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Hepatomegaly and Hepatic Steatosis as Presenting Features of GPD1-Related Transient Infantile Hypertriglyceridemia in a Consanguineous Family: A Case Report

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Abstract

GPD1-related transient infantile hypertriglyceridemia (HTGTI) is a rare autosomal recessive disorder characterized by early-onset hypertriglyceridemia, hepatomegaly, hepatic steatosis, and elevated aminotransferase levels, with hepatic fibrosis and persistent liver abnormalities reported in some cases. We describe a young child with abdominal distension, marked hepatomegaly, hepatic steatosis on ultrasonography, and an initially reported alanine aminotransferase concentration of 83 U/L. Initial metabolic screening was reported as unrevealing. Solo whole-exome sequencing identified a homozygous GPD1 variant, NM_005276.3:c.953+1G>A, classified as likely pathogenic by the testing laboratory and interpreted as consistent with GPD1-related HTGTI. The available lipid panel showed triglycerides of 133 mg/dL, which does not demonstrate hypertriglyceridemia using the laboratory's stated desirable threshold of less than 150 mg/dL; fasting status and historical lipid results remain to be confirmed. Parent-reported fasting-associated symptoms have not been confirmed by documented glucose measurements. This case highlights the role of molecular testing in unexplained childhood hepatomegaly and steatosis while emphasizing the need to distinguish a molecular diagnosis from biochemical features that are not documented in the available record. Longitudinal assessment of the lipid profile and liver disease, parental variant testing, and genetic counseling are warranted.

Categories: Genetics, Pediatrics, Endocrinology/Diabetes/Metabolism
Keywords: case report, child, gpd1, hepatic steatosis, hepatomegaly, transient infantile hypertriglyceridemia, whole-exome sequencing

Introduction

Unexplained hepatomegaly and hepatic steatosis in infancy and early childhood require evaluation for infectious, inflammatory, endocrine, nutritional, toxic, and inherited metabolic causes. In young children, an inherited disorder may be present despite normal development and nondiagnostic screening tests. GPD1 encodes cytosolic glycerol-3-phosphate dehydrogenase 1, an enzyme involved in glycerol-phosphate metabolism. Biallelic pathogenic variants in GPD1 cause transient infantile hypertriglyceridemia (HTGTI), an autosomal recessive condition first delineated in families with childhood hypertriglyceridemia and fatty liver, sometimes followed by hepatic fibrosis [1]. Subsequent reports have expanded the phenotypic and molecular spectrum, including occasional fasting hypoglycemia and insulin resistance [2-4].

We report a young boy with marked hepatomegaly and hepatic steatosis, a largely unrevealing initial metabolic workup, and a homozygous likely pathogenic GPD1 splice-site variant identified by solo whole-exome sequencing. The case emphasizes diagnostic reasoning and the need for follow-up even when the child appears developmentally well.

Case Presentation

The patient is a three-year-old boy, the third child of consanguineous parents who are first-degree relatives. No parental genetic testing has been performed. No other family history of genetic or metabolic disease was reported. There were no reported perinatal complications. A previous pregnancy resulted in a premature infant who died at five days of age from respiratory distress syndrome. The parents also have another healthy daughter aged five years.

The child was breastfed until one year of age. At approximately one year of age, the family noticed abdominal distension (Figure *1*). During an admission, aminotransferases were elevated, with an initially reported alanine aminotransferase (ALT) concentration of 83 U/L, approximately three times the upper limit of normal. Abdominal ultrasonography showed diffuse hepatomegaly with fatty infiltration. No splenomegaly was reported. Echocardiography was normal.



FIGURE 1: Abdominal distension as a result of hepatomegaly.

The initial metabolic evaluation was reported as unrevealing: ammonia, lactate, pyruvate, plasma amino acid chromatography, urine organic acid chromatography, and the acylcarnitine profile were normal. A newborn metabolic screen was also reported to have been normal. No anemia or thrombocytopenia was reported. Fundoscopy performed to assess for features of a storage disorder was normal. Enzyme activities for Gaucher disease and Niemann-Pick disease types A and B were also reported as normal.

