***N*-Acetylcysteine Therapy in an Infant with Transaldolase Deficiency Is Well Tolerated and Associated with Normalization of Alpha Fetoprotein Levels**

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Abstract Transaldolase deficiency is a rare autosomal recessive disorder of the pentose phosphate pathway that presents clinically with infantile-onset hepatopathy progressing to cirrhosis, nephropathy, connective tissue abnormalities resembling cutis laxa, coagulopathy, cytopenias, and increased risk of hepatocellular carcinoma. In many cases, death occurs in infancy or early childhood. There is no established treatment for transaldolase deficiency in humans. Recent work in a knockout mouse model of transaldolase deficiency has demonstrated a benefit to supplementation with the glutathione precursor *N*-acetylcysteine (NAC). We describe an infant with genetically confirmed transaldolase deficiency with multisystem involvement, including liver enlargement and markedly elevated alpha fetoprotein. Acetaminophen was strictly avoided. Treatment with oral NAC over a 6-month period was well tolerated and was associated with a sustained normalization of alpha fetoprotein levels and stable clinical course. The clinical significance of normalized serum alpha fetoprotein in this patient is not certain, although it may reflect decreased hepatocyte injury and reduced hepatocarcinogenesis as has been suggested in the mouse disease model. NAC supplementation may provide benefit in humans with transaldolase deficiency. Longer follow-up and data on the response of additional patients with transaldolase deficiency to NAC supplementation will be required to further evaluate efficacy and optimize dosing.

Introduction

Transaldolase deficiency is a rare autosomal recessive disorder of the pentose phosphate pathway. The latter is a major pathway for the production of NADPH, which is required for numerous biosynthetic reactions and reduction of oxidized glutathione (Wamelink et al. 2008). Transaldolase deficiency presents clinically with infantile-onset hepatopathy progressing to cirrhosis, nephropathy, connective tissue abnormalities resembling cutis laxa, coagulopathy, cytopenias, congenital heart disease, and increased risk of hepatocellular carcinoma (Eyaid et al. 2013; Leduc et al. 2014). In many cases, death occurs in infancy or early childhood. There is no established treatment for transaldolase deficiency in humans. Recent work in a knockout mouse model of transaldolase deficiency has demonstrated a benefit to supplementation with the glutathione precursor *N*-acetylcysteine (NAC) (Hanczko et al. 2009). We present the case of an infant with genetically confirmed transaldolase deficiency with multisystem disease treated with NAC for 6 months.

Case Report

The patient was of Emirati ancestry. He was the product of a non-consanguineous union. He was born at 36 3/7 weeks gestational age following an uncomplicated pregnancy. Birth weight was 2,125 g. He spent his first month in hospital for poor feeding, ultimately requiring placement of a nasogastric tube. He was also noted to have hepatomegaly, elevated transaminases, abnormal clotting profile, thrombocytopenia, and loose wrinkled skin. Based on his clinical presentation, he was diagnosed with transaldolase deficiency at 6 months of life. Molecular testing demon-

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Table 1 Laboratory values at 9 and 16 months

	9 months	16 months	Normal (units)
AST	84	90	2–40 (U/L)
ALT	45	54	3–30 (U/L)
GGT	27	25	12–55 (U/L)
Alkaline phosphatase	379	293	110–400 (U/L)
Albumin	45	49	30–46 (g/L)
Bilirubin, total	6.8	6.8	5.1–20.5 (μmol/L)
Bilirubin, direct	1.7	<1.7	0–6.8 (μmol/L)
Alpha fetoprotein	457	60	1–87 (μg/L)
PTT	45	36.5	25–37 (s)
INR	1.62	1.14	
WBC	4.65	6.96	7.73–13.12 (cells/μL)
PLT	132	191	223–461 (cells/μL)
Hb	110	103	104–125 (g/L)
Creatinine	17.7	17.7	17.7–35.3 (μmol/L)
BUN	6.8	9.6	1.8–6.4 (μmol/L)
Urine beta-2 microglobulin/creatinine	189,360	190,904	0–300 (mcg/g)
Microalbumin/creatinine	401.2	297.7	0–20 (mg/g)

strated homozygosity for the pathogenic variant p.R192C in exon 1 of the TALDLO1 gene.

