Hepatic phenotypes of \textit{HNF1B} gene mutations: A case of neonatal cholestasis requiring portoenterostomy and literature review

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Abstract

Hepatocyte nuclear factor 1-\(\beta\) (\textit{HNF1B}) defects cause renal cysts and diabetes syndrome (RCAD), or \textit{HNF1B}-maturity-onset diabetes of the young. However, the hepatic phenotype of \textit{HNF1B} variants is not well studied. We present a female neonate born small for her gestational age [birth weight 2360 g; -2.02 standard deviations (SD) and birth length 45 cm; -2.40 SD at the 38th gestational week]. She developed neonatal cholestasis due to biliary atresia and required surgical intervention (portoenterostomy) when 32-d old. Following the operation, icterus resolved, but laboratory signs of liver dysfunction persisted. She had hyperechogenic kidneys prenatally with bilateral renal cysts and pancreatic hypoplasia postnatally that led to the diagnosis of an \textit{HNF1B} deletion. This represents the most severe hepatic phenotype of an \textit{HNF1B} variant recognized thus far. A review of 12 published cases with hepatic phenotypes of \textit{HNF1B} defects allowed us to distinguish three severity levels, ranging from neonatal cholestasis through adult-onset cholestasis to non-cholestatic liver impairment, all of these are associated with congenital renal cysts and mostly with diabetes later in life. We conclude that to detect \textit{HNF1B} variants, neonates with cholestasis should be checked for the presence of renal cysts, with special focus on those who are born small for their gestational age. Additionally, patients with diabetes and renal cysts at any age who develop cholestasis and/or exocrine pancreatic insufficiency should be tested for \textit{HNF1B} variants as the true etiological factor of all disease components. Further observations are needed to confirm the potential reversibility of cholestasis in infancy in \textit{HNF1B} mutation/deletion carriers.

Key words: Hepatocyte nuclear factor 1-\(\beta\); Renal cysts and diabetes syndrome; Maturity-onset diabetes of the young; Biliary atresia; Portoenterostomy

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cause renal cysts and diabetes syndrome (renal cysts and diabetes; HNF1B-maturity-onset diabetes of the young), but little is known on liver in these patients. We succeeded to detect the most severe hepatic phenotype of an HNF1B gene deletion in a female neonate with cholestasis due to biliary atresia. She required portoenterostomy when 32-d old. She had bilateral renal cysts and pancreatic hypoplasia. A review of 12 published cases allows distinguishing three severity levels of liver impairment in HNF1B defects, ranging from neonatal cholestasis through adult-onset cholestasis to non-cholestatic liver disease. All have renal cysts and later-onset diabetes.

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INTRODUCTION

The hepatocyte nuclear factors (HNFs) are key transcriptional regulators of embryonic and fetal liver development and differentiation of the biliary system. Their life-long expression in human hepatocytes (HNF4A and HNF6) and in biliary epithelial cells (HNF1B, HNF3A and HNF3B) suggests that they have a role in postnatal cell survival, function and regeneration[1-3]. Of these, the hepatocyte nuclear factor 1-β (HNF1B), encoded by the HNF1B gene, is involved in transcriptional and functional regulation not only of the liver and biliary system but also of the kidneys, urogenital tract and pancreatic β-cells. Deficiency of this gene due to HNF1B point mutations or whole gene deletions was first recognized in a small subgroup of patients with maturity-onset diabetes of the young (MODY) and was originally designated as MODYS[4-6]. It has been demonstrated that HNF1B is involved in regulating the β-cell transcription factor network[7]. Due to the frequent co-occurrence of MODYS diabetes with renal cysts and/or other inborn urogenital abnormalities, the syndrome associated with HNF1B defects is now referred to as RCAD (renal cysts and diabetes). In a recent single centre study, 9% of adult patients with chronic renal failure carried a pathogenic HNF1B variant[8]. Most of the HNF1B variants are de novo whole gene deletions[9-12]. However, the hepatic and biliary phenotype of HNF1B defects has been recognized only in single patients up to this point.