At the most recent clinical assessment, the child had age-appropriate psychomotor development and behavior, with increased appetite and a preference for sweet foods. The parents' description raises the possibility of fasting intolerance but does not establish biochemical hypoglycemia. Examination revealed abdominal distension and marked hepatomegaly; the liver span was reported as approximately 15 cm, which was above the 95th percentile for normal liver size for age. Repeat ultrasonography confirmed hepatomegaly and hepatic steatosis, with normal kidneys (Figure *2*).

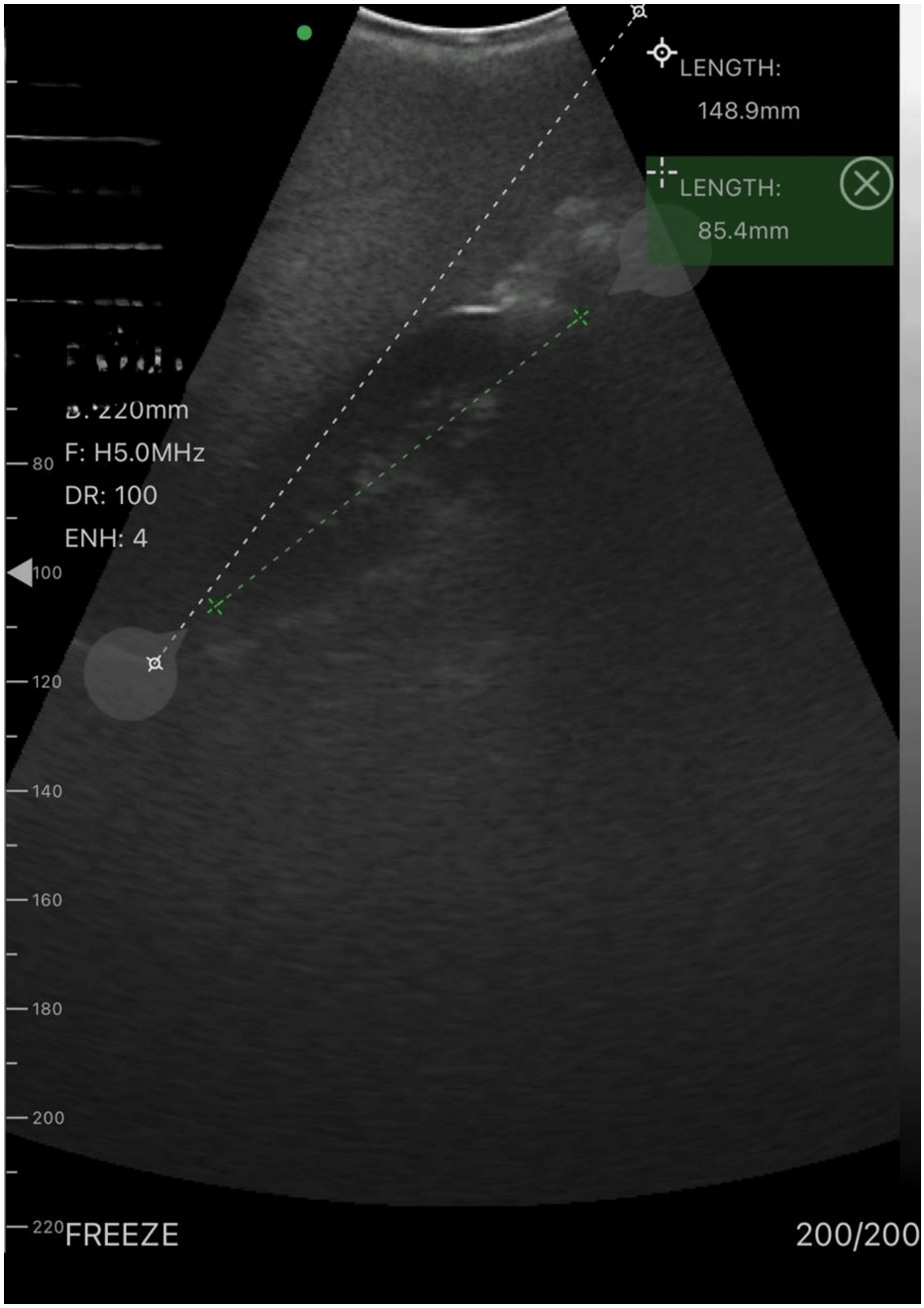


FIGURE 2: Ultrasound of the abdomen showing hepatomegaly with diffuse hepatic steatosis.

Table *1* summarizes the available numerical results and indicative reference intervals. Intervals vary by laboratory and age, and the reporting laboratory's ranges should take precedence.

Analyte	Result	Indicative reference/desirable value	Interpretation/note
ALT, initial	83 U/L	Approximately 5-45 U/L in young children; laboratory-specific	Elevated; reported as approximately 3× the local upper limit of normal
Glucose	60 mg/dL	Fasting: approximately 70-100 mg/dL	Low relative to the typical fasting range; timing and fasting status are unknown
Uric acid	7.6 mg/dL	Approximately 2.0-5.5 mg/dL in young children; age- and laboratory-dependent	Above the stated laboratory interval of 2.6-7.0 mg/dL
Total cholesterol	199 mg/dL	Desirable: <170 mg/dL for children	Above the usual pediatric desirable threshold; fasting status should be confirmed
Triglycerides	133 mg/dL	Fasting: <75 mg/dL (<10 years); nonfasting: <85 mg/dL (pediatric guidance); laboratory-listed desirable value: <150 mg/dL	Not elevated according to the local laboratory's stated threshold; fasting status and earlier values are needed
HDL cholesterol	69.5 mg/dL	>45 mg/dL desirable in children	Within the desirable range
Lactate	0.91 mmol/L	Approximately 0.5-2.2 mmol/L	Within the typical reference interval
Pyruvate	20 µmol/L	Reference interval not supplied; assay-dependent	Confirm the reporting laboratory's reference interval and specimen handling
