JIMD Reports
DOI 10.1007/8904_2018_116

RESEARCH REPORT

Apparent Acetaminophen Toxicity in a Patient with Transaldolase Deficiency

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Received: 25 March 2018 / Revised: 14 May 2018 / Accepted: 18 May 2018 / Published online: 20 June 2018

Abstract Transaldolase deficiency (MIM#: 606003) is a rare autosomal recessive defect in the pentose phosphate pathway. Affected individuals are at risk for progressive liver failure and hepatocarcinoma. In the transaldolase-deficient mouse model (*Taldo1*$^{-/-}$), these hepatic complications are accentuated by oxidative stress related to acetaminophen administration. We report a 13-month-old transaldolase-deficient male who developed mild liver failure after receiving standard doses of acetaminophen during a febrile respiratory syncytial virus infection. He was admitted for respiratory distress with neutropenia and thrombocytopenia, but developed an enlarged nodular liver with accompanying splenomegaly and rising alpha-fetoprotein which peaked 2 weeks after acetaminophen exposure. Whole exome sequencing revealed compound heterozygous variants c.512_514delCCT (p.Ser171del) and c.931G > T (p.Gly311Trp) in *TALDO1* (HGNC:11559), which encodes transaldolase (EC 2.2.1.2), a key enzyme in ribose metabolism. Urine polyols and plasma metabolomics confirmed the diagnosis of transaldolase deficiency. Studies on the *Taldo1*$^{-/-}$ mouse model demonstrate acetaminophen-induced liver failure can be prevented by administration of the antioxidant *N*-acetylcysteine. Moreover, a published report showed treatment of a transaldolase-deficient patient with *N*-acetylcysteine was associated with a decrease in alpha-fetoprotein levels. After discontinuation of acetaminophen and prior to initiation of *N*-acetylcysteine treatment, our patient demonstrated resolving alpha-fetoprotein levels suggesting acetaminophen incited the liver failure.

Conclusion: Our observations support the conclusion from mouse model studies that transaldolase-deficient patients are uniquely sensitive to acetaminophen and should avoid this antipyretic. Recognition of this individualized toxicity and avoidance of acetaminophen are essential for management of these patients.

Communicated by: Verena Peters

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Introduction

Transaldolase deficiency (MIM#: 606003) is a rare inborn error of pentose metabolism first described in a Turkish family in 2001 (Verhoeven et al. 2001). Typical features include intrauterine growth restriction, triangular faces, loose wrinkly skin at birth, and development of progressive liver failure (Eyaid et al. 2013). Transaldolase (EC 2.2.1.2) is encoded by *TALDO1* (HGNC:11559) and catalyzes the rate-limiting reversible conversion of sedoheptulose-7-P and glyceraldehyde-3-P to erythrose-4-P and fructose-6-P, an essential step in the pentose phosphate pathway. Deficiency impairs

recycling of ribose-5-P through the non-oxidative branch of the pentose phosphate pathway and leads to reduced synthesis of antioxidants NADPH, NADH, and glutathione (Hanczko et al. 2009). As a result, these patients are predicted to be sensitive to oxidant stress. Consistent with this prediction, the transaldolase-deficient mouse model, *Taldo1*$^{-/-}$, demonstrates increased oxidative stress and sensitivity to acetaminophen toxicity (Hanczko et al. 2009; Perl et al. 2011). Here, we report on a 13-month-old transaldolase-deficient boy who developed nodular hepatosplenomegaly after receiving standard doses of acetaminophen during a respiratory syncytial virus infection. Our observations support the suggestion that these patients are uniquely sensitive to standard doses of acetaminophen and stress the importance of early diagnosis and informed management of this disorder.