In mice, HNF1B is expressed in the embryonic gall bladder, liver and intrahepatic bile ducts[13]. Furthermore, it is expressed in the adult liver. It has been shown to co-regulate morphogenesis of the biliary system[14]. HNF1B knockout mice suffer from severe neonatal cholestasis and jaundice due to the abnormally developed gall bladder and dysfunctional intrahepatic bile ducts. In addition, HNF1B and HNF1A control genes that affect bile acid transport and metabolism[14,15].

Kitanaka et al[16] first described a patient with neonatal cholestasis, liver dysfunction and hypercholesterolemia caused by a heterozygous mutation, H153N, in HNF1B. The patient later developed non-autoimmune diabetes and was diagnosed with bilateral renal cysts. Two of his paternal ancestors died from hepatic cancer and liver cirrhosis, and multiple family members suffered from chronic renal insufficiency and/or liver disease. Unfortunately, a detailed phenotypic characterization and genotyping of his family members was unavailable.

Additionally, two patients with severe hepatic and biliary phenotype due to monoallelic HNF1B mutations/deletions were described by Beckers et al[17] and by Raile et al[18]. Both patients presented with severe neonatal jaundice, a paucity of intrahepatic bile ducts at liver biopsy and a tendency toward improvement in cholestasis in the late stages of the first year of life. Recently, another patient with a de novo HNF1B mutation, S148L, and renal and hepatic dysfunction diagnosed at 3 mo of age was reported in Turkey when he was investigated for failure to thrive[19]. However, he had no signs of cholestasis.

Adult-onset cholestasis due to HNF1B mutations developed in three patients with known diabetes; the first signs of cholestasis were noted at ages 33, 53 and 30 years[20]. The authors found normal anatomy of the intra- and extrahepatic bile ducts, but the patients were lacking primary cilia on their cholangiocytes. The authors proposed that HNF1B mutations might be classified as ciliopathy.

CASE REPORT

The female patient reported here is the offspring of healthy unrelated parents of Czech origin. There was no family history of known diabetes, hepatic or renal disease. She was born from a first pregnancy in the 38th gestational week with a birth weight of 2360 g (-2.02 standard deviation (SD)) and birth length of 45 cm (-2.40 SD; according to normative data[21]). Fetal hypotrophy and hyperechogenic kidneys were recognized by ultrasound at the 30th gestational week.

Since the first day of life, she had apparently acholic stools and gradually developed jaundice. At day 4, her total bilirubin was 104 μmol/L and her conjugated bilirubin was 32 μmol/L. Her level of γ-glutamyltransferase was markedly increased (23.3 μkat/L), but her levels of alkaline phosphatase (2.3 μkat/L) and alanine-aminotransferase (0.42 μkat/L) were normal. Her aspartate-aminotransferase level was mildly elevated (1.27 μkat/L) (Table 1).

Abdominal ultrasound revealed bilateral renal cysts with diameters up to 5 mm. Her liver had nor-
nal echogenicity and echotexture; however, her gallbladder was small. Her pancreas was hypoplastic with absent body and tail, the spleen was normal, and no additional abnormalities were found. Her kidney function was normal. An infectious, metabolic or immunological basis for neonatal cholestasis was not found.

Due to progressive conjugated hyperbilirubinemia and acholic stools, endoscopic retrograde cholangiopancreatography (ERCP) was performed at 30 d of age. Normal pancreatic ducts were observed, but extrahepatic bile ducts were unrecognizable, which led to the indication for explorative surgery that was then provided at 32 d. Surgery revealed an atrophic gallbladder. Her choledochus and proximal extrahepatic bile ducts were completely atretic and had been replaced by connective tissue. The surgeon performed portoenterostomy sec. Kasai. Liver histology from a preoperatively obtained wedge biopsy showed cholestasis without signs of gigantocellular hepatocyte transformation or bile duct proliferation. Portal fields were dilated with connective tissue, having thin or atretic bile ducts. Close to the porta hepatis, the configuration of bile ducts resembled the findings typical of biliary atresia.

