INDEX OF SUSPICION

Fever, Diarrhea, and Dehydration in a Term Neonate: Beyond Common Causes

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CASE PRESENTATION

A newborn baby boy is born at term via uncomplicated spontaneous vaginal delivery to first-degree cousins. Birth growth parameters include weight 3.4 kg (75th percentile), length 51 cm (75th percentile), and head circumference 35.5 cm (75th percentile), with Apgar scores of 9 at 1 minute and 5 minutes. Initial physical examination reveals a vigorous newborn with no dysmorphic features or congenital anomalies.

Breastfeeding begins within 1 hour postpartum. At 6 hours of life, the infant develops 3 loose, watery stools with abdominal distension despite preserved feeding reflexes and absence of vomiting or respiratory distress. By 12 hours, post-feeding diarrheal episodes persist with maintained hemodynamic stability. The clinical team recommends admission for monitoring and further workup, but the family elects discharge against medical advice on postnatal day 2 despite extensive counseling regarding potential risks.

Over the subsequent 72 hours at home, the neonate's condition deteriorates progressively. Watery bowel motions increase to 10 to 12 episodes daily with progressive abdominal distension, decreased wet diapers, and increasing lethargy. By postnatal day 5, the neonate is brought to the emergency department critically ill, requiring immediate admission to the neonatal intensive care unit.

On admission, the infant exhibits profound dehydration with sunken fontanelles, decreased skin turgor with delayed recoil exceeding 3 seconds, and capillary refill time greater than 4 seconds. Vital signs demonstrate hyperthermia of 38.9°C (102.0°F), tachycardia at 180 beats per minute, and severe weight loss to 2.7 kg (20% birth weight loss). The abdomen is distended but soft with no palpable hepatosplenomegaly. Neurological examination shows decreased responsiveness but preserved primitive reflexes. Otherwise, the physical examination is unremarkable.

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Laboratory investigations reveal extreme hypernatremia peaking at 188 mmol/L, severe metabolic acidosis (pH 7.18, bicarbonate 6.8 mmol/L), and acute kidney injury (urea 245 mg/dL, creatinine 1.8 mg/dL). Urinalysis demonstrates microscopic hematuria exceeding 100 red blood cells per high-power field. Stool analysis shows positive reducing substances (3+), acidic pH (5.2), and elevated sodium content (140 mmol/L) consistent with osmotic diarrhea. Inflammatory markers, including C-reactive protein and procalcitonin, yield negative results. Blood, urine and cerebrospinal fluid cultures are requested. Table 1 summarizes the initial investigations.

Immediate therapeutic interventions focus on judicious correction of the profound fluid and electrolyte imbalances, with meticulous attention to sodium correction at a rate below 0.5 mEq/L/h to mitigate the risk of cerebral edema, a potential catastrophic complication of rapid correction of chronic hypernatremia. Metabolic acidosis is addressed with sodium bicarbonate supplementation (2 mEq/kg) alongside rehydration therapy, with careful monitoring of calcium and magnesium levels during treatment.

Given the clinical presentation suggestive of possible sepsis, empirical antimicrobial therapy is initiated with ampicillin and cefotaxime, intentionally avoiding gentamicin because of its known nephrotoxicity in the setting of acute kidney injury. Subsequent microbiological investigations, including blood and cerebrospinal fluid cultures, as well as inflammatory markers, yield negative results, prompting discontinuation of antimicrobial therapy after 72 hours.

Nutritional support is established via total parenteral nutrition to ensure adequate caloric and nutrient provision during the period of intestinal rest, providing necessary

