Case Report

A Novel Homozygous Missense Mutation in the YARS Gene: Expanding the Phenotype of YARS Multisystem Disease

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Abbreviations: ACE, angiotensin converting enzyme; ARS, aminoacyl-tRNA synthetase; CHOP, Children’s Hospital of Philadelphia; CNS, central nervous system; FT4, free thyroxine; FTT, failure to thrive; G6PD, glucose-6-phosphate dehydrogenase; GIR, glucose infusion rate; G-Tube, gastrostomy tube; IV, intravenous; MR, magnetic resonance; RBC, Rainbow Babies and Children’s Hospital; TSH, thyrotropin (thyroid-stimulating hormone); YARS, tyrosyl-tRNA synthetase 1.

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Abstract

Aminoacyl-tRNA synthetases (ARSs) are crucial enzymes for protein translation. Mutations in genes encoding ARSs are associated with human disease. Tyrosyl-tRNA synthetase is encoded by YARS which is ubiquitously expressed and implicated in an autosomal dominant form of Charcot-Marie-Tooth and autosomal recessive YARS-related multisystem disease.

We report on a former 34-week gestational age male who presented at 2 months of age with failure to thrive (FTT) and cholestatic hepatitis. He was subsequently diagnosed with hyperinsulinemic hypoglycemia with a negative congenital hyperinsulinism gene panel and F-DOPA positron-emission tomography (PET) scan that did not demonstrate a
focal lesion. Autopsy findings were notable for overall normal pancreatic islet size and morphology. Trio whole exome sequencing identified a novel homozygous variant of uncertain significance in \textit{YARS} (c.611A > C, p.Tyr204Cys) with each parent a carrier for the \textit{YARS} variant. Euglycemia was maintained with diazoxide (max dose, 18 mg/kg/day), and enteral dextrose via gastrostomy tube (G-Tube). During his prolonged hospitalization, the patient developed progressive liver disease, exocrine pancreatic insufficiency, acute renal failure, recurrent infections, ichthyosis, hematologic concerns, hypotonia, and global developmental delay. Such multisystem features have been previously reported in association with pathogenic \textit{YARS} mutations. Although hypoglycemia has been associated with pathogenic \textit{YARS} mutations, this report provides more conclusive data that a \textit{YARS} variant can cause hyperinsulinemic hypoglycemia. This case expands the allelic and clinical heterogeneity of \textit{YARS}-related disease. In addition, \textit{YARS}-related disease should be considered in the differential of hyperinsulinemic hypoglycemia associated with multisystem disease.

\textbf{Key Words:} Chronic liver disease, hyperinsulinemic hypoglycemia, multisystem disease, tyrosyl-tRNA synthetase, \textit{YARS}

The aminoacyl-tRNA synthetases (ARSs), also called tRNA-ligases, consist of a family of enzymes mainly known for their primary function in the first step of protein synthesis. They also provide additional regulation of biological processes, including translational control, transcription regulation, signal transduction, cell migration, angiogenesis, inflammation, apoptosis, tumorigenesis, and interferon gamma (IFN-\gamma) and p53 signaling. In human cells, most ARSs localize to the cytoplasm (ARS or ARS1), mitochondria (ARS2), or both. Human tyrosyl-tRNA synthetase is a cytoplasmic enzyme that is encoded by the \textit{YARS} gene [1-3].

Tyrosyl-tRNA synthetase (\textit{YARS}) is responsible for tyrosyl-tRNA aminoacylation. The functional enzyme exists as a homodimer, has potent leukocyte and monocyte chemotaxis activity, and stimulates production of myeloperoxidase, tumor necrosis factor-\(\alpha\), and tissue factor. A shift in the monomer:dimer equilibrium could result in dysregulation of the cytokines function [4, 5].

Recently, many diseases have been associated with specific mutations of aminoacyl-tRNA synthetases. In fact, 34 of the 37 genes that encode ARSs, including the \textit{YARS} gene, have been implicated in early-onset, multisystem, recessive disease [5, 6]. Nowaczyk et al described 2 siblings with compound heterozygosity in \textit{YARS} catalytic and C-terminal domains. Affected children suffered from growth failure, developmental delay, abnormal brain white matter, liver dysfunction, and lung cysts [5].

In an effort to expand the phenotype of this rare autosomal recessive disorder, we report on a male infant with a multisystem disease, including hyperinsulinemic hypoglycemia, who was found to have a novel homozygous variant of uncertain significance in the \textit{YARS} gene (c.611A>C, p.Tyr204Cys) [7].