Following surgery, the color of her stools normalized, and both the bilirubin and γ-glutamyltransferase levels declined to mildly elevated values. Post-operative ultrasound follow-up revealed abnormal echotexture of her left hepatic lobe that was suspicious of a cystic malformation. A magnetic resonance cholangiopancreatography (MRCP) identified multiple cystic dysplasia of the left hepatic lobe at 2 years of age. Seven cysts were found with diameters ranging from 2 to 7 mm (Figure 1). By the current age of 2 years, she is growing along the 3rd centile and her PELD score is “1”. She has normal blood glucose, fecal elastase activity and renal function. Mild hypomagnesemia was observed (0.66 mmol/L).

Following the parents’ written consent, the child was included into a study to investigate genetic causes of primary biliary atresia. The study was previously approved by the institutional ethical committee of the University Hospital Prague-Motol. Genetic testing was initiated by direct sequencing of the \( \text{HNF1B} \) gene, mutations in which are recognized as a major cause of Alagille syndrome and some additional cases of severe biliary atresia\(^{[21]} \). The findings were negative. The investigations continued with testing for \( \text{HNF1B} \) using Multiple Ligation Probe-dependent Amplification (MLPA) and subsequent array Comparative Genomic Hybridization methods. She was found to carry an entire \( \text{HNF1B} \) gene deletion spanning 1698 kb, which was previously reported as causative in a patient with MODY diabetes\(^{[23]} \). None of her parents carry an \( \text{HNF1B} \) gene deletion, indicating that the mutation has arisen de novo in the proband.

### DISCUSSION

Interestingly, the detailed hepatic phenotypes available for the 12 patients with pathogenic \( \text{HNF1B} \) variants tend to cluster into three severity degrees of liver dysfunction, ranging from neonatal cholestasis through late-onset cholestasis to the mildest form and non-cholestatic liver impairment.

### Review of published cases with hepatic involvement

Most of the published cases with \( \text{HNF1B} \) variants were assessed for the presence of diabetes and/or renal impairment, mostly renal cysts. To the best of our knowledge, five detailed published reports have focused on the hepatic phenotype in \( \text{HNF1B} \) mutation/whole gene deletion carriers. From these reports, and with the addition of our own observations, we managed to collect clinical and laboratory data on liver disease in 12 subjects, which are summarized in Table 2.

### Table 1: Laboratory data before and after portoenterostomy sec. Kasai that was performed at age 32 d

| Age | Total bilirubin, \( \mu \text{mol/L} \) | Conjugated bilirubin, \( \mu \text{mol/L} \) | AST, \( \mu \text{kat/L} \) | ALT, \( \mu \text{kat/L} \) | GGT, \( \mu \text{kat/L} \) | ALP, \( \mu \text{kat/L} \) | Urea, \( \text{mmol/L} \) | Creatinine, \( \mu \text{mol/L} \) | Cholesterol, \( \mu \text{mol/L} \) | Albumin, \( \mu \text{g/mL} \) | INR | Mg, \( \mu \text{mol/L} \) |
|-----|----------------------------------|--------------------------------|----------------|----------------|----------------|----------------|------------------|----------------|----------------|----------------|----------------|----------------|
| 4 d | 104                             | 32                             | 1.27           | 0.42           | 23.3           | 2.3            | 4.7              | 31              | 2.7            | 36.0           | 0.91           | NA              |
| 27 d| 145                             | 100                            | 1.57           | 0.92           | 10.2           | 7.2            | 2.2              | 29              | 3.7            | 36.8           | 1.05           | NA              |
| 5 mo| 135                             | 110                            | 2.59           | 2.24           | 6.8            | 8.1            | 5.2              | 22              | 9.5            | 42.0           | 0.84           | NA              |
| 19 mo| 30                             | 25                             | 3.15           | 3.09           | 7.5            | 11.4           | 5.3              | 18              | 6.7            | 42.7           | 0.95           | 0.90            |
| 2 yr | 33                             | 28                             | 3.10           | 3.13           | 6.4            | 10.7           | 5.5              | 21              | 6.7            | 43.9           | 0.92           | 0.66            |

