



Misdiagnosis of Total Parental Nutrition-Related Riboflavin Deficiency: Three Case Reports of Diagnostic Error

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AJP Rep 2023;13:e11–e16.

Abstract

Total parental nutrition (TPN) is a critical component of neonatal intensive care. Supply shortages leading to deficiencies in TPN constituents can have devastating consequences for critically ill patients in the neonatal intensive care unit (NICU), who may be initially misdiagnosed as potential inborn errors of metabolism. Here, we present three cases of patients with prolonged TPN dependence due to intra-abdominal pathology who presented with signs and symptoms concerning for metabolic disorders and who were ultimately determined to be a result of vitamin deficiencies in the TPN after unnecessary testing and interventions had occurred. These diagnostic errors highlight the need for clinicians to maintain a high index of suspicion for nutritional deficiencies when treating patients in the NICU with potential metabolic disorders during times when TPN constituents are not available, as well as advocating to ensure that adequate supplies are maintained for this vulnerable population.

Keywords

- ▶ NICU
- ▶ neonatology
- ▶ total parental nutrition
- ▶ vitamin deficiency
- ▶ diagnostic error

Critically ill patients in the neonatal intensive care unit (NICU) have high nutrient requirements and low nutrient stores, which make appropriate administration of essential nutrition.¹ Patients in the NICU often depend on total parental nutrition (TPN) for the entirety of their nutritional intake for extended periods of time. Thus, TPN-constituent product shortages can have clinically devastating adverse consequences in this population.² As these shortages may not be apparent to the health care teams at the bedside, clinicians may not recognize the resultant deficiencies as a potential etiology of a clinical presentation which may mimic congenital metabolic disorders.¹ Here, we present three cases of riboflavin deficiency

(ariboflavinosis) as a result of inadequate TPN constituents, which were initially misdiagnosed as metabolic disorders.

Case 1

Case 1 is a male neonate born at 26^{5/7} weeks' gestational age (GA) to a 39-year-old G6P3 mother. Mother had premature rupture of membranes 7 days before delivery and developed chorioamnionitis leading to delivery at 26 weeks' GA. The mother received betamethasone for fetal lung maturation a week before delivery and magnesium for neuroprotection before delivery. The neonate's birth weight was 1.13 kg, was

received
September 27, 2022
accepted after revision
February 3, 2023
accepted manuscript online
February 10, 2023

DOI <https://doi.org/10.1055/a-2032-9737>.
ISSN 2157-6998.

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intubated in the delivery room, and then admitted to the NICU at an outside hospital for further evaluation and management of prematurity.

This neonate had a complicated course at the outside hospital with multiple complications of prematurity including: severe bronchopulmonary dysplasia with ventilator dependence, multiple courses of antibiotics for suspected infection for clinical and laboratory abnormalities, as well as *Pseudomonas aeruginosa* bacteremia on day of life (DOL) 57, pancytopenia requiring multiple blood product transfusion as well as treatment with epoetin alfa and filgrastim as well as grade IV intraventricular hemorrhage in the brain. The neonate also suffered from multiple episodes of necrotizing enterocolitis requiring exploratory laparotomies on DOL 56 at 34 weeks' corrected gestational age (CGA) and DOL 70 at 36 weeks' CGA. As a result, the patient required intravenous TPN for the entirety of the hospitalization. Moreover, the patient experienced persistent metabolic acidosis with a newborn screen that resulted on DOL 51 as positive for isovaleric acidemia. Further workup included urine organic acid testing that resulted in possible multiple acyl-CoA dehydrogenase deficiency (MADD)/glutaric aciduria type II (see ►Table 1 for an overview of metabolic workup). The patient was started on riboflavin, carnitine, and CoQ10 supplementation. The patient was transferred to our institution on DOL 82 (38 weeks' CGA) for further workup of presumed metabolic disorder. At the time of transfer, the patient required chronic mechanical ventilation and continuous pharmacological sedation with persistent metabolic acidosis.

The metabolic diagnostic investigation continued at our institution; it was determined that due to a vitamin shortage

originating with the manufacturer, that patient had not been receiving adequate riboflavin in TPN at the outside institution. This information had not been apparent to the treating clinicians previously. This revelation led the clinical teams to suspect that riboflavin deficiency was the etiology of the symptoms and not an inborn error of metabolism. Our institution had obtained a quantity of multivitamin (INFUVITE pediatric formulation, which contains vitamins C, A, D3, thiamine [B1], riboflavin [B2], pyridoxine [B6], niacinamide, dexpanthenol, vitamin E, vitamin K1, folic acid, biotin, and vitamin B12), which was added to the patient's TPN once TPN was ordered at our institution. On DOL 85, the patient developed overwhelming sepsis secondary to *P. aeruginosa* bacteremia and died on DOL 86 despite the maximal resuscitative effort. Postmortem DNA-based testing was negative for MADD or riboflavin transport deficiencies. The parents declined a comprehensive autopsy. This case was highlighted and discussed in depth in our morbidity and mortality meeting with input from metabolic specialists and representation from our neonatology network locations across Southern California.