\textbf{Case Report}

The patient was an African American male born at 34 weeks gestation. Growth parameters were appropriate for gestational age (birth weight 2.09 kg; z-score 0.80). Parents denied consanguinity, and Ohio newborn screening (NBS) was normal. Initial 10 days of life were significant for bronchiolitis complicated with multi-organ failure that eventually worsened leading to patient death at 12 months of age. Patient was taken care of by a multidisciplinary team at Rainbow Babies and Children’s Hospital (RBC) and at Children’s Hospital of Philadelphia (CHOP).

\textbf{Gastroenterology and Hepatology}

At 3.4 months of age (corrected 2.2 months), the patient met criteria for severe protein calorie malnutrition based on his weight and length z-scores and was started on enteral nutrition therapy. Weight z-score was –4.54 (3.74 z-score decline since birth), weight for length z-score was −1.6, and mid upper arm circumference z-score was −3.34. Admission workup was notable for elevated liver enzymes (alanine aminotransferase, 531 U/L; aspartate aminotransferase, 144 U/L), gamma-glutamyl transferase (96 U/L), and direct hyperbilirubinemia (total and direct bilirubin were 2.8 mg/dL and 1.6 mg/dL, respectively) but no evidence of acute liver failure. Abdominal ultrasound revealed a normal-sized liver and was not suggestive of any obstructive causes of cholestasis. Workup for infectious
causes of hepatitis, alpha-1-antitrypsin deficiency, Wilson disease, Menkes disease, and hereditary tyrosinemia was negative. Patient was subsequently found to suffer from mild to moderate exocrine pancreatic insufficiency (fecal pancreatic elastase, 100 μg/g) requiring pancreatic enzyme replacement.

Upon admission at 8 months of age, the patient was found to have worsening cholestatic hepatitis, severe coagulopathy (prothrombin time/international normalized ratio ranging from 14.4 to 42.8 seconds and 1.2 to 3.81, respectively) and hypoalbuminemia. Ammonia peaked at 128 μmol/L. He also developed hepatomegaly with severe ascites requiring diuretic therapy and therapeutic paracentesis. Abdominal ultrasound also showed increased resistive indices of the common hepatic and left hepatic artery but otherwise antegrade flow. He was started on ursodiol for worsening cholestasis and underwent an interventional radiology guided liver biopsy. Serum-ascites albumin gradient (SAAG) was more than 1.1 g/dL. Liver biopsy (Fig. 1A) showed portal and periportal fibrosis (Ludwig stage III) with bile duct proliferation, severe lobular cholestasis with diffuse bile rosettes, focal perisinusoidal fibrosis, and prominent macrovesicular steatosis. Patient was discharged home after his clinical status had stabilized, ascites improved on diuretics and angiotensin converting enzyme (ACE) inhibitors, and his liver enzymes trended down. However, he was readmitted a few days later with worsening abdominal distension due to severe ascites ascribed to portal hypertension, as Doppler studies were significant for reversal of flow in the left portal vein. Patient had a rapid decompensation and developed abdominal compartment syndrome, acute kidney failure, and acute respiratory failure.

**Endocrinology**

At 3 months of age, the patient started to have recurrent hypoglycemia. A critical sample (Table 1) obtained during an episode of hypoglycemia ruled out growth hormone deficiency and adrenal insufficiency. Optic nerves were normal on ophthalmology examination. However, insulin levels were detectable with suppressed ketones and free fatty acids. He underwent a glucagon challenge test (1 mg glucagon IV) with a rise of glucose (serum glucose 47 mg/dL, 45 mg/dL, 73 mg/dL, and 92 mg/dL at baseline, 10 minutes, 20 minutes, and 30 minutes, respectively), confirming the diagnosis of hyperinsulinism. Despite maximizing