NA: Not available; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; INR: International normalized ratio.
| Ref. | Sex/Origin | GW/BW g (BW SDS) | First clinical symptoms (age) | Laboratory results | Kidney ultrasound | Kidney function | Liver biopsy | Pancreas morphology | Pancreatic exocrine function | Onset of clinical diabetes (age) | Diabetes treatment | Intellectual development | Genotype (inherited from) |
|------|------------|------------------|-------------------------------|--------------------|-------------------|----------------|-------------|-----------------|--------------------------|-----------------------------|-------------------|------------------------|---------------------------|
| **Severe neonatal cholestatic icterus** | | | | | | | | | | | | | |
| Present report | F/Czech | 38/2660 (-2.02) | Neonatal cholestasis (first week of life) | Anemia; progressively increasing, mainly cholestatic; liver tests | Multiple bilateral cortical cysts (maximal diameter 5 mm), prenatally hypechoenic kidneys | Normal by 2 yr | Paucity of intrahepatic bile ducts, severe biliary stasis, marked periportal fibrosis | Absent body and tail | Normal | Normoglycaemia by 2 yr | Not applicable | Normal | 1698 kb deletion including HNF1B (de novo) |
| [17] | M/Sardinian | 37/1520 (-3.70) | Neonatal cholestasis (first weeks of life) | High but resolving hyperbilirubinemia; fluctuating liver enzymes; high triglyceridemia | Left kidney agenesis; enlarged and hypechoenic right kidney; multiple cortical cysts (right, four cysts of 10-20 mm diameter; left, one cyst of 10 mm diameter) | Progressive chronic renal insufficiency by 18 yr | Paucity of intrahepatic bile ducts, severe biliary stasis, slight periportal fibrosis | Progressive atrophy from birth up to 16 yr | Progressive decline; need for enzyme replacement by 16 yr | Transient neonatal hyperglycaemia; permanent diabetes since 5 yr | Insulin 1.26 U/kg per day by 18 yr | NA | c. 499_504delGCTC TGinsCCCCT (de novo) |
| [16] | M/ Japanese | 39/2390 (-2.54) | Neonatal respiratory distress; neonatal cholestasis (first weeks of life) | Hyperbilirubinemia (resolving by 9 mo); transiently high cholesterol; constantly high AST, ALT | Multiple bilateral cysts (right, four cysts of 10-20 mm diameter; left, one cyst of 10 mm diameter) | Mild chronic renal insufficiency by 13 yr | NA | NA | NA | Insulin 0.4 U/kg per day after therapy onset | Slightly delayed | c. 457C>A (de novo or paternal) |
| **Late-onset cholestaticis** | | | | | | | | | | | | | |
| [18] case No. 1 | M/German | 35/1780 (-2.08) | Neonatal cholestasis (first weeks of life) | Elevated AST/ALT/GGT | Cystic dysplasia; hydronephrosis due to urethral stenosis | Chronic renal insufficiency by 18 yr | Intrahepatic cholestasis due to paucity of bile ducts | Hypoplastic | Fecal elastase deficiency | 13 yr | Insulin 1.34 U/kg per day by 18 yr | Retarded | 1590 kb deletion including HNF1B (de novo or paternal) |
| [20] case No. 1 | F/?? | NA | Jaundice (29 yr) | Progressively increasing, mainly cholestatic, liver tests; hypomagnesaeemia | Renal cysts | Mild chronic renal insufficiency by 33 yr | Non-specific changes; slight steatosis | Atrophic | NA | 14 yr | NA | Normal | 1423 kb deletion including HNF1B (NA) |
| [20] case No. 2 | M/?? | NA | "Chronic pancreatitis" (44 yr) | Progressively increasing, mainly cholestatic, liver tests; hypomagnesaeemia | Renal cysts | Mild chronic renal insufficiency by 53 yr | Minor sinusoidal dilatation | Atrophic | NA | 51 yr | NA | Retarded | 1427 kb deletion including HNF1B (NA) |
Four patients who manifested with progressive neonatal cholestasis within first weeks of life have shown the most severe phenotypes. All of them were born small for their gestational age, with birth weights below -2 SD after adjustment for gestational age. Because only one of them manifested transient neonatal hyperglycemia, the intrauterine growth restriction was very unlikely to be due to insulin deficiency. The reason for this growth restriction is still unknown [15-17].

