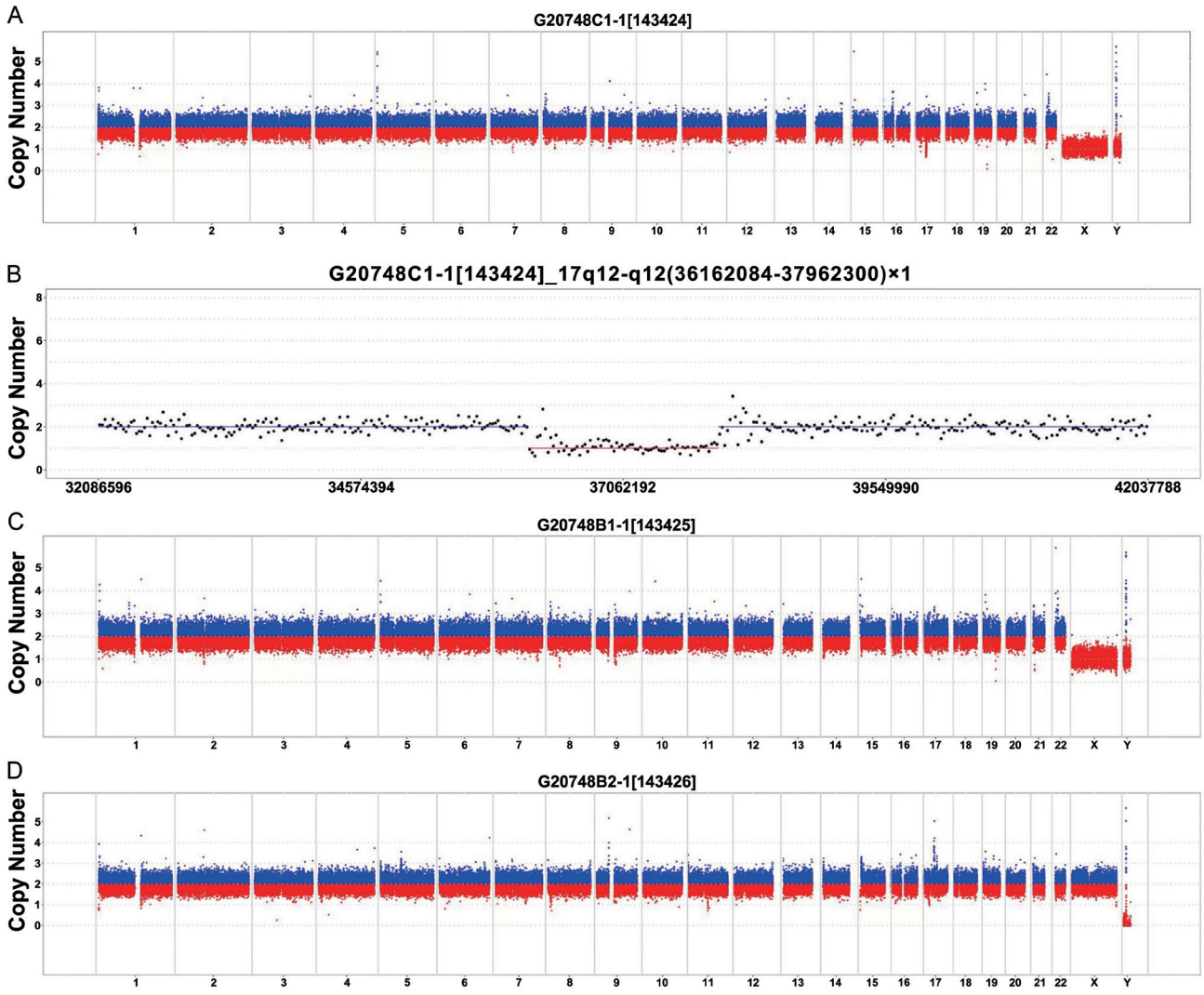

Fig. 2. Verification of copy number variation sequencing on pathogenic deficiency of *HFN1B* gene. (A) Copy number variation was detected in chromosome 17 of our patient. (B) A copy number heterozygous deletion variation was observed in the region of 17q12q12, associated with *HFN1B* gene mutation. (C, D) No evidence of abnormal gene-related proband was found in his mother and father.

cular systems, although it is not expressed in blood vessel endothelial cells, and highlight a novel pathological feature for the identification of *HNF1β*-related cholestasis.

