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A cross-sectional ED survey of infantile subclinical methemoglobinemia*

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To the Editor

The prevalence of clinically significant methemoglobinemia (MHb) is unknown among previously healthy infants presenting to the emergency department (ED) with diarrhea and dehydration. However, it is well described in these infants and, when present, can be associated with significant morbidity [1-4]. Nevertheless, it may not be clinically apparent until levels reach almost 7 times normal levels [5]. Based on this, we hypothesized that dehydrated infants younger than 3 months with diarrhea would commonly have MHb levels above normal but below that causing cyanosis and obvious distress.

We conducted a cross-sectional study of MHb in acyanotic dehydrated infants with diarrhea and a comparison group of well-hydrated febrile infants, all 3 months old or younger, presenting to an urban pediatric ED. The age group and severity of illness of the dehydrated patients were chosen for the highest likelihood of MHb [3]. A sample size of 10 was needed in each group, with a one-tailed α level of .05 and power of 80% to detect a mean group MHb level of $5\% \pm 5\%$. (An MHb level of 5% was chosen as a cutoff level for which symptoms are likely to occur but clinical signs will not be evident.)

A convenience sample was enrolled during 1 year from among age-appropriate patients with diarrhea and diagnosis of dehydration as determined by the on-duty attending pediatric emergency physician. Diarrhea was defined as 3 or more loose or watery stools in the prior 24 hours. Degree of dehydration was established by the use of a generally accepted pediatric

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emergency dehydration scale [6]. Well-hydrated comparison patients were selected from a convenience sample of well-hydrated infants in the same age range undergoing a fever evaluation. Patients were excluded if they had a history of MHb, an acidemia-inducing illness (eg, metabolic disorder), or received oxidizing medication via breast milk or direct ingestion.

The research was approved by the hospital's institutional review board. Written informed consent was obtained from the parents of all infants. The study was conducted at the Children's National Medical Center General Clinical Research Center.

Thirty patients were approached for enrollment and 3 parents refused (1 in the dehydration group and 2 in the fever group). We enrolled a total of 27 subjects: 10 with dehydration and 17 febrile patients. The mean age of the entire study population was 59 ± 29 days; 70% were boys. The 2 groups were demographically similar (Table 1). The prevalence of subclinical MHb (sMHb) (ie, MHb $>1.5\%$) was 2 of 10 (20%; 95% CI, 2.5-55.6) dehydrated subjects and 1 of 17 (5.9%; 95% CI, 0.2-28.7) well-hydrated comparison patients ($P = \text{NS}$). It is noteworthy that of the patients with sMHb, the 2 dehydrated patients had levels of 5.9% and 6%, whereas the single well-hydrated patient had a level of 1.9%.

None of the potential risk factors for sMHb were significantly associated with group designation. Among all 27 patients enrolled, χ^2 analysis and the Student t test revealed the following factors significantly associated with sMHb: lower mean body weight percentile ($P = .027$) and higher mean chloride level ($P = .033$) (Table 2).

Despite the often described MHb etiology of oxidant stress from enteritis, it remains unclear why an otherwise healthy infant with diarrhea develops MHb when another does not. Traditionally, acidemia from dehydration has been thought to be the underlying factor in these children [7-13]. Despite this, a single inciting factor for methemoglobinemia in these patients has not been identified and several factors are thought to play a contributory role. First, by virtue of enzymatic immaturity, infants have only slightly more than half of the functioning MHb reductase levels of healthy adults [14]. In addition, fetal hemoglobin is more easily oxidized than adult hemoglobin. Finally, the high pH level in an infant's gut promotes the growth of nitrite-producing flora that can lead to added oxidative stress.

In this investigation, we identified a potentially clinically important, but not statistically significant, difference in the prevalence of sMHb and degree of elevation between an ED group of dehydrated infants and a group of well-hydrated infants. The lack of statistical significance for this finding is prone to type II error given the small sample size. Of note, it is not clear whether the elevated MHb levels in either group are causal for morbidity or merely an indicator of disease status. The lack of a true control group (ie, healthy infants) is an additional limitation.

Previous studies of infantile MHb had included obviously ill or hospitalized patients [12]. These had only limited applicability to ED patients, in whom sMHb is probably more likely to go unsuspected and therefore undetected before disposition. Our data provide a first estimation of the prevalence of elevated MHb levels in dehydrated infants with diarrhea presenting to the ED.