We evaluated the patient at 9 months of age. Height and weight were both less than the first percentile (z scores of −2 and −4, respectively), and head circumference was on the 35th percentile. Face was triangular in shape. There was reduced subcutaneous fat. Skin appeared loose and mildly wrinkled. He had two small capillary hemangiomas. Liver edge was palpable at the level of the umbilicus and spleen tip was palpable. Developmental assessment and neurological examination were age appropriate.

Urine polyol analysis demonstrated sedoheptulose level of 12,012 μmol/mL creatinine (normal <95), ribitol of 1,398 (normal 52–158), erythritol of 3,257 (normal 450–1,572), and arabitol of 3,335 (range 210–578) consistent with his known diagnosis. Baseline liver enzymes and function tests, serum alpha fetoprotein, CBC, creatinine, BUN, and urine tests of tubular and glomerular function are summarized in Table 1. Plasma fatty acid profile was normal. Cholesterol was reduced to 1.9 mmol/L. Total plasma glutathione was 798 μM (normal

range 544–1,228). Quantitative urine organic acids demonstrated elevations of glutaric acid at 106 mmol/mol creatinine (range 0–6) and multiple citric acid cycle intermediates: citric acid 1,150 mmol/mol creatinine (normal 120–675), 2-oxoglutaric acid 560 (normal 0–152), succinic acid 133 (normal 0–80), fumaric acid 73 (normal 0–8), and malic acid 86 (normal 0–13). Plasma cystine was mildly reduced at 20 μmol/L (laboratory reference range for age 24–51). There were no additional amino acid deficiencies. Abdominal U/S demonstrated an enlarged nodular appearing liver with heterogenous course echotexture and mild splenomegaly.

The family was counselled on the risks and benefits of an empiric treatment trial with *N*-acetylcysteine (NAC). An institutional innovative therapy protocol was filed. A goal NAC dose of 100 mg/kg/day in three divided doses was selected based on reported dosing in ethylmalonic encephalopathy, another disorder associated with theoretical glutathione depletion (Banne et al. 2015). The patient was initiated on 17 mg/kg/day (100 mg) of NAC, and dosing was increased by 17 mg/kg/day approximately every 3 weeks until target dosing was reached after 4 months (13 months of age). The NAC was well tolerated with no reported adverse effects.

Over the treatment period, the only other modifications to the patient's management were replacement of the patient's longstanding infant formula, Monogen, with Pediasure 45 kcal/oz at 13 months of age, and G-tube placement at 14 months of age for failure to thrive. The family was cautioned to avoid any exposure to acetaminophen.

At most recent follow-up at 16 months of age, head circumference was on the 75th percentile, length was on the 5th percentile (z-score of −1.6), and weight was on the 2nd percentile (z-score of −1.98). Liver was palpable just below the umbilicus and spleen was not palpable.

Repeat urine polyols demonstrated sedoheptulose level of 7,178 μmol/ml creatinine (normal <95), ribitol of 776 (normal 52–158), erythritol of 2,622 (normal 450–1,572), and arabitol of 2,079 (normal 210–578). Repeat plasma total glutathione level on treatment was 865 μM, similar to baseline level. Total cholesterol level was normal at 2.6 mmol/L. Plasma cystine level was normal at 41 μmol/L (laboratory reference range for age 18–52). See Table 1 for liver enzymes and function tests, serum alpha fetoprotein, CBC, creatinine, BUN, and urine tests of tubular and glomerular function at most recent follow-up. *Note the normalization of serum alpha fetoprotein, which is plotted over time in Fig. 1.* The most recent abdominal ultrasound at 13 months of age demonstrated interval increase in hepatomegaly; spleen was normal in size. There were two echogenic lesions not visualized on the previous ultrasound that were suspicious for hemangiomas.