Currently, specific treatments directly aimed at mutated genes remain underdeveloped, and patients with genetic mutations are usually treated for their symptoms. In our case, the patient was diagnosed with a hepatic lesion caused by *HNF1β* deficiency, with the obvious symptom of cholestasis. Therefore, our therapeutic strategy primarily focused on mitigating the cholestatic condition to protect the injured liv-

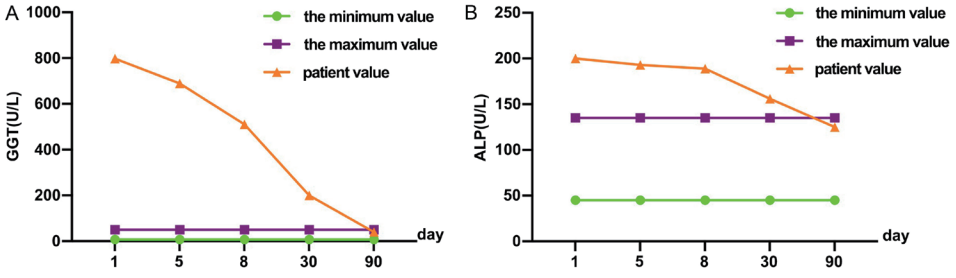

Fig. 3. Serum GGT and ALP levels in our patient were effectively improved by treatment with UDCA. (A) Serum GGT and (B) ALP levels of the patient were detected on the indicated examination days during the treatment and fell into the normal range at the end of therapy. GGT, glutamine transferase; ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid.

er. UDCA is currently the most widely used therapeutic agent for the treatment of cholestatic hepatopathies.[7] Hence, we administered it to our patient. Mechanistically, UDCA exhibits higher hydrophilicity than most bile acids, which endows it with the ability to displace potentially toxic hydrophobic endogenous bile acids, reducing bile acid-mediated hepatic injury involved in cell necrosis and apoptosis.[17,18] Moreover, UDCA represses the rate-limiting metabolizing enzyme Cyp7a1 in the BA-biosynthetic pathway and upregulates the expression of bile acid transporters such as canalicular export pumps Mrp2 and Bsep, consequently reducing excessive production and accumulation of bile acids in hepatocytes.[19] Although UDCA does not repair damaged bile ducts in the *HNF1β*-mutated congenital disorders, its application in our patient improved his symptoms by markedly reducing ALP and GGT levels to the normal range. The efficacy of UDCA in our case is ascribed to its multiple protective effects on bile acid-induced impairment of hepatocytes, suggesting the broad spectrum of UDCA in the treatment of cholestasis. Further research focused on therapeutic strategies involving gene modulation holds promise for significant advancements in the treatment of gene mutation diseases.

Conclusions

In this report, we have presented a novel case of late-onset cholestasis related to *HNF1β* in an adult, characterized by two concurrent pathological features: renal cysts and a paucity of the portal area accompanied by the absence of interlobular bile ducts and blood vessels. These features aid in differentiating *HNF1β* mutations from other causes, such as AGS. Treatment with UDCA in this case effectively improved cholestatic symptoms, evidenced by significant reductions of ALP and GGT levels to within the normal ranges.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (ZY, HF), acquisition of data (KL, XZ, XL), analysis and interpretation of data (WZ, JS, SY), drafting of the manuscript (XZ), and critical revision of the manuscript for important intellectual content (ZY, HF). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study was performed following the ethical standards of the institutions to which we are affiliated and in line with the principles outlined in the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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