Short Communication

Blue Babies with a Red Flag: Methemoglobinemia as a Sentinel Sign of Cow's Milk Protein Intolerance in Infants – A retrospective Case Series

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ABSTRACT

Background: Cow's milk protein intolerance (CMPI), often referred to as cow's milk protein allergy (CMPA), is among the most prevalent food hypersensitivities in children, typically manifesting with gastrointestinal symptoms, including diarrhea and vomiting. Methemoglobinemia is an exceedingly rare complication of CMPI, a life-threatening illness marked by the pathological oxidation of hemoglobin, resulting in impaired tissue oxygen transport and clinically observable cyanosis. Since the precise pathophysiologic mechanism linking intestinal inflammation to methemoglobin accumulation remains unclear, this uncommon association poses diagnostic and therapeutic challenges. This study was done to describe the clinical presentation, diagnostic evaluation, and outcomes of infants with methemoglobinemia due to CMPI, to facilitate early identification and prompt dietary intervention. **Materials and Methods:** A retrospective case series of 6 infants with methemoglobinemia associated with CMPI is presented here. All patients were either term or late preterm infants with a history of formula or combination feeding. Clinical and laboratory data, encompassing symptomatology, acid-base status, and sequential methemoglobin levels, were systematically evaluated. **Results:** All six newborns exhibited diarrhea, metabolic acidosis, and elevated methemoglobin levels, with a median methemoglobin concentration of 26% (range 11–30.7%). The therapeutic intervention involved transitioning to extensively hydrolyzed or amino acid-based elemental formulations, together with pharmaceutical treatment of methylene blue and/or ascorbic acid (vitamin C). All patients had full clinical and biochemical remission within 2-3 days of initiating medication. **Conclusion:** CMPI must be included in the differential diagnosis of unexplained infantile methemoglobinemia. Timely recognition and removal of cow's milk protein from the diet, along with appropriate pharmacological treatment, can lead to rapid and lasting recovery.

Key words: Methemoglobinemia, Diarrhea, Infantile, Milk Hypersensitivity, Food Hypersensitivity, Methylene Blue.

Cow's milk protein allergy (CMPA) is the most prevalent food allergy in neonates and infants, affecting approximately 2–3% of children in early childhood [1]. Clinical manifestations, including vomiting and/or diarrhea, typically emerge within the first month of life and may be accompanied by failure to thrive, metabolic acidosis, and hemodynamic compromise [2]. CMPA is predominantly mediated through IgE or non-IgE antibody pathways, with both cow's milk and soy proteins recognized as significant triggers of allergic enterocolitis. The delayed-onset, non-IgE-mediated variant is characteristically dominated by gastrointestinal symptomatology, with cutaneous and respiratory manifestations being comparatively infrequent [1]. Transient methemoglobinemia with concurrent metabolic acidosis, though reported with CMPA, this occurrence remains exceedingly uncommon in neonates [3].

Methemoglobinemia is a time-critical cause of apparent hypoxemia in infancy, arising from pathological oxidation of hemoglobin iron to the ferric state (Fe^{3+}), which impairs oxygen binding and peripheral tissue delivery, clinically manifesting as cyanosis and disproportionately low pulse oximetry (SpO_2) readings relative to the degree of respiratory compromise. Infants are inherently predisposed to this condition owing to developmental deficiency of Nicotinamide Adenine Dinucleotide Phosphate (NADPH-cytochrome b5 reductase, the principal enzyme responsible for reducing methemoglobin to functional oxyhemoglobin, compounded by elevated dietary nitrate exposure and the heightened oxidative susceptibility of fetal hemoglobin [4].

Within the spectrum of acquired methemoglobinemia, acute diarrheal illness and enterocolitis have been increasingly recognized as precipitating triggers, wherein intestinal inflammation promotes the proliferation of nitrate-reducing bacteria that generate nitrites capable of oxidizing circulating hemoglobin [5, 6].

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Cow's milk protein intolerance (CMPI) associated non-IgE-mediated enterocolitis represents a particularly underrecognized driver of this phenotype. Dietary antigen exposure perpetuates mucosal inflammation and gut dysbiosis, sustaining intestinal nitrite generation and producing cyanosis refractory to supplemental oxygen therapy [7, 8]. Physiologic methemoglobin levels are maintained below 1–2%; elevations exceeding 10% produce clinically apparent cyanosis, while concentrations surpassing 20–30% are associated with symptomatic tissue hypoxia necessitating urgent intervention [4, 9]. Recognition of this pathophysiological cascade is clinically imperative, as SpO_2–PaO_2 discordance on pulse oximetry, wherein SpO_2 readings are falsely reassuring despite true tissue hypoxia, may misdirect clinicians toward cardiopulmonary diagnoses, critically delaying the definitive intervention of cow's milk protein elimination.