Fig. 1 Serum alpha fetoprotein levels plotted over time. The arrow indicates the time of initiation of NAC therapy. The normal range of AFP is indicated by the dotted lines

Discussion

The pentose phosphate pathway is a metabolic pathway that converts glucose-6-phosphate into fructose-6-phosphate and glyceraldehyde-3-phosphate. It consists of an irreversible oxidative phase that produces NADPH, as well as a reversible non-oxidative phase (see Fig. 2). NADPH is an important source of reducing equivalents for a number of biosynthetic reactions, including fatty acid elongation and cholesterol biosynthesis, as well as the regeneration of reduced glutathione (Wamelink et al. 2008).

Several disorders in the pentose phosphate pathway have been described to date. Perhaps the best known and most common disorder is glucose-6-phosphate dehydrogenase deficiency, which presents with drug and diet-induced hemolytic anemia. Ribulose-5-phosphate isomerase deficiency has been reported in one kindred to date in association with leukoencephalopathy (Wamelink et al. 2008).

Transaldolase deficiency has been reported in approximately 30 patients to date (Banne et al. 2015). It follows autosomal recessive inheritance, and a number of common mutations have been reported. The p.R192C mutation in the TALDO1 gene has previously been reported in the Emirati population, and a founder effect has been suggested. Despite the common genotype, there is significant phenotypic variability (Al-Shami et al. 2015). Common features include hepatosplenomegaly, liver dysfunction, anemia, thrombocytopenia, wrinkly skin, cardiac defects and cardiomyopathy, neonatal edema, renal tubulopathy, and abnormal platelet aggregation (Eyaïd et al. 2013; Banne et al. 2015). The liver disease is often progressive, although it may wax and wane and there are reports of hepatomegaly with preserved liver function (Banne et al. 2015). Many patients succumb to liver failure in infancy or childhood (Eyaïd et al. 2013). Patients may also develop early onset

hepatocellular carcinoma (Leduc et al. 2014). Development is typically normal, although three patients with developmental delay have been described (one of whom was found to have sensorineural hearing loss) (Banne et al. 2015). Hemangiomas of skin and liver have also been reported (Eyaïd et al. 2013). A number of cases have presented with hydrops fetalis (Banne et al. 2015).

The pathogenesis of transaldolase deficiency has not been entirely elucidated. It is theorized to result from a combination of toxic metabolite accumulation (e.g., sedoheptulose 7-phosphate and lipid hydroperoxides) as well as depletion of NADPH and reduced glutathione. Glutathione is a crucial antioxidant, and deficiency results in increased oxidative damage. Secondary mitochondrial dysfunction has also been described (Wamelink et al. 2008; Eyaïd et al. 2013).

NAC, a precursor for glutathione synthesis, functions to replenish depleted hepatic glutathione stores, and has been used for this purpose in acetaminophen overdose and ethylmalonic encephalopathy, an inborn error of metabolism resulting in accumulation of hydrogen sulfide and glutathione depletion (Viscomi et al. 2010).

Transaldolase knockout mice spontaneously develop hepatocellular carcinoma, and when exposed to acetaminophen develop hepatic failure. Their livers are characterized by accumulation of sedoheptulose 7-phosphate and lipid hydroperoxides, depleted NADPH and glutathione, and mitochondrial dysfunction. Alpha fetoprotein expression is increased, and is associated with the development of hepatocellular carcinoma in the mice. Lifelong treatment with NAC in these mice is protective against acetaminophen-induced liver failure and blocks hepatocarcinogenesis (Hanczko et al. 2009).

We present for the first time the effects of 6 months of NAC supplementation in a patient with transaldolase deficiency. The treatment was well tolerated with no adverse effects. On therapy, we demonstrate a progressive normalization of alpha fetoprotein levels despite an interval mild increase in liver size. Although we cannot directly prove a causal relationship, we believe that this improvement is due to the NAC, and this is supported by the data from the knockout mouse model (Hanczko et al. 2009). Although it is difficult to predict the clinical implications of this normalization of alpha fetoprotein levels, we believe that this may signify decreased hepatocellular injury and a reduced risk of hepatocarcinogenesis.