Materials and Methods

High-Throughput Sequencing

The family was submitted to the Baylor-Hopkins Center for Mendelian Genomics. Genomic DNA was purified from fresh whole blood using the Gentra Puregene Kit (Qiagen Sciences, Germantown, MD). SureSelect Human All Exon 50 Mb Kit (Agilent Technologies, Santa Clara, CA) was used for exon targeting and paired end 100 bp reads using the Illumina HiSeq2000 platform (Illumina, Inc., San Diego, CA). Read alignment to reference genome (NCBI human genome assembly build 36) (Hubbard et al. 2009) was performed using the Burrows-Wheeler Alignment tool (Li and Durbin 2009). We also performed local realignment and base call quality recalibration using GATK (McKenna et al. 2010). Using the PhenoDB Variant Analysis Tool (Sobreira et al. 2015), we analyzed the whole exome sequencing data by applying a filter designed to prioritize rare (Minor Allele Frequency $< 1\%$) functional variants (missense, nonsense, splice site variants, and indels) that were homozygous or compound heterozygous in the proband. Urine polyol and sugar analysis was performed by Baylor Genetics Laboratories by gas chromatography-mass spectrometry stable isotope dilution analysis. Plasma metabolomics were performed by Baylor Genetics Laboratories using a combination of liquid chromatography-mass spectrometry/mass spectrometry technologies.

Results

Our 13-month-old patient was the 2.3 kg (4th percentile) product of a 37.5-week gestation in a 39-year-old G4P1122 woman whose pregnancy was complicated only by onset of intrauterine growth restriction starting at approximately 30 weeks of gestation. Birth length was 47.6 cm (30th percentile), and head circumference was 31.5 cm (7th percentile). At birth, he had a bronzed, aged appearance with wrinkled skin, decreased subcutaneous fat, prominent subcutaneous veins, open sagittal suture, enlarged anterior fontanelle, and pointed nasal tip (Fig. 1a). Complete blood count revealed leukopenia (7.8×10^9/L), thrombocytopenia (100×10^9/L), and normal hemoglobin (151 g/L). He required a 4-day stay in the neonatal intensive care unit for hypothermia (35.4°C) and hypoglycemia (glucose nadir 1.89 mmol/L).

Over the first year of life, he continued to have a bronzed, aged appearance with minimal subcutaneous fat, prominent wrinkles in the skin of his hands, visible scalp veins, a large abdomen without reported hepatomegaly, and thin extremities (Fig. 1a). He was followed monthly by his pediatrician until the age of 7 months. His growth curve remained below the third percentile with length $Z = -3.5$ and weight $Z = -2.77$ (Fig. 1b). He had no prior hospitalizations and exhibited mild language delays with two words ("mama"/"dada") at 13 months.

At 13 months of age, he was admitted to the hospital with fever and stridor secondary to a respiratory syncytial virus positive illness of 4 days duration. He received three doses of acetaminophen at home over 3 days prior to admission and two doses in the hospital over the first day of admission (all 10–15 mg/kg/dose). By the second day of admission, he developed firm, nodular hepatosplenomegaly. Ultrasound and MR imaging of his liver on the third hospital day revealed a 9 cm liver (sagittal measurement) with numerous T1 hyperintense nodules throughout, the largest measuring 1.1 cm (Fig. 1c). Elastography stiffness measurement of 2.7 m/s correlated with moderate to advanced hepatic fibrosis. His spleen measured 8.8 cm in length with a volume of 115 cm, consistent with mild splenomegaly. The nodular hepatomegaly has remained stable (9–9.5 cm sagittal measurement on ultrasound) for 1 year since admission. His splenomegaly has since resolved.

Laboratory investigation during his hospitalization revealed elevated alpha-fetoprotein (AFP) (peak 319 μg/L), elevated alanine aminotransferase (ALT, 73 units/L), prolonged INR (1.3), leukopenia, and thrombocytopenia (white blood cell count 1.4×10^9/L, hemoglobin 105 g/L, platelets 53×10^9/L). Plasma amino acids were remarkable for a mildly elevated methionine (58 μmol/L, normal range 7–43) suggestive of hepatocellular dysfunction. Urine organic acids 12 days after acetaminophen dosing showed increased fumarate, glutarate and significantly increased excretion of 2-ketoglutarate suggestive of a disturbance of mitochondrial energy metabolism. The peak of 5-oxoproline (pyroglutamate) was within normal for age. He had normal results for total bilirubin, direct bilirubin, aspartate amino transferase (AST), and a mildly shortened prothrombin time (11.4 s) and activated partial thromboplastin time (29 s).