Management of CMPI-related methemoglobinemia necessitates a dual approach addressing both the underlying allergic enteropathy and the acute hematological disturbance. The fundamental aspect of treatment is the immediate removal of cow's milk protein by switching to extensively hydrolyzed or amino acid-based elemental formulas, which target the underlying intestinal inflammatory process, reduce ongoing nitrite formation, and avert recurrence [4, 7, 8, 10]. In cases of acute methemoglobinemia, intravenous methylene blue (MB) in a dosage of 1–2 mg/kg is the primary pharmacological antidote, functioning as an electron carrier that converts methemoglobin back to functional oxyhemoglobin through the NADPH -dependent methemoglobin reductase pathway. Ascorbic acid (vitamin C) acts as an auxiliary or alternative agent, especially in circumstances where methylene blue is inaccessible or contraindicated, operating via a gradual, NADH-independent reduction pathway [9, 11].

Supportive interventions, such as the correction of metabolic acidosis and hemodynamic stability, are essential to holistic therapy. Although there are isolated case reports detailing this unusual relationship, comprehensive case series outlining the complete clinical profile, therapeutic approaches, and outcomes of CMPI-associated methemoglobinemia are scarce in the literature [3, 5, 7, 8]. This study offers a systematic examination of six consecutive instances, intending to improve early clinical identification and formulate evidence-based management procedures for this diagnostically complex illness.

MATERIALS AND METHODS

This was a retrospective case series undertaken at the newborn Intensive Care Unit (NICU) of Rainbow Children's Hospital, Hyderabad. The study was done from January 2022 to December 2025. A total of 73 neonates admitted with suspected or confirmed CMPI during the study period were evaluated for eligibility. Six instances of simultaneous methemoglobinemia resulting from CMPI were diagnosed and incorporated into the final analysis. The cases were verified by examining the admission diagnoses, electronic laboratory records for increased methemoglobin levels using co-oximetry, and discharge summaries indicating a diagnosis of CMPI or CMPA.

The inclusion criteria were infants under 60 days old, presenting with gastrointestinal symptoms indicative of non-IgE-mediated CMPI or CMPA, such as diarrhea, vomiting, or both, and with a verified methemoglobin (MetHb) level of ≥10% on arterial or venous blood co-oximetry. A confirmatory diagnosis of CMPI was established by the diagnostic criteria of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) for non-IgE-mediated CMPA, characterized by the alleviation of gastrointestinal symptoms and the normalization of MetHb levels following a transition to an extensively hydrolyzed or amino acid-based elemental formula [12]. Ten cases were excluded upon identification of an alternative etiology for methemoglobinemia, including congenital MetHb reductase deficiency (determined by enzyme assay or molecular testing), hemoglobin M disease, exposure to oxidizing agents, or administration of MetHb-inducing medications (e.g., benzocaine or nitrates).

Data was collected utilizing a standardized, pre-structured case report form to ensure uniformity and mitigate bias. The collected variables encompassed patient demographics (gestational age, birth weight, sex, and age at presentation); comprehensive feeding history (type of formula and duration of cow's milk protein exposure); clinical presentation (characteristics and duration of symptoms, vital signs, and SpO_2 on room air); laboratory investigations (arterial blood gas (ABG) analysis, serum lactate, complete blood count, MetHb levels via co-oximetry, serum electrolytes, and renal and liver function tests); treatment specifics (MB dosage, ascorbic acid administration, and formula replacement); and clinical outcomes such as time to MetHb normalization and total length of hospitalization. Descriptive statistics were employed for all analyses owing to the small sample size characteristic of this uncommon clinical entity. The Institutional Ethics Committee of Rainbow Children's Hospital provided a waiver of informed consent due to the retrospective nature of this study.

RESULTS

The index clinical condition in all six newborns was methemoglobinemia, manifesting as cyanosis and/or oxygen saturation disproportionately low relative to respiratory examination, in the setting of acute diarrheal illness suggestive of enterocolitis. Six infants aged 20–44 days (median 28 days; three boys, three females) had recently been fed intact cow's milk protein-based formula, either exclusively (Cases 4 and 5) or mixed formula and breastfeeding. All newborns were late preterm or term, ranging from 36 to 38 weeks. In all six cases, diarrhea was present. Additional features included vomiting, tachypnea, cyanosis, failure to thrive, and fever (Table 1).