Case 2

Case 2 is a female neonate born at 26^{1/7} weeks' GA to a 29-year-old G2P1 at an outside hospital. The mother presented in active labor, which progressed despite medical management and necessitated delivery via C-section due to transverse fetal lie. The neonate's birth weight was 1.02 kg. The mother received one dose of betamethasone for lung maturation just prior to delivery. The neonate was stabilized in the delivery room on noninvasive ventilation, then admitted to the NICU for further management of prematurity.

The patient underwent a complicated course at an outside hospital with multiple problems related to prematurity. This included prolonged respiratory failure requiring noninvasive positive pressure ventilation support with several failed attempts to wean off respiratory support. The patient was noted to have a large patent ductus arteriosus which improved to moderate after a treatment course of acetaminophen. The patient also had several infection evaluations requiring empiric antibiotics courses and underwent a treatment course for pneumonia as well.

The neonate had difficulty tolerating enteral feeds, initially, with distended abdomen that was thought to be related to the distending pressure from noninvasive ventilation support. Later, the patient underwent a treatment course for presumed medical necrotizing enterocolitis due to the abdominal distension. As a result, the patient required TPN nutrition for several weeks. Of note, the outside institution outsources their TPN to a third-party vendor and received a multivitamin cocktail with vitamins B1, B6, B9, B12, C, and K, as well as trace elements (zinc, copper, and selenium) but did not receive riboflavin, biotin, or vitamins A, D, and E due to national shortage of pediatric multivitamin preparations. By 4 weeks of life, the patient remained on TPN support with a distended abdomen and unable to advance feeds. Mild metabolic acidosis was noted at that time.

Table 1 Case 1 metabolic workup

DOL	Workup
7	NBS positive for SCID and CAH Follow-up lymphocyte subset panel normal with low IgE and IgM, but normal IgA and IgG levels Follow-up 17-OHP level normal
51	Repeat NBS (sent DOL 34) positive for IVA Urine organic acid testing—concerning for IVA but not diagnostic Repeat urine organic acids—suggestive of MADD7/glutaric aciduria type II or riboflavin transporter defect/nutritional riboflavin deficiency Genetic testing for IVA sent—negative
68	Acylcarnitine profile abnormal—suggestive of MADD/glutaric aciduria type II or riboflavin transporter defect/nutritional riboflavin deficiency
72	Repeat acylcarnitine profile and urine acylglycines sent
73	Genetic testing (MADD panel) sent—negative
82	Transferred to our institution
86	Patient died—postmortem DNA isolated and skin biopsy for fibroblasts culture was obtained

Abbreviations: CAH, congenital adrenal hypoplasia; DOL, day of life; Ig, immunoglobulin; IVA, isovaleric aciduria; MADD, multiple acyl-CoA dehydrogenase deficiency; NBS, newborn screen; SCID, severe combined immunodeficiency; 17-OHP, 17-hydroxyprogesterone.

Table 2 Case 2 metabolic workup

DOL	Workup
7	NBS positive for homocystinuria
23	Repeat NBS (sent DOL 21) positive for MADD Urine acylglycines testing sent and resulted as concerning for MADD, or a disorder of riboflavin metabolism/deficiency
34	Urine organic acid and acylcarnitine profiles sent and resulted as concerning for disorder of riboflavin metabolism/deficiency
35	Transferred to our institution and started on TPN with INFUVITE pediatric multivitamin
59	Acylcarnitine profile after receiving riboflavin in TPN within normal limits

Abbreviations: DOL, day of life; MADD, multiple acyl-CoA dehydrogenase deficiency; NBS, newborn screen; TPN, total parenteral nutrition.

During this hospitalization, the initial newborn screen flagged as positive for homocystinuria (elevated methionine) with a repeat screen that was positive for MADD. As a result of the discussion at our institution's mortality and morbidity conference of the first case with attendance of clinicians from all over our network which includes 14 NICUs across the region, the medical team at that hospital was made aware of the previous case related to riboflavin deficiency in the TPN, and as such, riboflavin deficiency was then suspected to be the etiology of the patient's presentation. The metabolic service at our institution was consulted, and per their recommendations, the team at the outside hospital attempted enteral supplementation with riboflavin. However, the patient did not tolerate enteral supplementation, so the patient was transferred to our institution on DOL 34 for further evaluation and management.