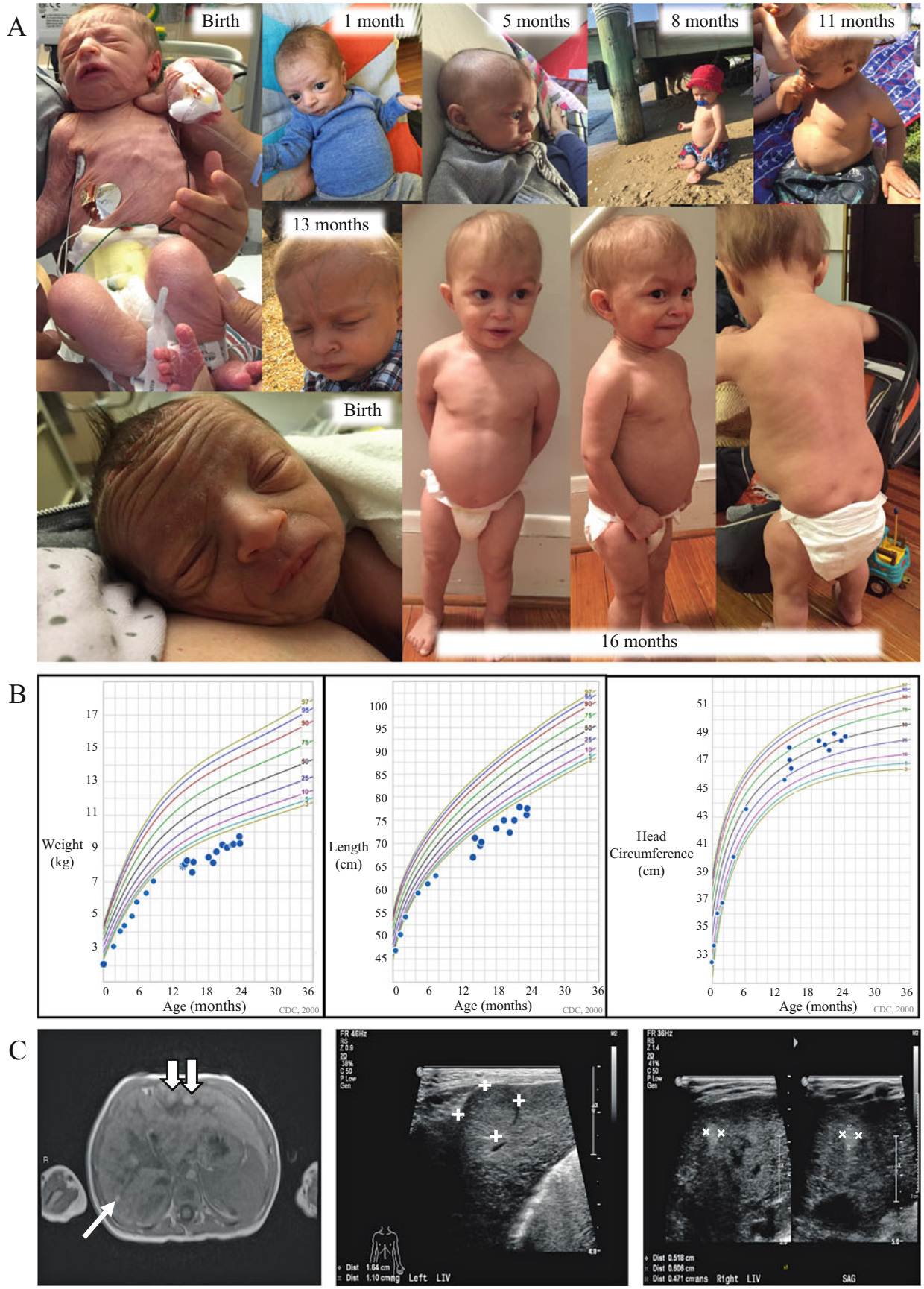

Fig. 1 Physical features. (**a**) Our patient was noted to have extensive skin wrinkling particularly at birth and decreased subcutaneous fat with easy visualization of vessels. (**b**) He continued to grow at less than the fifth percentile for both weight and height, with normal head