ABG analysis revealed metabolic acidosis in all infants, with arterial pH ranging from 7.00 to 7.20 and base excess ranging from −11 to −24 mmol/L. Co-oximetry confirmed significantly elevated MetHb levels in all six cases, ranging from 11% to 30.7%, with a median of 26%. Extended metabolic screening, including glucose-6-phosphate dehydrogenase (G6PD) assay, was normal in all infants, excluding G6PD deficiency as a predisposing factor. Stool examination was done in all six infants and consistently showed evidence of intestinal inflammation. Pus cells were present in the feces of all six infants (10 to 30 cells per high power field. Positive occult blood was observed in cases 1, 3, 4, and 6, and fat globules were seen in cases 2, 3, and 6, demonstrating fat malabsorption compatible with enterocolitis. Fecal calprotectin was elevated in three infants (Cases; 1: 280 µg/g, 3: 320 µg/g, and 4: 290 µg/g), consistent with substantial intestinal mucosal inflammation as the mechanistic substrate for MetHb generation. Weight-gain trajectories across the cohort demonstrated recovery following dietary intervention, achieving 20-30 g per day at discharge. At three-month follow-up, all six infants demonstrated satisfactory weight gain on hypoallergenic formulas: weights ranged from 3.55 kg (Case 2, with BW 1.7 kg) to 4.9 kg (Case 1), consistent with catch-up growth trajectories.

Management followed a dual-pronged strategy targeting both the methemoglobinemia and the underlying cow's milk protein enterocolitis. With respect to dietary intervention, all six infants had intact cow's milk protein eliminated and were transitioned to an extensively hydrolyzed formula (EHF; Aptamil Pepti) or, in cases with severe enterocolitis, to an amino acid–based elemental formula (AAF; *Neocate LCP*). Breastfeeding was continued concurrently in Cases 1, 2, 3, and 6, with maternal dietary elimination of cow's milk protein advised. For Cases 4 and 5, who were exclusively formula-fed, complete formula substitution was achieved. Regarding pharmacological management, MB was administered intravenously at a dose of 1–2 mg/kg per dose in Cases 1, 3, and 4. Case 1 required three doses of MB, given the highest MetHb level of 30.7% and a prolonged clinical course, with MetHb normalization achieved over 48–72 hours. Cases 3 and 4 each received two doses of MB with a prompt response within 24 hours. Ascorbic acid was administered intravenously at a dose of *100–200 mg/day* in Cases 2, 3, and 4 as an adjunctive agent. Cases 5 and 6 had lower MetHb levels (11% and 24%, respectively) and were managed with dietary elimination alone without pharmacological antidote therapy, both achieving MetHb normalization within 48 hours.

Clinical exome sequencing was performed in three of the six infants (Cases 1, 4, and 5) and returned normal results in all three, effectively excluding congenital causes of methemoglobinemia such as cytochrome b5 reductase deficiency or hemoglobin M variants in these patients. In other cases, it was deferred by parents for one of the following reasons: rapid recovery with formula feed elimination, and financial constraints. All six infants had full clinical and biochemical recovery. Normalization of MetHb levels was observed before the remission of gastrointestinal symptoms, with MetHb levels reverting to the physiological range (<2%) within 24 to 72 hours of initiating combination dietary and pharmacological treatment. Diarrhea and vomiting resolved within three to five days.

The duration of hospitalization ranged from 3 to 16 days (median, 6 days; mean, 7.2 days). Case 1, the outlier with 16 days of hospitalization, exhibited the highest MetHb level (30.7%), the most severe metabolic acidosis (pH 7.1, BE -19), and was administered three doses of MB, corroborating the established relationship between MetHb burden and clinical severity and supporting a lower threshold for antidote initiation in infants with levels approaching 20–30%. No fatalities, enduring neurological sequelae, or recurrences were seen during the follow-up period. All infants were discharged on hypoallergenic formulas, with concurrent breastfeeding maintained when feasible, and a systematic outpatient follow-up scheduled for one and three months. Table 1 shows the clinical and biochemical features of the study participants during the study period.