The patient was started on TPN at our institution, which contained the INFUVITE pediatric formulation of vitamins. Initial laboratory workup was consistent with riboflavin deficiency. The patient responded well to treatment with normalization of laboratories—see ▶Table 2 for an overview of the workup. As the patient was advanced to full enteral feeds, TPN was weaned off, and no additional supplementation was required. Once stabilized on full enteral feeds, the patient was transferred back to the referring institution. At the referring hospital, the patient's respiratory support was weaned as tolerated, and enteral feeds by mouth (PO) were introduced. The patient was eventually discharged home on DOL 102 with low-flow nasal cannula oxygen and full PO feeds.

Case 3

Case 3 is a male neonate born at 32^{0/7} weeks' GA to a 20-year-old G1 at an outside hospital. Pregnancy was complicated with fetal growth restriction (< 3%) and concern for echogenic bowel on some of the prenatal ultrasounds. The mother was referred from the obstetric clinic to labor and delivery for further monitoring and noted to have a prolonged fetal deceleration, which necessitated emergent de-

livery via C-section. The neonate's birth weight was 1.22 kg. The patient was intubated in the delivery room, then admitted to the NICU for further management of prematurity and concern for echogenic bowel on prenatal imaging.

Patient was noted to have bilious residuals and distended abdomen after birth. Extensive workup was not diagnostic—including ruling out Hirschsprung's disease by rectal biopsy. The patient was ultimately taken to the operating room (OR) for exploratory laparotomy. Intraoperatively, the patient was found to have a 180-degree volvulus involving the mid-ileum and inspissated meconium. The bowel was repaired and decompressed with no bowel resection required.

Postoperatively, the patient was initially convalescing and was able to be extubated and weaned off vasoactive support. However, the abdomen remained distended precluding the introduction of enteral feeds. As a result, the patient required TPN nutrition for several weeks. Of note, this outside institution, similarly to the institutions in the two previous cases, outsources TPN to a third-party vendor, and due to national shortages, did not have full pediatric multivitamins in the TPN—the patient received vitamins B1, B6, B9, B12, C, and K, as well as trace elements (zinc, copper, and selenium) but did not receive riboflavin, biotin, or vitamins A, D, and E.

On DOL 17, the patient developed unexplained metabolic acidosis with clinical decompensation requiring reintubation and initiation of vasoactive support. Abdominal radiographs and ultrasounds were negative for acute findings. Patient was noted to have anemia and thrombocytopenia requiring multiple blood product transfusions and persistent neutropenia. The abdomen remained distended during this time. Infectious workup was negative, and there was no improvement on broad-spectrum antimicrobial therapy. The neonate then developed widespread skin excoriation and breakdown during this time. Given clinical worsening with no clear etiology, the patient underwent a second surgery on DOL 27 for a repeat exploratory laparotomy. No acute intra-abdominal pathology was identified during the operation, and an ileostomy was created. Postoperatively, patient had persistent metabolic acidosis (despite maximal therapy including continuous infusion of sodium bicarbonate) and clinical illness. As in the second case, through attendance at our institution's morbidity and mortality conference in which the first case was discussed, the team at the outside institution became aware of deficiencies in TPN constituents and became concerned that riboflavin deficiency may be the etiology of decompensation. The patient was transferred to our institution for further management on DOL 28.

On arrival at our hospital, the patient's constellation of findings was assessed to be consistent with essential vitamin deficiency. Of note, at this point, the team at our institution was familiar with clinical results due to riboflavin deficiency, given our experience with multiple previous cases. TPN containing INFUVITE pediatric multivitamin and enteral repletion with riboflavin and carnitine supplementation were started. The patient responded promptly to therapy with resolution of metabolic acidosis and improvement in other clinical parameters within a few days of starting treatment.

Table 3 Summary of case 3 metabolic workup

Day of life	Workup
7, 21, 25	NBS 1, 2, and 3 while on TPN without pediatric multivitamin with elevated leucine
28	Acylcarnitine profile abnormal—suggestive of MADD/riboflavin transporter defect/riboflavin deficiency Transferred to our institution and started on TPN with INFUVITE pediatric multivitamin
29	Acylglycine profile normal
30	Acylcarnitine profile resent and remained abnormal
57	Acylcarnitine, acylglycine, plasma amino acid profile—all normalized
59	Genetic testing (MADD panel)—negative

Abbreviations: MADD, multiple acyl-CoA dehydrogenase deficiency; NBS, newborn screen; TPN, total parenteral nutrition.