Whole exome sequencing performed through the Baylor-Hopkins Center for Mendelian Genomics at 15 months of age revealed compound heterozygous variants in the *TALDO1* gene: maternally inherited c.512_514delCCT (p.Ser171del) and paternally inherited c.931G > T (p.Gly311Trp). The p.Gly311Trp variant is not reported in gnomAD (Lek et al. 2016). Glycine-311 is part of a highly conserved hydrophobic cluster which contributes to β-strand packing (Thorell et al. 2000). An alternative variant in the same codon, p.Gly311Arg, was previously described in a nonconsanguineous Chinese child with transaldolase deficiency (Balasubramaniam et al. 2011). The second variant, deletion of Ser-171, causes inactivation and proteasome-mediated degradation of transaldolase (Grossman et al. 2004) and was the causative variant identified in a consanguineous Turkish patient with transaldolase deficiency (Verhoeven et al. 2001). Urine polyol and sugar profiling demonstrated elevated arabitol, erythritol, ribitol, and sedoheptulose with normal xylitol and galactitol consistent with a diagnosis of transaldolase deficiency. Plasma metabolomic testing revealed elevated ribitol, ribonate, erythronate, and arabitol (*Z*-scores all greater than 4.6), numerous elevations of other compounds involved in primary and secondary bile acid metabolism consistent with liver dysfunction, and decreased levels (*Z*-scores less than −2.3) of compounds involved in sphingolipid metabolism.

AFP levels peaked to 319 μg/L 12 days after the last acetaminophen dose and then decreased over the following weeks, most recent level 12 μg/L 429 days after admission (Fig. 2, left axis). AST and ALT peaked 4 days after the last acetaminophen dose (maximum AST 70 units/L, ALT 73 units/L) followed by a downward trend. The patient started *N*-acetylcysteine (NAC) at 15 mg/kg/day 73 days after admission (Fig. 2, right axis) titrating the dose to a treatment goal of 100 mg/kg/day (Rodan and Berry 2016). AFP levels have continued to decrease (Fig. 2).

Discussion

Transaldolase deficiency is a rare inborn error that can progress unrecognized until significant liver damage has been acquired. *Taldo1*$^{-/-}$ mouse studies demonstrate increased sensitivity to acetaminophen toxicity (Hanczko et al. 2009; Perl et al. 2011) – consistent with our clinical observation of nodular hepatosplenomegaly with elevated AFP after administration of standard doses of acetaminophen in a transaldolase-deficient patient. Our report is the first description of suggested increased sensitivity to acetaminophen in humans with transaldolase deficiency.

Prior to his presentation, our patient's symptoms were mild, and his liver was not noted to be enlarged. His parents deny acetaminophen administration until the time of the illness that lead to his hospitalization at 13 months old. The stable nodular hepatomegaly in our patient 1 year after his admission, despite now near-normal AFP levels, suggests the acetaminophen and possibly the viral infection acutely exacerbated underlying liver disease. There are case reports of children with transaldolase deficiency with the presence of liver cirrhosis presenting at ages younger than our proband although the exposure of these patients to acetaminophen is unknown (Eyaid et al. 2013; Balasubramaniam et al. 2011; Verhoeven et al. 2005).

Urine organic acids on our patient were suggestive of a disturbance in mitochondrial energy metabolism, with increased fumarate, glutarate, and significantly elevated 2-ketoglutarate, similar to results in other patients with transaldolase deficiency (Engelke et al. 2010). *Taldo1*$^{-/-}$ mice hepatocytes also demonstrate mitochondrial dysfunction with decreased mitochondrial membrane potential, mitochondrial mass, nitric oxide production, glutathione, NADH, and NADPH/NADP ratio (Hanczko et al. 2009). Human transaldolase-deficient lymphoblasts demonstrate reduced NADPH (Qian et al. 2008). The impaired ability to tolerate oxidative stress likely increased the pathogenicity of acetaminophen in our patient, compounded by possible reactive hepatitis which has been observed with respiratory syncytial virus infections (Oh et al. 2016). Despite our patient's markers of mitochondrial energy disturbance, the level of 5-oxoproline (pyroglutamate) on urine organic acids was within normal limits for age. This contrasts the reports of pyroglutamic acidosis with acetaminophen toxicity or chronic exposure in patients without transaldolase deficiency (Fenves et al. 2006) – however, our patient's sample was collected 12 days after exposure.