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**Figure 1. Pathologic findings.** A. Liver biopsy at 9 months of age shows numerous bile rosettes, bile ductular hyperplasia, and portal and periportal fibrosis (H&E, 4×). B. Liver at autopsy (12 months of age) shows extensive portal and lobular fibrosis with bile duct proliferation consistent with end-stage cirrhosis (H&E, 4×). C. Sections of the pancreas demonstrated intact lobular architecture with occasional mildly enlarged islets within the range of normal size variation; no islet cell nucleomegaly was identified (H&E, 4×). D. Thyroid gland at autopsy was enlarged and shows marked variation in the size of follicles (H&E, 4×). E. Mesenteric lymph node at autopsy shows activated macrophages with numerous phagocytosed cytoplasmic red blood cells (H&E, 40×). F. Cerebellum at autopsy shows focal necrosis and mineralization (H&E, 20×).
diazoxide (18 mg/kg/day) and chlorothiazide (27.6 mg/kg/day) dosages, he continued to have intermittent hypoglycemia requiring feeds every 2 hours and intravenous (IV) dextrose (8 mg/kg/min). Diazoxide was then discontinued, and his IV glucose infusion rate (GIR) increased to 18 mg/kg/min. He was transferred to CHOP for further evaluation of hyperinsulinemic hypoglycemia. Comprehensive hyperinsulinism sequencing and deletion/duplication panel testing (University of Chicago) for ABCC8, AKT2, CACNA1D, FOXA2, GCK, GLUD1, HADH, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, PGM1, PMM2, SLC16A1, TRMT10A, and UCP2 was negative. 18F-DOPA PET scan showed no evidence of focal congenital hyperinsulinism. A gastrostomy tube was placed and he returned to RBC on continuous feeds (0.9 kcal/mL), continuous enteral dextrose (GIR of 4.2 mg/kg/min), diazoxide (12 mg/kg/day), and chlorothiazide (24 mg/kg/day). During an episode of critical illness at 8 months of life that resulted in multi-organ failure, the patient developed insulin-requiring hyperglycemia resulting in discontinuation of diazoxide. After resolution of critical illness, normoglycemia was maintained with a combination of continuous G-Tube feeds (GIR 8.8 mg/kg/min) and continuous enteral dextrose administration (GIR 3.7 mg/kg/min) for a total GIR of 12.5 mg/kg/min.

The patient was diagnosed with primary hypothyroidism. His newborn screening thyroid-stimulating hormone (TSH) was normal (16 mIU/L). However, he had persistent elevation of TSH that started at 103 days of life (TSH, 6.10 mIU/L; free thyroxine, 1.48 ng/dL), and persisted at 4 months of age (TSH, 9.2 mIU/L; free thyroxine, 1.16 ng/dL) prompting starting oral levothyroxine 37.5 mcg (10 mcg/kg/day). During his hospital course, the patient required levothyroxine dose adjustment and at discharge levothyroxine dose was 56 mcg/day (6 mcg/kg/day).

Table 1. Laboratory Results at Times of Hypoglycemia

| Tests          | Sample 1     | Sample 2     |
|----------------|--------------|--------------|
| POC glucose    | 50 mg/dL     | 42 mg/dL     |
| Serum glucose  | 43 mg/dL     | 47 mg/dL     |
| Insulin        | 1 µIU/mL     | 1 µIU/mL     |
| BOHB           | 0.19 mmol/L  | 0.15 mmol/L  |
| Free fatty acid| N/A          | 0.3 mEq/L    |
| Ammonia        | N/A          | 75 µmol/L    |
| Cortisol       | 22.5 mg/dL   | N/A          |
| GH             | 16.1 mg/dL   | N/A          |

Abbreviations: BOHB, beta-hydroxybutyrate; GH, growth hormone; N/A, not available; POC, point of care.

Infectious Disease and Immunology

At 3 months of age, the patient started to show an inflammatory reaction with neutrophilic leukocytosis and varying thrombocytosis. He also had multiple hospital-acquired infections including bacteremia (Methicillin-resistant Staphylococcus aureus, Klebsiella, and Serratia marcescens), endotracheitis (Pseudomonas and Staphylococcus aureus) and pneumonia. Immunology evaluation included a normal immunodeficiency profile, normal Toll-like receptor assay, and mitogen test.

Nephrology

The patient had normal renal and urinary tract anatomy. However, during his second hospital admission at 8 months of life, he developed acute renal failure requiring temporary hemodialysis. His renal function recovered, and he was maintained on diuretics and ACE inhibition.

Central Nervous System

The patient was noted to suffer from global developmental delay. His brain/pituitary magnetic resonance (MR) imaging was unremarkable at 6 months of life but was noted to develop mild to moderate diffuse cerebral volume loss at 9 months of life. MR spectroscopy identified a small, nonspecific lactate peak in nearly all of the voxels placed over the basal ganglia.

