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Decoding Pediatric Hepatic Dysfunction: A Case Report of Rare Triad of Genetic Disorders

Advanced Biochemical Analysis Reveals Tangier Disease, G6PD Deficiency, and Sickle Cell Trait

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Abstract: We present a rare pediatric case of decompensated chronic liver disease in a 2-year-old boy caused by Tangier disease, a rare autosomal recessive lipid storage disorder. The child also had co-existing G6PD deficiency and sickle cell trait, further compounding his hepatic pathology. Clinical features included progressive abdominal distension, jaundice, and epistaxis. Biochemical analysis revealed hyperbilirubinemia, hypoalbuminemia, coagulopathy, and strikingly low HDL levels. Liver biopsy showed cirrhotic changes with PAS-D positive deposits. Whole exome sequencing confirmed a homozygous ABCA1 mutation. This case underscores the importance of integrating histopathology, metabolic work-up, and molecular genetics in unexplained pediatric liver disease.

INTRODUCTION

Chronic liver disease in children is a diagnostic challenge, given the wide differential encompassing infectious, metabolic, autoimmune, and genetic causes. Tangier disease—caused by mutations in the ABCA1 gene—is a rare lipid metabolism disorder characterized by near absence of HDL cholesterol and tissue cholesterol accumulation. Though typically associated with neuropathy and lymphoid hypertrophy, hepatic involvement is rarely documented. This case illustrates a novel presentation of Tangier disease in a child with decompensated liver disease, further complicated by G6PD deficiency and sickle cell trait. It demonstrates how multisystemic genetic disorders can interact to produce complex hepatic manifestations.

CASE REPORT

A 2-year-old male child presented with a 6-month history of abdominal distension, 2-month history of yellow discoloration of eyes, and repeated episodes of epistaxis while crying. Despite these symptoms, the child remained active and playful. The patient had no history of seizures, congenital heart disease, tuberculosis, delayed milestones, hematemesis, melena, or similar family complaints. He was born full-term via cesarean section with a birth weight of 3.5 kg. Clinical examination revealed a distended abdomen with midline umbilicus and prominent engorged veins (caput medusae), indicating portal hypertension. Hepatomegaly was present, but initial splenomegaly was not observed, though it was later noted on imaging.

BIOCHEMICAL ASSESSMENT

A. Hematology

Parameter	Patient's Value	Reference Range (2 years)	Interpretation
Hb	9.0 g/dL	10.5–13.5 g/dL	Low
WBC	7,310/µL	6,000–17,000/µL	Normal
Platelets	85,000/µL	150,000–400,000/µL	Low
ESR	20 mm/hr	0–20 mm/hr	Normal

B. Liver Function Tests

Test	Patient's Value	Reference Range	Interpretation
Total bilirubin	11.0 mg/dL	0.1–1.0 mg/dL	High
Direct bilirubin	4.25 mg/dL	0–0.2 mg/dL	High
SGPT (ALT)	151.6 U/L	7–40 U/L	High
SGOT (AST)	482.3 U/L	15–50 U/L	High
ALP	158.6 U/L	100–350 U/L	Mildly low/normal
GGT	88 U/L	5–32 U/L	High
Total protein	5.3 g/dL	6.0–8.0 g/dL	Mildly reduced
Albumin	2.5 g/dL	3.5–5.0 g/dL	Low
Globulin	2.5 g/dL	2.0–3.5 g/dL	High

C. Renal Function & Iron Studies

- Urea: 11.8 mg/dL (normal)
- Creatinine: 0.22 mg/dL (low-normal)
- Iron: 154 µg/dL (high)
- TIBC: 293 µg/dL (normal)
- Transferrin: 199 mg/dL (low)
- Ferritin**:** 323 ng/mL (high)

D. Coagulation Profile

Test	Value	Reference Range	Interpretation
PT	14 s	11–15 s	Normal
INR	1.03	0.8–1.2	Normal
APTT	31 s	24–36 s	Normal
Fibrinogen	252 mg/dL	150–400 mg/dL	Normal

At decompensation:

- PT: 22.6 s, INR: 1.69 (prolonged)
- aPTT: 48.2 s (prolonged)

E. Immunology

- C3: 0.81 g/L (low)
- C4: 0.07 g/L (low)
- ASO titre: Negative
- EBV IgG/IgM: IgG negative, IgM positive
- CMV DNA PCR: Not detected
- ANA: 2.45 U/mL (mildly positive)
- IgG: 18.99 g/L (high)

F. Lipid Profile

Test	Value (mg/dL)	Reference Range	Interpretation
Total Cholesterol	90	<170	Low
LDL	67	<110	Low-normal
HDL	13.7	>45	Markedly low
VLDL	15	<30	Normal