The metabolic team followed this patient as well during admission. Workup for inborn errors of metabolism was negative—see ►Table 3 for an overview of the workup and ►Table 4 for detailed results. The patient was able to be extubated, weaned off vasoactive support, and hematologic parameters were normalized. The patient tolerated initiation of enteral feeds, which were advanced without difficulty with weaning off TPN, then was taken back to the OR with our pediatric surgical service for ileostomy take-down and re-anastomosis on DOL 77. Postoperatively, the patient was advanced without difficulty to full PO feeds and

discharged to home on room air and full PO enteral feeds on DOL 90.

Discussion

These cases highlight the harm that can be caused by shortage in critical TPN constituents. While the decision to change TPN constituents was made by the outside vendors due to shortages, this change was not systematically communicated to the clinical teams at the various referral sites. As a result, while portions of the administrative and leadership teams at each hospital were aware of the change, this was not clear to the bedside teams and as thus all three patients experienced adverse clinical effects and excessive and unnecessary investigation and therapies. In one case, a nondiagnostic and nontherapeutic surgical intervention resulted from the delay in diagnosis, as TPN constituent deficiencies were not readily apparent to the treating clinical teams. Previous shortages in TPN nutrients have had similar adverse effects on patients, and a recent case report by Mares Beltran et al also described riboflavin deficiency in a NICU patient with prolonged TPN dependence at an institution with shortages in TPN constituents.^{1,3,4}

A lack of essential nutrients can be devastating for patients who are entirely TPN dependent for nutrition. Among the critical nutrients in TPN, riboflavin (vitamin B2) is a water-soluble vitamin that is an essential component of two major coenzymes, flavin mononucleotide (also known as riboflavin-5'-phosphate) and flavin adenine dinucleotide.⁵ It is an essential nutrient that is not endogenously synthesized. Defects in the riboflavin metabolic pathway can lead to MADD.⁵ For critically ill TPN-dependent patients such as preterm infants

Table 4 Detailed abnormalities noted from metabolic workup in case 3

Laboratory test	Results (reference ranges)
Newborn screens	First NBS leucine 334 $\mu\text{mol/L}$ (< 250 $\mu\text{mol/L}$) Second NBS leucine 621.8 $\mu\text{mol/L}$ (< 250 $\mu\text{mol/L}$) Third NBS leucine 2,219.7 $\mu\text{mol/L}$ (< 250 $\mu\text{mol/L}$)
Admission metabolic laboratories	Carnitine, total: 7.77 $\mu\text{mol/L}$ (26–66 $\mu\text{mol/L}$) Carnitine, free: < 2.3 $\mu\text{mol/L}$ (21–53 $\mu\text{mol/L}$) C2, acetylcarnitine 9.53 $\mu\text{mol/L}$ (1.62–16.06 $\mu\text{mol/L}$) C4, butyrylcarnitine/isobutyrylcarnitine 0.89 $\mu\text{mol/L}$ (< 0.73 $\mu\text{mol/L}$) C5, isovalerylcarnitine/2-methylbutyrylcarnitine/pivaloylcarnitine 1.27 $\mu\text{mol/L}$ (< 0.39 $\mu\text{mol/L}$) C10:1 decenoylcarnitine 0.20 $\mu\text{mol/L}$ (< 0.18 $\mu\text{mol/L}$) Leucine 320 $\mu\text{mol/L}$ (48–160 $\mu\text{mol/L}$) Valine 337 $\mu\text{mol/L}$ (64–294 $\mu\text{mol/L}$)
Metabolic laboratories after initiation of riboflavin and carnitine supplementation/initiation of TPN with INFUVITE pediatric multivitamin	Carnitine, total: 82.6 $\mu\text{mol/L}$ (26–66 $\mu\text{mol/L}$) Carnitine, free: 72.3 $\mu\text{mol/L}$ (21–53 $\mu\text{mol/L}$) C2, acetylcarnitine 19.97 $\mu\text{mol/L}$ (1.62–16.06 $\mu\text{mol/L}$)—due to enteral carnitine supplementation C4, butyrylcarnitine/isobutyrylcarnitine 0.24 $\mu\text{mol/L}$ (< 0.73 $\mu\text{mol/L}$) C5, isovalerylcarnitine/2-methylbutyrylcarnitine/pivaloylcarnitine 0.24 $\mu\text{mol/L}$ (< 0.39 $\mu\text{mol/L}$) Leucine 121 $\mu\text{mol/L}$ (48–160 $\mu\text{mol/L}$) Valine 241 $\mu\text{mol/L}$ (64–294 $\mu\text{mol/L}$) Acylglycine profile—normal Urine organic amino acids—normal