Table 1. Clinical and laboratory characteristics of infants presenting with methemoglobinemia

Case	Sex	GA (weeks)	Age (days)	BW (kg)	AW (kg)	Clinical Features	Feeding	MetHb (%)	pH	BE (mmol/L)	Management	LOS (day)	3moWt (kg)
1	M	37.8	20	3.47	3.29	Diarrhea, vomiting, tachypnea, cyanosis	F+BF	30.7	7.1	-19	BF/HF + MB	16	4.9
2	M	38	38	1.7	2	Diarrhea, FTT	F+BF	19	7.2	-16.5	BF/HF + VC	6	3.55
3	F	37.2	24	2.5	2.47	Diarrhea, vomiting, cyanosis	F+BF	28	7	-24	BF/HF + MB + VC	7	3.9
4	F	36	28	2.1	2.36	Diarrhea, tachypnea, cyanosis	F	28	7.1	-18	HF + MB + VC	6	3,9
5	M	36	28	2.9	2.65	Diarrhea, fever	F	11	7.2	-11	HF	3	4.25
6	F	36.2	44	3	3	Diarrhea, vomiting, FTT, tachypnea	F+BF	24	7.1	-17	BF/HF	5	4.5

Abbreviations: GA: Gestational Age, BW: Birth Weight, AW: Admission Weight, BF: Breastfeeding, F: Formula, HF: Hydrolyzed Formula, MetHb: Methemoglobin, BE: Base Excess, MB: Methylene Blue, VC: Vitamin C, FTT: Failure To Thrive, LOS: Length Of Stay.

DISCUSSION

This retrospective case series represents one of the largest single-center cohorts systematically characterizing methemoglobinemia as a presenting manifestation of CMPI-associated enterocolitis in young infants. Methemoglobinemia was the sentinel presenting feature in all six infants, preceding or overshadowing the recognition of the underlying dietary intolerance, underscoring the diagnostic risk of anchoring on cardiopulmonary etiologies in cyanotic infants with diarrhea. MetHb normalized within 24–72 hours of initiating combined dietary elimination and pharmacological therapy, with complete gastrointestinal resolution by day three to five, no mortality, and satisfactory catch-up growth trajectories at three-month follow-up [9,11].

The seminal report by Murray and Christie first delineated the association between dietary protein intolerance and methemoglobinemia with diarrhea in three infants, documenting resolution following protein elimination and establishing the foundational pathophysiological hypothesis of enteric nitrite generation [3]. Kurian et al. subsequently described a single neonate presenting with methemoglobinemia attributable to CMPA, corroborating the causal link and emphasizing the diagnostic importance of co-oximetry in neonates with unexplained cyanosis, consistent with the diagnostic approach employed in the present series [7]. Bahabri et al. extended this phenotype to the broader food protein–induced enterocolitis syndrome (FPIES) spectrum, reporting a life-threatening presentation with methemoglobinemia requiring urgent MB therapy and advocating for elemental formula as the definitive dietary intervention [8]. Similarly, Malin et al. described FPIES-triggered hypovolemic shock concurrent with methemoglobinemia, highlighting the potential for hemodynamic compromise to compound the clinical picture, a feature observed in the present cohort in Cases 1 and 3, both of whom presented with cyanosis and severe acidosis [13]. The case series by Jajoo et al., comprising four infants with acquired methemoglobinemia associated with acute diarrhea, reported a comparable MetHb range and clinical trajectory, though their cohort was not restricted to CMPI as the etiological substrate, precluding direct dietary attribution in all cases [5].

The present series is distinguished from prior reports by its larger cohort size, systematic stool inflammatory profiling, structured documentation of weight-gain trajectories, and uniform application of ESPGHAN diagnostic criteria for non-IgE-mediated CMPA, lending greater diagnostic rigor and clinical completeness. Across all series, a consistent theme emerges that MB remains effective and rapidly acting in moderate-to-severe methemoglobinemia (MetHb ≥20%), while dietary elimination is the indispensable definitive intervention without which recurrence is inevitable, findings fully mirrored in the present cohort [9,11].

Though warranted by the rarity of this clinical entity, the limited sample size of six instances restricts statistical power and generalizability. All six infants were not uniformly tested for congenital methemoglobinemia, including cytochrome b5 reductase enzyme assay and molecular testing. While the acquired clinical context and complete resolution with dietary elimination make a congenital etiology unlikely in the untested cases, this omission represents a methodological gap. Without a control group, causal inference is limited. Future research should prioritize multicenter prospective registries to correctly estimate CMPI-associated methemoglobinemia incidence, characterize risk factors for susceptible infants, and establish consensus pharmacological intervention levels.

CONCLUSION

Methemoglobinemia, though rare, is a potentially life-threatening manifestation of CMPI in early infancy that demands prompt recognition. The diagnostic triad of cyanosis, diarrhea, and cow's milk protein exposure should trigger urgent co-oximetry, with immediate dietary elimination and targeted pharmacotherapy yielding rapid and complete recovery without sequelae.

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