Amylase	34 IU/L	Approximately 30-100 U/L; method- and age-dependent	Within a commonly used interval
CPK/CK	45 IU/L	Approximately 30-200 U/L; age-, sex-, and method-dependent	Within a commonly used interval
Lipase	11 U/L	Approximately 13-60 U/L in many laboratories; method- and age-dependent	May be slightly below some laboratory intervals; clinical significance depends on the local reference range
ALP	Mildly elevated; value unavailable	Pediatric reference interval is age- and growth-dependent	Numerical result and laboratory range were unavailable
LDH	Mildly elevated; value unavailable	Approximately 120-300 U/L in many laboratories; method-dependent	Numerical result and laboratory range were unavailable

TABLE 1: Available laboratory results and indicative reference intervals.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CK, creatine kinase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDH, lactate dehydrogenase; ULN, upper limit of normal

Solo whole-exome sequencing performed at a clinical laboratory identified a homozygous GPD1 variant, NM_005276.3:c.953+1G>A, affecting the canonical donor splice site. The laboratory classified the variant as likely pathogenic and concluded that the result was consistent with autosomal recessive GPD1-related HTGTI. No further clinically relevant variants related to the reported phenotype were detected. Genetic counseling and parental testing were recommended given the parents' first-degree consanguinity.

Discussion

Hepatomegaly accompanied by hepatic steatosis and elevated aminotransferases in infancy or early childhood warrants a systematic evaluation for infectious, inflammatory, endocrine, nutritional, toxic, and inherited metabolic disorders. The differential diagnosis includes viral infections, autoimmune liver disease, medication-related hepatic injury, endocrine abnormalities, and inborn errors of metabolism. Important metabolic causes include glycogen storage diseases, lysosomal acid lipase deficiency, tyrosinemia type I, galactosemia, hereditary fructose intolerance, mitochondrial disorders, fatty acid oxidation defects, and selected lysosomal storage diseases.