TABLE 1. Initial Investigations

Test	Result	Normal Range
Sodium (initial)	177 mmol/L (177 mEq/L)	135–145 mmol/L (135–145 mEq/L)
Sodium (peak)	188 mmol/L (188 mEq/L)	135–145 mmol/L (135–145 mEq/L)
Potassium	4.2 mmol/L (4.2 mEq/L)	4.0–7.9 mmol/L (4.0–7.9 mEq/L)
Chloride	110 mmol/L (110 mEq/L)	100–111 mmol/L (100–111 mEq/L)
Calcium (ionized)	4.6 mg/dL (1.15 mmol/L)	4.2–5.5 mg/dL (1.05–1.37 mmol/L)
Magnesium	2.1 mg/dL (0.85 mmol/L)	1.7–2.4 mg/dL (0.72–1.00 mmol/L)
Phosphorus	5.9 mg/dL (1.9 mmol/L)	5.6–8.0 mg/dL (1.8–2.6 mmol/L)
Venous pH	7.18	7.35–7.45
Bicarbonate	6.8 mmol/L (6.8 mEq/L)	22–26 mmol/L (22–26 mEq/L)
Urea	245 mg/dL (87.4 mmol/L)	7–20 mg/dL (2.5–7.1 mmol/L)
Creatinine	1.8 mg/dL (159 μmol/L)	0.3–0.7 mg/dL (27–62 μmol/L)
Hemoglobin	16.8 g/dL (168 g/L)	13.4–19.9 g/dL (134–199 g/L)
Hematocrit	52% (0.52)	42–65% (0.42–0.65)
White blood cells	12.5×10^3/μL (12.5×10^9/L)	$9.0–30.0 \times 10^3$/μL ($9.0–30.0 \times 10^9$/L)
Neutrophils	7.2×10^3/μL (7.2×10^9/L)	$6.0–26.0 \times 10^3$/μL ($6.0–26.0 \times 10^9$/L)
Lymphocytes	4.5×10^3/μL (4.5×10^9/L)	$2.0–11.0 \times 10^3$/μL ($2.0–11.0 \times 10^9$/L)
Monocytes	0.8×10^3/μL (0.8×10^9/L)	$0.4–1.8 \times 10^3$/μL ($0.4–1.8 \times 10^9$/L)
Platelets	131×10^3/μL (131×10^9/L)	$150–450 \times 10^3$/μL ($150–450 \times 10^9$/L)
Albumin	3.2 g/dL (32 g/L)	2.8–4.4 g/dL (28–44 g/L)
AST	42 U/L (42 U/L)	16–55 U/L (16–55 U/L)
ALT	18 U/L (18 U/L)	1–23 U/L (1–23 U/L)
Alkaline phosphatase	285 U/L (285 U/L)	130–831 U/L (130–831 U/L)
Total bilirubin	8.5 mg/dL (145 μmol/L)	<1.4 mg/dL (<24 μmol/L)
Glucose	78 mg/dL (4.3 mmol/L)	70–150 mg/dL (3.9–8.3 mmol/L)
Urinalysis		
Red blood cells	>100/hpf	0–2/hpf
Stool analysis		
Reducing substances	3+	Negative
pH	5.2	6.0–7.5
Sodium	140 mmol/L (140 mEq/L)	<20 mmol/L (<20 mEq/L)
C-reactive protein	<3 mg/L (<3 mg/L)	<7 mg/L (<7 mg/L)
Procalcitonin	<0.25 ng/mL (<0.25 μg/L)	<0.25 ng/mL (<0.25 μg/L)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

macronutrients, micronutrients, and electrolytes required for growth and metabolic stability. Following stabilization and correction of metabolic derangements, cautious reintroduction of enteral nutrition is attempted with breast milk, followed by systematic trials of lactose-free formula, extensively hydrolyzed formula, and amino acid-based formula. Notably, the neonate exhibits immediate recurrence of profuse diarrhea following exposure to breast milk and all tested formulas, confirming formula-resistant diarrhea. The persistent feeding intolerance necessitates continued nil per os status with ongoing total parenteral nutrition while comprehensive diagnostic evaluation proceeds for suspected congenital diarrhea syndrome.

Metabolic diseases screening, including amino acid profile, acylcarnitine analysis, and organic acid quantification, reveals no abnormalities. Neuroimaging and renal ultrasonography demonstrate normal findings. Abdominal radiograph shows diffuse bowel distension without pneumatosis intestinalis. Further evaluation ultimately establishes the diagnosis.

DISCUSSION

Differential Diagnosis

The presentation of neonatal fever with hypernatremia and severe diarrhea necessitates systematic evaluation of congenital, infectious, and metabolic etiologies. Neonatal sepsis, initially suspected because of fever and lethargy, is excluded following negative blood, urine, and cerebrospinal fluid cultures, normal inflammatory markers, and resolution of fever with rehydration rather than antimicrobial therapy. Lactose intolerance and cow's milk protein allergy are unlikely given the lack of improvement with specialized formulas.

Necrotizing enterocolitis is ruled out by the absence of pneumatosis intestinalis on abdominal imaging, which remains the pathognomonic radiographic finding for this condition.[1] Congenital chloride diarrhea (CCD), a rare autosomal recessive disorder, is dismissed based on normal stool chloride level, as well as acidic stool pH, which is inconsistent with CCD's characteristic alkaline stools.[2] CCD presents with metabolic alkalosis rather than the metabolic acidosis observed in this case.

Microvillus inclusion disease and tufting enteropathy, which are congenital enteropathies causing intractable diarrhea, are considered but are typically associated with secretary rather than osmotic diarrhea.[3] The 2025 multicenter study by the PediCODE Consortium has significantly advanced understanding of congenital diarrhea and enteropathies (CODEs), identifying novel genetic causes in nearly 48% of cases through next-generation sequencing.[4] This represents a remarkable improvement from previous diagnostic yields and highlights the importance of early genetic evaluation in suspected CODE cases.