We did not demonstrate a notable increase in total plasma glutathione on NAC therapy, although this measurement likely does not accurately reflex intrahepatic glutathione stores nor does it distinguish between reduced and oxidized forms. There was no change on treatment in renal tubular/glomerular dysfunction or cytopenias. Quantitative urine organic acid results in our patient were consistent with mitochondrial dysfunction, as has been

Fig. 2 Oxidative and non-oxidative components of the pentose phosphate pathway

reported in transaldolase deficiency (Wamelink et al. 2008). Baseline plasma cystine level was reduced, potentially due to increased utilization of this semi-essential amino acid in the biosynthesis of glutathione due to increased losses of glutathione in the oxidized form; repeat levels on NAC supplementation with improved nutrition were normal.

Equally important to our patient's management was the strict avoidance of acetaminophen since individuals with transaldolase deficiency may be exquisitely vulnerable to acetaminophen-induced glutathione depletion and hepatic injury based on the animal data (Hanczko et al. 2009).

Finally, it should be emphasized that treatment with NAC only addresses the reduced availability of glutathione for antioxidant defense, and does not correct the additional biochemical perturbations in this disorder including NADPH deficiency and the accumulation of toxic intermediates resulting from the enzymatic block.

In conclusion, supplementation of NAC in a patient with transaldolase deficiency appears to be well tolerated and is associated with biochemical improvement in the form of normalized alpha-fetoprotein levels. The clinical significance of this is not certain, although it may reflect decreased hepatocyte injury and reduced hepatocarcinogenesis. Longer follow-up and data on the response of additional patients with transaldolase deficiency to NAC supplementation will be required to answer these questions and optimize dosing.

Synopsis

N-acetylcysteine therapy in an infant with transaldolase deficiency was well tolerated and associated with normalization of serum alpha fetoprotein levels. NAC may provide benefit in humans with transaldolase deficiency, but additional cases and longer follow-up are required.

Author Contributions

Lance H. Rodan: Preparation of manuscript

Gerard T. Berry: Critical revision of manuscript, supervisor

Guarantor

Lance H. Rodan

Competing Interest Statement

Lance H. Rodan and Gerard T. Berry have nothing to declare.

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Compliance with Ethics Guidelines

Not required

Patient Consent Statement

Not applicable since the report does not contain any identifying patient information.

Conflict of Interest

There is no conflict of interest.

References

Al-Shami AM, Ben-Salem S, Hertecant J et al (2015) Transaldolase deficiency caused by the homozygous p.R192C mutation of the

TALDO1 gene in four Emirati patients with considerable phenotypic variability. *Eur J Pediatr* 174(5):661–668

Banne E, Meiner V, Shaag A et al (2015) Transaldolase deficiency: a new case expands the phenotypic spectrum. *JIMD Rep*

Eyaid W, Al Harbi T, Anazi S et al (2013) Transaldolase deficiency: report of 12 new cases and further delineation of phenotype. *J Inherit Metab Dis* 36:997–1004

Hanczko R, Fernandez DR, Doherty E et al (2009) Prevention of hepatocarcinogenesis and increased susceptibility to acetaminophen-induced liver failure in transaldolase-deficient mice by N-acetylcysteine. *J Clin Invest* 119(6):1546–1557

Leduc CA, Crouch EE, Wilson A et al (2014) Novel association of early onset hepatocellular carcinoma with transaldolase deficiency. *JIMD Rep* 12:121–127

Viscomi C, Burlina AB, Dweikat I et al (2010) Combined treatment with oral metronidazole and N-acetylcysteine is effective in ethylmalonic encephalopathy. *Nat Med* 16:869–871

Wamelink MMC, Struys EA, Jakobs C (2008) The biochemistry, metabolism and inherited defects of the pentose phosphate pathway. *J Inherit Metab Dis* 31:703–717