Genetics

The patient was first evaluated by genetics/metabolism service at 3 months of life. Cholestasis gene panel (Emory Genetics Laboratory), disorders of copper metabolism gene panel (Invitae), congenital hyperinsulinism panel (University of Chicago), basic metabolic screening, as well as screening for congenital disorders of glycosylation were all normal and did not reveal an underlying cause for his clinical picture. A hemolytic anemia gene panel (Mayo Clinic Laboratories) revealed a pathogenic G6PD variant consistent with G6PD enzyme deficiency (GPD A-) that can lead to mild to moderate hemolysis but did not explain...
his entire clinical picture. A chromosomal microarray analysis at CHOP revealed a likely benign chromosome 15q11.2 deletion, and mitochondrial genome sequencing was negative. Whole exome sequencing trio analysis at CHOP showed homozygosity for a variant of uncertain significance in the YARS gene at c.611A>C (p.Tyr204Cys) with parents being heterozygous carriers for this variant [7]. This change is located in exon 6 of the YARS gene and has not been reported in the scientific literature or disease-associated variant databases. This variant has a minor allele frequency of 0.0032% (1/31388 alleles, 0 homozygotes) in the Genome Aggregation Database and allele frequency of 0.01 115% (1/8712) in the African subpopulation. This mutation is in the catalytic region of the YARS gene and missense mutations just downstream of this mutation in the same exon have been reported in affected individuals [5]. In silico computational tools (PolyPhen-2, SIFT, and Mutation Taster) suggest a potentially deleterious effect of this change on the protein function.

Autopsy Results

A complete autopsy was performed and was significant for end-stage fibrotic liver disease with cholestasis (Fig. 1B). Sections of the pancreas demonstrated intact lobular architecture with occasional mildly enlarged islets within the range of normal size variation; no islet cell nucleomegaly was identified (Fig. 1C). He was found to have an enlarged thyroid gland with an admixture of micro- and macrofollicles and no significant lymphocytic infiltrate (Fig. 1D) and a mesenteric lymph node with lymphohistiocytic hemophagocytosis (Fig. 1E). The brain demonstrated noninflammatory leukodystrophy (Fig. 1F). Additionally, cardiomegaly with left ventricular hypertrophy and post-infectious chronic lung disease with persistent bronchiolitis were noted. The cause of death was multi-organ failure.

Discussion

The spectrum of disease phenotype associated with mutations in the cytoplasmic aminoacyl transfer RNA synthetase genes is expanding. Fuchs et al identified 107 patients with cytosolic and combined cytosolic and mitochondrial gene mutations [8]. Common symptoms (defined as present in ≥4/13 ARS deficiencies) included abnormalities of the central nervous system (CNS) and/or senses (13/13); FTT (10/13); feeding problems (4/13); gastrointestinal symptoms (5/13); lung disease (≥7/13); bone marrow abnormalities (>4/13); kidney disease (>4/13), including acute kidney failure, liver disease (4/13); and endocrinology abnormalities (4/13), including diabetes, precocious puberty, and hypothyroidism. Symptoms were more severe in the first year of life and during infections [8]. Heterozygous mutations in YARS were first identified in 3 unrelated families found to have dominant intermediate Charcot-Marie-Tooth disease with associated motor and sensory neuropathy (OMIM # 118220) [9]. Charcot-Marie-Tooth disease caused by YARS variants exhibits an autosomal dominant pattern of inheritance. In contrast, our patient's novel phenotype exhibits an autosomal recessive inheritance pattern. A YARS-associated phenotype partially overlapping the phenotype of our patient was recently reported [5, 10]. Williams et al reported 7 related children homozygous for a novel YARS variant (c.499C>A, p.Pro167Thr) showing poor growth, variable degrees of development delay, brain dysmyelination, thinning of corpus callosum, progressive cholestatic liver disease, exocrine pancreatic insufficiency, recurrent infection, hypoalbuminemia, anemia, hypoglycemia, and chronic lung disease [10]. Nowaczyn et al reported 2 siblings with compound heterozygous YARS variants (c.638C>T, p.Pro213Leu and c.1573G>A, p.Gly525Arg) with a condition affecting growth, liver, lung, and brain [5]. Tracewkska-Siemiatkowska et al reported a homozygous YARS variant (c.806T>C, p.Phe269Ser) in a Swedish proband with a phenotype characterized by progressive retinal degeneration with congenital nystagmus, profound congenital hearing impairment, primary amenorrhea, agenesis of the corpus callosum, and liver disease [11].