The infant's fever, initially suggestive of sepsis, is attributed to hypernatremia-induced hypothalamic thermoregulatory dysfunction.[5] Plasma hyperosmolality exceeding 375 mOsm/kg activates osmoreceptors in the anteroventral third ventricle, cross-stimulating thermoregulatory neurons and triggering prostaglandin-independent fever, a mechanism distinct from infectious pyrogens. Recent research has confirmed that hypernatremia can cause noninflammatory hyperthermia in critically ill patients, independent of systemic inflammation.

Microscopic hematuria arises from hypercalciuria and acute tubular injury, secondary to renal hypoperfusion in the setting of severe dehydration and acute kidney injury.[6]

The constellation of findings, including striking hypernatremia, extreme dehydration, and characteristic stool analysis showing positive reducing substances with acidic pH, provides crucial diagnostic clues for distinguishing between various causes of intractable neonatal diarrhea.

Actual Diagnosis

The pattern of persistent diarrhea that remains unresponsive to systematic trials of various specialized formulas, including lactose-free, extensively hydrolyzed protein and amino acid-based formulas, strongly suggests an underlying congenital malabsorption syndrome. After extensive diagnostic investigations yielded negative results, whole exome sequencing is conducted at 4 weeks of age. The genetic analysis identifies a homozygous variant in the SLC5A1 gene (c.866G>A; p.Trp289Ter), which results in truncation of the SGLT1 protein at transmembrane domain 5, confirming glucose-galactose malabsorption (GGM). Subsequent parental genetic testing confirmed heterozygosity for this variant in both parents, establishing a pattern consistent with autosomal recessive inheritance.

The Condition

GGM is an extremely rare autosomal recessive disorder caused by pathogenic mutations in the SLC5A1 gene, which encodes the sodium–glucose cotransporter 1 (SGLT1) responsible for active, sodium-dependent absorption of glucose and galactose across the intestinal brush-border membrane.[7] Typically manifesting within the first days of life on initiation of lactose-containing feeds, it presents with profuse osmotic diarrhea exceeding 600 mL/kg/d, rapid-onset dehydration with hypernatremia often above 160 mmol/L, metabolic acidosis, and failure to thrive.[7] Structurally, SGLT1 comprises 14 transmembrane helices arranged in an APC-fold configuration, with key residues such as R499 and

Q457 essential for sodium binding and sugar translocation; truncating or missense mutations disrupt proper protein folding, membrane trafficking, and substrate binding, leading to complete transporter dysfunction.[8,9] Laboratory evaluation consistently reveals an acidic stool pH (<6.0), strongly positive reducing substances (3+), elevated stool sodium concentrations, and a high stool osmotic gap alongside normal inflammatory markers and negative microbiological studies. Definitive diagnosis relies on molecular genetic testing; over 80 pathogenic SLC5A1 variants have been documented. Management mandates strict elimination of glucose and galactose from the diet, using fructose-based formulas such as Galactomin 19 or carbohydrate-free preparations supplemented with fructose to bypass the defective SGLT1 pathway via GLUT5 transporters, resulting in rapid diarrhea resolution and fluid-electrolyte normalization within 24 to 48 hours.[7] Long-term outcomes are excellent when dietary restrictions are initiated early, with most patients achieving normal growth and neurodevelopment; however, ongoing monitoring for metabolic complications of chronic high-fructose intake, such as hepatic steatosis, is essential.

Solid foods are introduced between 4 and 6 months of age, emphasizing low-glucose, high-fructose options such as pureed peas, carrots, pears, and applesauce, with each new item offered singly over 3 to 5 days to assess tolerance, with vigilance for hidden glucose in sauces or additives. Long-term nutrition focuses on a high-fat, moderate-protein, low-carbohydrate regimen to sustain energy needs while preventing osmotic diarrhea.[10] Continuous collaboration with a pediatric dietitian ensures ongoing evaluation of growth parameters, macronutrient balance, and adjustment of dietary recommendations as children age, including cautious reintroduction trials of minimal glucose sources under supervision.

Treatment and Follow-Up

Following confirmation of GGM, we immediately initiate international procurement of the specialized fructose-based formula Galactomin 19 because no local or alternative supplies are available. Table 2 summarizes commercially available formulas suitable for patients with GGM. Galactomin 19 is the only commercially available formula specifically designed for GGM. Despite logistical hurdles causing a 2-week delay in delivery, we commence feeding at 120 kcal/kg/d on receipt. Within 24 hours of starting the fructose-only formula, diarrhea resolves completely, and daily weight gain resumes at 20 to 25 g, highlighting the decisive impact of targeted dietary therapy in GGM management. One week after initiating targeted therapy, the infant is discharged home in stable condition and continues close outpatient monitoring.