The decrease in compounds involved in sphingolipid metabolism may represent a hitherto undiscovered connec-

Fig. 1 (continued) circumference. (**c**) At 13 months of age, he had significant radiological abnormalities including a non-contrast T1-weighted MRI (*left*) demonstrating hepatomegaly and heterogeneous liver parenchyma with multiple hyperintense hepatic nodules including two within the anterior left hepatic lobe (*thick arrows*) and one within the right hepatic lobe (*thin arrow*). Representative ultrasound image of the larger left anterior hepatic nodule (*middle, between calipers*) demonstrates well-defined contour iso- to hypoechoic to surrounding fibrotic liver parenchyma with contrast enhancement pattern suggestive of regenerative nodule. Elastography stiffness measurement of 2.7 m/s correlates with moderate to advanced hepatic fibrosis. There is an additional persistent hyperechoic right-sided lesion (*right*), with MRI and ultrasound characteristics suggestive of lipid-rich adenoma versus atypical hemangioma

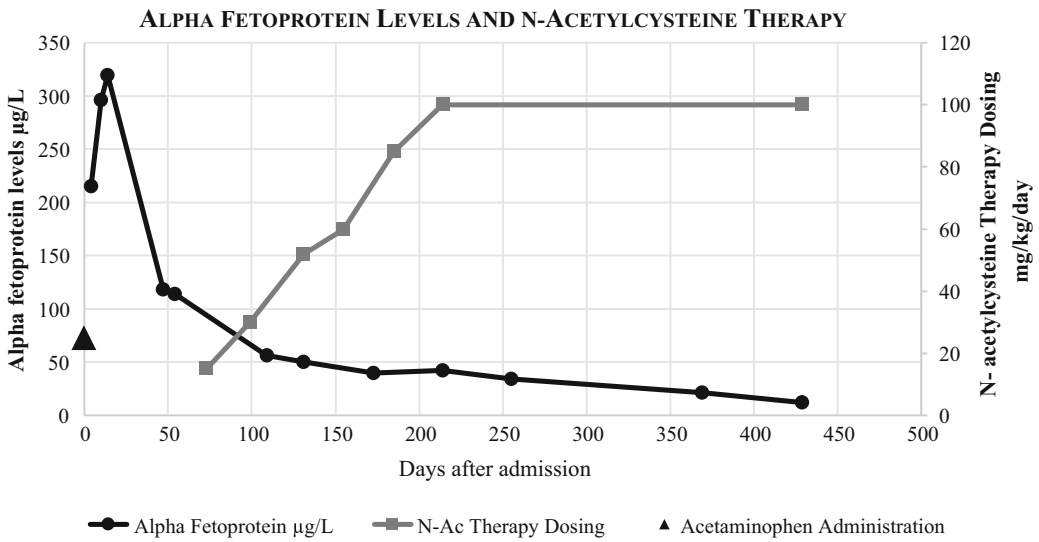

Fig. 2 Acetaminophen exposure, laboratory monitoring, and therapeutic strategy. The patient received five doses of acetaminophen over 4 days and was discontinued on the second day of admission. After acetaminophen was discontinued, the patient's alpha-fetoprotein levels continued to rise and then gradually fell over a period of 6 months (*left axis*). Therapy with *N*-acetylcysteine was titrated upward to a goal of 100 mg/kg/day (*right axis*)

tion between sphingolipid metabolism and the pentose phosphate pathway. Alternatively, this may relate to generalized liver dysfunction. For instance, in patients with chronic hepatitis B viral infection, there is a statistically significant decrease in several sphingolipid ratios independently related to the presence of cirrhosis – including ceramide d18:1/18:1 and sphingomyelin d18:1/18:1 which were also decreased in our patient (Zheng et al. 2015). The specific mechanism of these decreases has not been elucidated and may be related to the hepatitis B viral infective process rather than the cirrhosis – but this association warrants further investigation.