Abbreviation: TPN, total parenteral nutrition.

in the NICU who are entirely dependent on TPN for extended periods of time, deficiencies in TPN constituents can have devastating effects, with a clinical/biochemical presentation that mimics inborn errors of metabolism. During previous times of shortages in TPN constituents, deficiencies in essential nutrients have had deleterious effects on TPN-dependent patients.^{1,6,7} The symptoms displayed by the patients in this report (particularly gastrointestinal difficulties, metabolic acidosis and hematologic abnormalities) were consistent with riboflavin deficiency, which can lead to biochemical and clinical findings that mimic MADD, but are easily corrected with riboflavin supplementation.⁸ However, none of the presentations was initially recognized as a result of essential nutrient deficiencies as other etiologies were pursued. This led to the patients undergoing extensive workups for an inborn error of metabolism and, in one case, undergoing an exploratory laparotomy before the underlying etiology was determined to be TPN related.

These cases highlight the challenges of diagnosis in the complex NICU population. Diagnosis is a multifaceted process that unfolds over time within the setting of the health care system, and as a result, diagnostic error is often difficult to quantify.^{9,10} As noted by the National Academy of Medicine, there is currently no universally accepted definition of diagnostic error, and in a fast paced, complex environment such as the NICU, the rapidly changing clinical status of a critically ill patient generates a constant barrage of new diagnostic data points making a determination of whether or not a diagnostic error occurred challenging.¹⁰ When evaluating these cases for the presence of a diagnostic error, the concept of *missed opportunities* can be applied.¹¹ In this framework, a diagnostic error occurs if there is unequivocal evidence of a missed opportunity during the diagnostic process to establish a timely and accurate diagnosis, regardless of if harm occurred.¹² This is important in neonatal intensive care as the often-prolonged stay in the NICU means that the underlying diagnosis is eventually discovered, as has been previously demonstrated by Shafer and Suresh.¹³ When evaluating for the presence of a diagnostic error in the NICU, it is crucial to determine if there was an opportunity to make the diagnosis at an earlier point in time—creating the potential for preventable harm.¹⁴

Evaluating these cases through this framework, all three would qualify as diagnostic errors. There were opportunities to identify the vitamin shortage in the TPN as the etiology of the patients' symptoms earlier. At each clinical site, there are multiple layers of review designed to avoid this type of error: multiple reviews of changes in TPN constituents by pharmacy, physician, and administrative committees, systems to provide clear communication of changes to all levels of clinicians providing care to the affected population, etc. These layers are designed to prevent adverse effects from reaching the patients, for example, the Swiss Cheese Model.¹⁵ Unfortunately, in each of the cases presented in this report, multiple layers of the hospital staff were unaware of the change. This led to gaps in the system which caused harm to all three patients who underwent additional unnecessary testing and interventions with a delay in initiation of treatment.

This emphasizes the need for clinicians to keep TPN-induced vitamin deficiencies as a potential etiology in the differential of TPN-dependent infants suspected to have metabolic disorders. This is evidenced by our experience with patient 1, where sharing our findings across our neonatology network led to a more rapid diagnosis of vitamin deficiency in the second and third cases leading to immediate treatment once these patients arrived at our institution. These cases were reviewed at our institution via our formalized review process for evaluating medical errors. Additionally, the individual referring clinicians were directly informed of the concern for TPN-induced riboflavin deficiency and clinical course at our institution. Feedback was also provided to the clinical leadership at each of the referring sites for further review as needed via the formal mechanisms at those institutions. The parents of each patient were also updated on our team's concerns and treatment plan after arrival to our institution. This closed loop communication ensured adequate awareness of the potential for TPN-induced riboflavin deficiency across our network, and to date, no additional cases have been noted.

Conclusion

TPN-related vitamin deficiency may be misdiagnosed as metabolic disorders in TPN-dependent NICU patients. Clinicians should maintain a high index of suspicion for iatrogenic deficiencies when treating patients with prolonged TPN dependence during the times of constituent shortages, as diagnostic errors in this population can have devastating consequences. This highlights the need to ensure proper access to all necessary TPN constituents or to implement proper mitigation strategies when intravenous—multivitamin preparations are not available, to avoid harm to this critically ill population.

Funding

None.

Conflict of Interest

None declared.

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