By 3 months of age, he shows marked clinical improvement, and laboratory tests reveal normal serum electrolytes, restored renal function, and complete resolution of past microscopic hematuria. At 6 months of age, he attains substantial nutritional rehabilitation, reaching the 50th percentile for both weight and height; solid foods are introduced and advanced under dietitian guidance without recurrence of diarrhea. At 2 years, comprehensive evaluation confirms excellent adaptation to the fructose-based regimen with appropriate ongoing weight gain. Neurodevelopmental assessment demonstrates achievement of all age-appropriate milestones.

LESSONS TO THE CLINICIAN

- Severe hypernatremia (Na+>160 mmol/L) may induce a prostaglandin-independent fever via hypothalamic osmoreceptor activation; in neonates with negative sepsis workup, fever resolves promptly with fluid resuscitation and sodium correction.
- First-degree consanguinity significantly raises the risk of autosomal recessive disorders such as GGM; early genetic tests can shorten dependency on total parenteral nutrition and reduce morbidity if the diagnosis is not clear.
- Facilities should maintain an inventory of specialized formulas including fructose-based formulas (eg, Galactomin

TABLE 2. Commercially Available Milk Formulas for Patients With GGM

Formula Name	Manufacturer	Primary Carbohydrate Source	Protein Source	GGM Suitability	Requires Supplementation	Global Availability
Galactomin 19	Nutricia	Fructose	Cow's milk protein (calcium caseinate, sodium caseinate)	High—specifically designed for GGM	No	Europe, Australia, Middle East, some Asian countries
RCF	Abbott	No added carbohydrate	Soy-based	High—when supplemented with fructose	Yes—fructose must be added	United States, Australia, limited global distribution
3232A	Mead Johnson	No added carbohydrate	Casein hydrolysate (from milk)	High—when supplemented with fructose	Yes—fructose must be added	United States, limited global distribution

Abbreviations: GGM, glucose-galactose malabsorption; RCF, Ross Carbohydrate Free.

19) and pursue subsidy programs to mitigate procurement delays and financial burdens on families managing rare metabolic conditions.

- Microscopic hematuria in hypernatremic dehydration often signals tubular injury from renal hypoperfusion and possible hypercalciuria, underscoring the necessity of prompt, meticulous rehydration to avert acute kidney injury.
- A strict exclusion of both glucose and galactose from the diet is essential, particularly during the early years of life.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the congenital malformations of the gastrointestinal system in regards to bilirubin.
- Recognize disorders of acid-base balance.

References

1. Neu J, Walker WA. Necrotizing enterocolitis. *N Engl J Med*. 2011;364(3):255–264. PubMed doi: 10.1056/NEJMra1005408
2. Konishi KI, Mizuochi T, Yanagi T, et al. Clinical features, molecular genetics, and long-term outcome in congenital chloride diarrhea: a nationwide study in Japan. *J Pediatr*. 2019;214:151–157.e6. PubMed doi: 10.1016/j.jpeds.2019.07.039
3. Elkadri AA. Congenital diarrheal syndromes. *Clin Perinatol*. 2020;47(1):87–104. PubMed doi: 10.1016/j.clp.2019.10.010
4. Gaibee Z, Warner N, Bugda Gwilt K, et al. The genetic architecture of congenital diarrhea and enteropathy. *N Engl J Med*. 2025;392(13):1297–1309. PubMed doi: 10.1056/NEJMoa2405333
5. Ng PC, Chan HB, Fok TF, et al. Early onset of hypernatraemic dehydration and fever in exclusively breast-fed infants. *J Paediatr Child Health*. 1999;35(6):585–587. PubMed doi: 10.1046/j.1440-1754.1999.00428.x
6. Barman H, Das BK, Duwarah SG. Acute kidney injury in hypernatremic dehydration in exclusively breastfed babies: don't ignore it! *J Clin Neonatol*. 2014;3(2):124–125. PubMed doi: 10.4103/2249-4847.134716
7. Wang W, Wang L, Ma M. Literature review on congenital glucose-galactose malabsorption from 2001 to 2019. *J Paediatr Child Health*. 2020;56(11):1779–1784. PubMed doi: 10.1111/jpc.14702
8. Faham S, Watanabe A, Besserer GM, et al. The crystal structure of a sodium galactose transporter reveals mechanistic insights into Na+/sugar symport. *Science*. 2008;321(5890):810–814. PubMed doi: 10.1126/science.1160406
9. Lostao MP, Loo DD, Hernell O, et al. The molecular basis of glucose galactose malabsorption in a large Swedish pedigree. *Function (Oxf)*. 2021;2(5):zqab040. PubMed doi: 10.1093/function/zqab040
10. Chan AP, Namjoshi SS, Jardack PM, et al. Long-term dietary changes in subjects with glucose galactose malabsorption secondary to biallelic mutations of SLC5A1. *Dig Dis Sci*. 2021;66(12):4414–4422. PubMed doi: 10.1007/s10620-020-06792-4