Acetaminophen is one of the most commonly used antipyretics and analgesics in the pediatric population with recent usage by families reported in 10–26% of children (Vernacchio et al. 2009). Children with transaldolase deficiency represent a small but increasingly recognized population in which studies suggest that acetaminophen is toxic and liver damage can be present with only mild to no elevation in transaminases, as seen in our patient and cases in literature (Verhoeven et al. 2001, 2005; Tylki-Szymańska et al. 2009). Although the development of hepatomegaly and elevated AFP correlated well with our patient's nodular hepatomegaly, AFP is not routinely sent on pediatric patients and most acetaminophen administration occurs outside the hospital setting. Therefore, significant liver damage may occur prior to diagnosis.

Taldo1$^{-/-}$ mice are highly susceptible to development of hepatocellular carcinoma and acetaminophen-induced liver failure; however, these deleterious effects were blocked by lifelong administration of NAC (Hanczko et al. 2009). NAC in humans is well tolerated and was associated with decreasing AFP values in a transaldolase-deficient patient (Rodan and Berry 2016). Our patient's elevated AFP and ALT were resolving prior to initiation of NAC treatment (Fig. 2). This is possibly the result of his liver recovery after injury or the natural decline of AFP by age seen in other patients with transaldolase deficiency (Lipiński et al. 2018), rather than the presence of therapeutic dosing levels of NAC treatment. The impact on morbidity and mortality from NAC administration in humans remains to be studied.

Heterozygosity for loss of function *TALDO* variants is more frequent than complete loss of function. Whether or not this is of consequence under conditions of increased oxidative stress remains to be determined. The liver architecture of heterozygous *Taldo1*$^{+/-}$ mice demonstrates increased anisonucleosis and nodular dysplasia with a reduced NADPH/NADP ratio; however, *Taldo1*$^{+/-}$ mice do not demonstrate increased susceptibility to acetaminophen-induced liver failure (Hanczko et al. 2009). Our patient's parents deny any recognized adverse responses to acetaminophen.

Conclusion

We report liver damage in association with acetaminophen usage in a patient with transaldolase deficiency, supporting the clinical importance of avoidance of acetaminophen in individuals with transaldolase deficiency.

Acknowledgments The authors would like to thank the family for participating in this report. We thank Lisa Kratz at the Biochemical

Genetics Laboratory at the Kennedy Krieger Institute for her reanalysis for specific metabolites in our patient's sample. Dr. Bjornsson's salary is covered by a NIH Director's Early Independence Award (DP5OD017877). The Baylor-Hopkins Center for Mendelian Genomics is supported by a grant from the National Human Genome Research Institute, 1U54HG006493.

Synopsis

Our observations emphasize the individual susceptibility of patients with rare inborn errors of metabolism and specifically support the clinical importance of avoidance of acetaminophen in individuals with transaldolase deficiency.

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Details of Funding

No funding was provided for this manuscript.

Compliance with Ethics Guidelines

Conflict of Interest Statements

Jasmine Lee-Barber, Taylor E. English, Jacquelyn F. Britton, Nara Sobreira, Jason Goldstein, and David Valle declare that they have no conflict of interest. Hans Tomas Bjornsson is a consultant for Millennium Pharmaceuticals, Inc.

Informed Consent

Our study was approved by the Johns Hopkins Medicine Institutional Review Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from the parents of the proband for being included in the study. Additional informed consent was obtained from the parents of the proband for which identifying information is included in this article.

Institutional Committee for Care and Use of Laboratory Animals

This article does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Drs. Lee-Barber and Bjornsson conceived the study, wrote the manuscript, and provided clinical data. Drs. Sobreira and Valle performed sequencing and analyzed sequencing data. Drs. English and Goldstein and Mrs. Britton provided clinical data. All authors were involved in revisions.

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