In the present case, abdominal distension became apparent at approximately one year of age, with

ultrasonographic evidence of diffuse hepatomegaly and hepatic steatosis and an initial ALT concentration of 83 U/L. The reported liver span of 15 cm and abdominal girth of 60 cm further document the extent of the abdominal findings. Despite this phenotype, the initial metabolic evaluation, including ammonia, lactate, pyruvate, plasma amino acid chromatography, urine organic acid chromatography, and acylcarnitine profiling, was unrevealing. Echocardiography and fundoscopy were also reported as normal, and no splenomegaly was identified. These findings helped direct the investigation toward a genetic cause of steatotic liver disease.

GPD1 encodes cytosolic glycerol-3-phosphate dehydrogenase 1, an enzyme involved in glycerol-phosphate metabolism. Biallelic pathogenic variants in GPD1 cause HTGTI, an autosomal recessive disorder associated with early-onset hypertriglyceridemia, hepatic steatosis, hepatomegaly, and variable elevations in liver aminotransferases. The disorder was initially characterized in families in which fatty liver and hypertriglyceridemia were accompanied by hepatic fibrosis, establishing that the hepatic phenotype may be clinically important even when the lipid abnormality is described as transient [1]. Subsequent reports have expanded the recognized clinical and molecular spectrum [2-5].

In this child, solo whole-exome sequencing identified a homozygous GPD1 variant, NM_005276.3:c.953+1G>A, affecting the canonical splice-donor site. The clinical laboratory classified the variant as likely pathogenic and interpreted the finding as consistent with GPD1-related HTGTI. In the context of early-onset hepatomegaly, diffuse hepatic steatosis, and elevated aminotransferases, this molecular result provides substantial support for the diagnosis.

An important feature of this case is the difference between the molecular findings and the currently available lipid measurement. The recorded triglyceride concentration was 133 mg/dL, within the laboratory's stated desirable range. Thus, this single measurement does not establish current biochemical hypertriglyceridemia. The clinical diagnosis should be presented as genetically supported GPD1-related HTGTI with a currently non-elevated recorded triglyceride concentration. This distinction does not negate the significance of the molecular result, but it is important for accurate phenotypic characterization. This case may contribute to the clinical literature by illustrating the identification of a GPD1-associated disorder in a child whose available triglyceride measurement does not demonstrate the classic biochemical phenotype.

The parents report episodes during fasting that they describe as hypoglycemia, together with a tendency to eat approximately every four hours and a preference for sugary foods. These observations raise the possibility of fasting intolerance. A glucose value of 60 mg/dL was recorded in the available biochemical assessment. Fasting-associated hypoglycemia and insulin resistance have been described in some patients with GPD1-related HTGTI, demonstrating that the phenotype may extend beyond elevated triglyceride concentrations and hepatic steatosis [2].

The term transient in HTGTI primarily reflects the potential for triglyceride concentrations to improve with age; it should not be interpreted as evidence that hepatic steatosis or liver injury will invariably resolve. The original description of GPD1-related HTGTI included fatty liver and hepatic fibrosis [1]. Subsequent reports have documented a broader clinical spectrum, including fasting-associated hypoglycemia and insulin resistance [2], as well as persistent hepatic abnormalities and hepatic adenoma in a patient followed into childhood [5]. Additional case reports have contributed to the understanding of the disorder's variable presentation [3,4,6]. These observations do not imply that all affected children will develop progressive liver disease. They do, however, support continued surveillance, particularly in a child with marked hepatomegaly, diffuse steatosis, and a history of elevated aminotransferases.

The child's normal reported psychomotor development and otherwise reassuring clinical examination are favorable observations, but they do not establish the long-term hepatic prognosis. Longitudinal follow-up will be particularly valuable in determining whether hepatic steatosis and hepatomegaly improve, persist, or progress despite a triglyceride concentration currently within the laboratory's desirable range.