G. Other Relevant Biochemistry

- Folic acid: 6.12 ng/mL (normal)
- Vitamin B12: 494 pg/mL (normal-high)
- G6PD: 4.9 U/g Hb (low)
- Protein C/S: Normal
- Anti-thrombin III: 23% (low)
- Homocysteine: 26.6 µmol/L (high)
- Bile acid total: 26.1 µmol/L (high)
- Alpha 1 antitrypsin: 3.12 g/L (high)
- Ammonia: 338.9 µmol/L (very high)
- MMA: 615.8 nmol/L (high)
- Lactate: 42.7 mg/dL (high)

H. Urine & Ascitic Fluid Analysis

- UPCR: 1.24
- Urine copper (24h): 12.6 µg (normal)

- Ascitic fluid**:** Sugar 120 mg/dL, protein 36 g/L, HDL 13.7 mg/dL (very low), triglycerides 100.8 mg/dL (transudative ascites)

I. Acid-Base Balance (ABG)

pH	HCO_3^-	pCO_2	Lactate	Interpretation
7.346	14.7	21.7	1.5	Metabolic acidosis, compensated

IMAGING FINDINGS

- **Upper GI endoscopy:** small esophageal varices, gastroduodenopathy (gastritis and duodenitis), and "snake-like" stomach lining
- **Ultrasound Abdomen:** Hepatomegaly, gallbladder wall edema, mild ascites
- **CECT Abdomen:** Chronic liver disease, splenomegaly, liver lesion (hemangioma), portal vein thrombosis
- **Triphasic CT:** Gross ascites, altered liver parenchyma, collateral circulation—features of portal hypertension

LIVER BIOPSY FINDINGS

- **Histopathology:** Cirrhotic changes with mild PAS-D positive deposits
  - **PAS-D positive:** Indicates presence of non-glycogen, diastase-resistant storage material (suggests lipid/storage disorder)
- **Implication:** Triggered genetic testing (WES)

GENETIC & METABOLIC INVESTIGATIONS

Gene	Mutation	Interpretation
G6PD	Hemizygous	Enzyme deficiency → hemolysis, ↑ indirect bilirubin
HBB	Heterozygous (HbS 32.9%)	Sickle cell trait
ABCA1	Homozygous	Tangier disease → impaired HDL formation

INTEGRATED BIOCHEMICAL DIAGNOSIS

Condition	Pathophysiology	Biochemical/Molecular Basis
G6PD Deficiency	Hemolysis	↑ Indirect bilirubin, normal copper/ceruloplasmin, low Hb
Tangier Disease	HDL deficiency → hepatic lipid accumulation	Very low HDL in plasma & ascitic fluid
Sickle Cell Trait	Microvascular hepatic insult	HbS = 32.9% (Hb electrophoresis)

FINAL DIAGNOSIS

Decompensated Chronic Liver Disease with Portal Hypertension due to:

- G6PD deficiency
- Tangier disease (ABCA1 mutation)
- Sickle cell trait

DISCUSSION

Tangier disease is a rare autosomal recessive disorder caused by mutations in the ABCA1 gene, resulting in defective formation of high-density lipoprotein (HDL) and impaired cholesterol transport. This leads to extremely low HDL levels and accumulation of cholesterol esters in various tissues, including the liver, tonsils, and peripheral nerves.

In this case, the child presented with classic features of chronic liver disease and portal hypertension, including hepatomegaly, ascites, and esophageal varices, along with biochemical evidence of liver dysfunction (elevated transaminases, hyperbilirubinemia, hypoalbuminemia, coagulopathy) and metabolic derangements (markedly low HDL, high ammonia, high lactate). The diagnosis was further complicated by the presence of G6PD deficiency and sickle cell trait, both of which can contribute to hepatic injury via hemolysis and microvascular insults, respectively.

The liver biopsy revealed cirrhosis with PAS-D positive deposits, raising suspicion for a storage disorder, which was confirmed by genetic testing identifying a homozygous ABCA1 mutation. This finding, together with the biochemical and clinical profile, established the diagnosis of Tangier disease as a key contributor to the patient's liver pathology.

KEY LEARNING POINTS

- Tangier disease should be considered in pediatric chronic liver disease with markedly low HDL.
- PAS-D positive biopsy findings point toward lipid/storage disorders and warrant further molecular testing.
- A rare combination of G6PD deficiency, sickle cell trait, and ABCA1 mutation can act synergistically to cause severe liver dysfunction.
- Comprehensive biochemical profiling (LFT, lipid, ABG, urine/ascitic analysis) is essential for organ-specific and metabolic insight.
- Molecular diagnostics are indispensable in pediatric liver diseases with atypical or unexplained presentations.

This case highlights the importance of integrating clinical, biochemical, histopathological, and molecular findings for the diagnosis of rare metabolic liver diseases in children and underscores the need for a high index of suspicion for storage disorders in pediatric chronic liver disease with unusual biochemical profiles.