All four patients had similar findings at liver biopsy, including marked cholestasis, a paucity of intrahepatic bile ducts and a variable degree of perportal fibrosis. Our patient fulfilled the strict clinical criteria for surgical intervention due to severe biliary atresia with cholestasis and underwent portoenterostomy at 32 d of age, but three additional patients with apparently milder cholestasis only underwent conservative therapy. In at least two of them, hyperbilirubinemia partially resolved by the first birthday. All of them have multiple renal cysts (with additional unilateral kidney agenesis and a hyperechogenic contralateral kidney with multiple cortical
cysts in one case), and those who already reached in their second decade of life began proceeding to chronic renal insufficiency. Typically, they have pancreatic hypoplasia (with documented progressive pancreatic atrophy in one case) and impaired pancreatic exocrine function. Overt diabetes typically manifests within the first two decades of life and requires insulin therapy. Their intellectual development is variable.

The intermediate hepatic phenotype - late-onset cholestasis - was reported in three patients\(^\text{[20]}\). Their cholestasis first manifested at 29–44 years of age with accordingly milder biotic findings, presumably minor sinusoidal dilatation. All of them had concomitant renal involvement with renal cysts. However, their chronic renal insufficiency tended to occur later than in the former subgroup and was recognized when they were middle-aged adults. Their pancreas is atrophic, but data on their exocrine function are not available. Diabetes manifested between 14 and 51 years of life. Similar to the previous group, the intellectual development is variable.

The mildest hepatic phenotype relative to the other phenotypes includes five patients with non-cholestatic liver impairment\(^\text{[18,19]}\). They had a tendency toward intrauterine growth restriction and a variable first clinical presentation, ranging from failure to thrive or renal failure in infancy up to diabetic symptoms in the second decade of life. Renal cysts were present in most of these patients, but chronic renal insufficiency developed only in three of the five by the second decade of life. Their liver enzymes were clearly elevated; however, histological findings from the liver biopsies were milder than those from the previous subgroups. Diabetes manifested in all subjects within their first or second decade of life and required insulin administration in all cases. This less severe hepatic phenotype was also more frequently linked with normal pancreas morphology, normal exocrine function and, with one exception, normal intellectual development.

A similar phenotype was described in a family with four affected subjects\(^\text{[11]}\).

Regarding genetic findings, there was no apparent phenotypic difference between subjects with single base mutations or whole gene deletions.