The overlap in clinical phenotypes likely indicates a common underlying mechanism. The most likely hypothesis is reduced aminoacylation resulting in failure to meet translational demand in specific organs during periods of increased demands in the first year of life and during infection. However, secondary functions of these enzymes being interrupted cannot be excluded.

Here we report a novel homozygous variant in the YARS gene (c.611A>C, p.Tyr204Cys) causing a multisystem disease [7]. Our patient displayed FTT, chronic liver disease, anasarca requiring dialysis, exocrine pancreatic insufficiency, chronic lung disease, recurrent infections, persistent hemolytic anemia, developmental delay, MR imaging evidence of mild-moderate diffuse cerebral volume loss, primary hypothyroidism, and hyperinsulinemic hypoglycemia.

Pathologic findings at autopsy revealed some findings noted in previous reports, including cirrhosis, CNS leukodystrophy and chronic lung disease [5, 10]. Liver disease had progressed from severe cholestasis with portal and periportal fibrosis (Ludwig stage III) on biopsy 3 months prior to death to end-stage biliary cirrhosis with macrovesicular steatosis at the time of death. In addition to generalized CNS leukodystrophy, periventricular gliosis and foci of necrosis with mineralization in the cerebellum were noted.
Unique pathologic findings in our patient that correlate with his unusual clinical presentation were identified in the thyroid and lymph nodes. In addition, normal pancreatic islet cell size and morphology was identified. Thyroid gland changes were consistent with dys hormonogenic goiter and correlated with the history of primary hypothyroidism. Finally, lymphohistiocytic hemophagocytosis may reflect history of chronic infections, but this could also reflect a primary immunodeficiency related to the patient’s underlying genetic abnormality.

The child described here shares many of the clinical features with the 7 related children from a prior cohort report [10] and shares many features with other autosomal recessive ARS deficiencies [8]. Neuroimaging evidence of cortical and/or white matter abnormalities have been reported in ARS gene mutations [10, 12-15]. Liver dysfunction including cirrhosis has been reported [5, 8, 10, 11, 16-18]. Chronic anemia has been reported before but with no evidence of blood hemolysis [8, 10]. Our patient also had G6PD deficiency, which is associated with mild to moderate hemolysis. Our patient had deep-set eyes and cherubic facies; facial characteristics also reported in children with ARS gene mutation [5, 8, 10]. Our patient had a shiny, scaly rash on his trunk that spared lower extremities, consistent with ichthyosis. Skin abnormalities, including dry rough skin and increase skin elasticity have also been reported [8, 10]. Interestingly, persistent hypoglycemia was also reported in 5 patients with homozygous YARS mutation (c.499C>A, p.Pro167Thr) [10], who were managed with a combination of continuous feeds and continuous enteral dextrose. Only one of those patients had a critical sample at the time of hypoglycemia, which was obtained at 8 months of age and was reported as “inconclusive”, showing hypoketosis, undetectable insulin, normal C-peptide, and absent response to glucagon, although the patient “did respond to glucagon during the fed state”. The hypoketosis suggests hyperinsulinism as the underlying etiology, and a “normal” C-peptide likely means it was detectable, which is also consistent with hyperinsulinism. The absent response to glucagon may have been due to liver dysfunction and does not rule out hyperinsulinism as the underlying cause of hypoglycemia. Our report provides more conclusive data that an ARS variant can cause hyperinsulinemic hypoglycemia. The patient was not small for gestational age and did not have perinatal stress, suggesting that his hyperinsulinism would not be transient. This is further supported by his continued requirement of a high glucose infusion rate at the time of his death at 12 months of age.

Conclusion

Our findings support the previous reports that recessive mutations in the YARS gene may cause insufficient aminoacylation resulting in impaired protein synthesis that fails to meet specific organ demands. Mutations in the YARS gene may cause immune dysregulation based on the secondary function of the YARS protein that could be an essential role in the underlying disease pathphysiology. This case expands the allelic and clinical heterogeneity of YARS-associated human disease. YARS mutations should be considered in patients with multisystem disease. We believe further defining of the phenotype of these ARS deficiencies is important so that these diseases can be recognized and diagnosed earlier. We further expand the phenotype of YARS multisystem disease to include more conclusive data that a YARS variant can cause hyperinsulinemic hypoglycemia. Patients identified to have YARS mutations should be evaluated for hypoglycemia.

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Additional Information

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