GPD1-related HTGTI follows an autosomal recessive inheritance pattern. If both parents are heterozygous carriers of the same pathogenic variant, each subsequent pregnancy has a 25% probability of an affected child, a 50% probability of an unaffected carrier child, and a 25% probability of a child who inherits neither copy of the familial variant. Targeted testing of both parents is therefore recommended to confirm inheritance and support accurate recurrence-risk counseling. Genetic counseling should also address the implications for other family members and the potential role of cascade testing. The absence of a reported family history does not argue strongly against the diagnosis in an autosomal recessive condition because unaffected carrier parents may have no clinical manifestations.

This case illustrates the diagnostic value of molecular testing in a child with early-onset hepatomegaly and hepatic steatosis whose initial biochemical and metabolic investigations were largely unrevealing. The homozygous likely pathogenic GPD1 splice-site variant, interpreted by the clinical laboratory as consistent with HTGTI, provides a molecular explanation for the hepatic phenotype. The case also highlights the importance of accurately reporting the available biochemical evidence: the documented triglyceride

concentration of 133 mg/dL does not demonstrate current hypertriglyceridemia, and the reported fasting-associated symptoms have not been confirmed by glucose measurements obtained during episodes. The combination of a molecularly supported diagnosis, substantial hepatomegaly, and a currently non-elevated recorded triglyceride concentration makes careful phenotypic documentation and longitudinal follow-up particularly important.

Conclusions

GPD1-related HTGTI should be considered in the differential diagnosis of unexplained hepatomegaly and hepatic steatosis in infancy and early childhood, particularly when routine metabolic screening is nondiagnostic. In this child, the homozygous likely pathogenic GPD1 variant provides substantial molecular support for the diagnosis. However, the available triglyceride measurement does not demonstrate current hypertriglyceridemia, and the reported fasting-associated symptoms remain unconfirmed. Parental genetic testing, repeat lipid assessment, and longitudinal monitoring of hepatic status are warranted. The potentially variable natural history of GPD1-related disease supports ongoing surveillance rather than assuming that the condition is uniformly benign.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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References

1. Basel-Vanagaite L, Zevit N, Har Zahav A, et al.: Transient infantile hypertriglyceridemia, fatty liver, and hepatic fibrosis caused by mutated GPD1, encoding glycerol-3-phosphate dehydrogenase 1. Am J Hum Genet. 2012, 90:49-60. 10.1016/j.ajhg.2011.11.028
2. Tan Y, Ouyang W, Ma Y, et al.: Rare transient infantile hypertriglyceridemia with hypoglycemia and insulin resistance caused by a novel GPD1 mutation. Mol Syndromol. 2022, 13:433-9. 10.1159/000523764
3. Wang J, Sun X, Jiao L, et al.: Clinical characteristics and variant analyses of transient infantile hypertriglyceridemia related to GPD1 gene. Front Genet. 2022, 13:916672. 10.3389/fgene.2022.916672
4. Li JQ, Xie XB, Feng JY, et al.: A novel homozygous mutation in the glycerol-3-phosphate dehydrogenase 1 gene in a Chinese patient with transient infantile hypertriglyceridemia: a case report. BMC Gastroenterol. 2018, 18:96. 10.1186/s12876-018-0827-6
5. Kumar K, Malhotra S, Sibal A: Transient infantile hypertriglyceridaemia due to homozygous mutation in GPD1 presenting in childhood with hepatic adenoma. BMJ Case Rep. 2022, 15: 10.1136/bcr-2022-248801
6. Lin H, Fang Y, Han L, Chen J, Lou J, Yu J: Case report: Identification of a novel homozygous mutation in GPD1 gene of a Chinese child with transient infantile hypertriglyceridemia. Front Genet. 2021, 12:726116. 10.3389/fgene.2021.726116