Our analysis of the available clinical observations of the hepatic phenotype in HNF1B mutation/deletion carriers raises the following clinical implications for neonates, children and adults with cholestasis: (1) neonates with severe cholestasis should undergo renal ultrasound focusing on renal cortical cysts and additional renal developmental abnormalities. A concurrence of neonatal cholestasis with renal cysts is suspicious for an HNF1B defect; (2) in patients with neonatal cholestasis, a history of an intrauterine growth restriction is supportive of an HNF1B defect because the majority of other children with neonatal cholestasis have normal birth weight and birth length (unpublished observations of 96 neonates with biliary atresia). Interestingly, in HNF1B mutation/deletion carriers without a hepatic and/or biliary phenotype, IUGR is rare\(^\text{[24,25]}\), suggesting that the co-occurrence of abnormal HNF1B and biliary atresia predisposes individuals to diminished intrauterine growth and weight gain; (3) as demonstrated by other cases in which neonatal cholestasis due to an HNF1B defect spontaneously resolved within the first year of life, further clinical evidence is needed to develop recommendations on the optimal management for affected children; (4) patients of any age with known diabetes who develop pancreatic exocrine insufficiency and/or cholestasis should be investigated for renal cysts; and (5) if positive, they are highly likely to have an HNF1B defect. In these patients, the etiological genetic diagnosis may clarify the origin of the hepatic and/or exocrine pancreatic disease, which is not a complication of diabetes but rather an additional component of the primary disease. Hypomagnesaemia may be a strong supportive finding in favor of an HNF1B testing as it was demonstrated to occur in about half of subjects with HNF1B defects\(^\text{[26]}\). We propose to incorporate these clinical observations into an update of the general selection criteria for HNF1B gene analysis\(^\text{[27]}\).

In conclusion, the hepatic phenotype in HNF1B mutation/deletion carriers clusters into three different levels of severity, ranging from severe neonatal cholestasis through late-onset cholestasis in middle-aged adults up to a mild hepatic phenotype on the background of other, more pronounced symptoms and signs, such as diabetes and renal disease. However, a correct etiological diagnosis is undoubtedly beneficial for all three subgroups of patients, allowing not only a clear understanding of the underlying cause but also a prediction of the risks of additional disease components, including diabetes and exocrine pancreatic dysfunction, which are highly likely to develop within the subsequent years or decades of life.

**COMMENTS**

**Case characteristics**

A female neonate who was born small for her gestational age had apparently acholic stools since the first day of life, and gradually developed jaundice.

**Clinical diagnosis**

The clinical diagnosis was suggestive of neonatal cholestasis due to biliary atresia.

**Differential diagnosis**

Most children with neonatal cholestasis have isolated biliary atresia; however, some of them may have a syndromic condition.

**Laboratory diagnosis**

Laboratory findings at day 4 confirmed cholestatic jaundice with elevated levels of total (104 μmol/L) and conjugated bilirubin (32 μmol/L) and markedly increased level of gamma-glutamyltransferase (23.3 μkat/L).

**Imaging diagnosis**

Abdominal ultrasound revealed bilateral renal cysts, liver with normal echogenicity and echotexture, a small gallbladder and hypoplastic pancreas; endoscopic retrograde cholangiopancreatography showed normal pancreatic ducts, but extrahepatic bile ducts were unrecognized.

**Pathological diagnosis**

Molecular genetic testing using Multiple Ligation Probe-dependent Amplification
(MLPA) lead to recognition of a de novo HNF1B gene deletion spanning 198 kb, which was previously reported as causative in a patient with MODY diabetes.

**Treatment**

Explorative surgery provided at age 32 d revealed an atriove pulmonale mass and completely atrophic choledochus and proximal extrahepatic bile ducts; the surgeon performed portocaval shunt, Kasai.

**Related reports**

Most of the published cases with HNF1B variants were assessed for the presence of diabetes and/or renal impairment, mostly renal cysts; only five reports have focused on the hepatic phenotype which was always milder than that observed in the patient.

**Term explanation**

MLPA is a method of genetic testing directed towards recognition of whole gene deletions.

**Experiences and lessons**

This observation represents the most severe hepatic phenotype of an HNF1B variant recognized thus far.

**Peer-review**

The manuscript is really attractive and worthy, and the content is prospective, which is relevant and well presented for publication. The manuscript is really attractive and worthy, and the content is prospective, which is relevant and well presented for publication.

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