References

- [1]. Babbitt CJ, Garrett JS. Diarrhea and methemoglobinemia in an infant. *Pediatr Emerg Care* 2000;16:416-7. [PubMed: 11138885]
- [2]. Gebara BM, Goetting MG. Life-threatening methemoglobinemia in infants with diarrhea and acidosis. *Clin Pediatr* 1994;33:370-3.
- [3]. Lebby T, Roco JJ, Arcinue EL. Infantile methemoglobinemia in infants with diarrhea and acidosis. *Am J Emerg Med* 1993;11:471-2. [PubMed: 8363684]

- [4]. Oski JA. A 5-week-old infant with cyanosis, diarrhea, and dehydration. Case report. *Curr Opin Pediatr* 1995;7:73–6. [PubMed: 7728207]
- [5]. Lanir A. Transient methemoglobinemia with acidosis and hyper-chloremia in infants. *Am J Pediatr Hematol Oncol* 1986;8:353–5. [PubMed: 3799938]
- [6]. Shaw, KN. Dehydration. In: Fleisher, GR.; Ludwig, S., editors. *Textbook of pediatric emergency medicine*. Vol. 4th ed. Lippincott, Williams & Wilkins; Philadelphia: 2000. p. 197-202.
- [7]. Bricker T, Jefferson LS, Mintz AA. Methemoglobinemia in infants with enteritis [Letter]. *J Pediatr* 1983;102:161.
- [8]. Danish EH. Methemoglobinemia in infants with enteritis [Letter]. *J Pediatr* 1983;102:162–3.
- [9]. Hanugloku A, Fried D, Dodner D. Methemoglobinemia in infants with enteritis [Letter]. *J Pediatr* 1983;102:161–2.
- [10]. Lebby T, Roco JJ, Acinue EL. Infantile methemoglobinemia associated with acute diarrheal illness. *Am J Emerg Med* 1993;11:471–2. [PubMed: 8363684]
- [11]. Seeler RA. Methemoglobinemia in infants with enteritis [Letter]. *J Pediatr* 1983;102:162.
- [12]. Pollack ES, Pollack CV. Incidence of subclinical methemoglobinemia in infants with diarrhea. *Ann Emerg Med* 1994;24:652–6. [PubMed: 8092592]
- [13]. Yano SS, Danish EH, Hsia YE. Transient methemoglobinemia with acidosis in infants. *J Pediatr* 1982;100:415–8. [PubMed: 7062175]
- [14]. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;34:646–56. [PubMed: 10533013]

Table 1

Demographics and clinical variables by group

	Dehydrated	Febrile	Significance
Male sex [n (%)]	7 (70)	12 (71)	RR = 0.99 (0.59 to 1.64)
Breastfed [n (%)]	4 (40)	13 (76)	RR = 0.53 (0.24 to 1.18)
Median age (d [IQR])	64 [38-84]	52 [32-81]	$P = .69$
Mean weight (percentile)	52 $\pm$ 36	61 $\pm$ 30	$P = .55$ (-22 to 39) ^a
Mean temperature (°C)	38.2 $\pm$ 1	38.4 $\pm$ 1	$P = .66$ (-1 to 1) ^a
Mean pulse (beats/min)	175 $\pm$ 24	164 $\pm$ 16	$P = .23$ (-30 to 8) ^a
Mean respirations (beats/min)	41 $\pm$ 8	41 $\pm$ 10	$P = .98$ (-7 to 7) ^a
Mean oxygen saturation (arterial) (%)	99 $\pm$ 2	99 $\pm$ 1	$P = .33$ (-1 to 2) ^a
Median dehydration level (%) [IQR]	5 [5-10]	0 [0-0]	$P < .001$
Total	10	17	

^aThe 95% CI of the difference in the means.

Table 2

Clinical and laboratory measurements by presence of sMHb

	MHb >1.5%	MHb ≤1.5%	Significance
Breastfed [n (%)]	0 (0)	8 (33)	OR = 0.07 (0.00 to 1.54)
Median age (d [IQR])	55 [42-59]	62 [36-86]	$P = .64$
Mean weight (percentile)	20 ± 9	63 ± 30	$P = .027$ (5 to 79) ^a
Mean temperature (°C)	38.7 ± 0.5	38.2 ± 1	$P = .22$ (1.3 to -0.4) ^a
Median dehydration level (% [IQR])	10 [0-10]	0 [0-5]	$P = .10$
Mean anion gap	11 ± 3	12 ± 5	$P = .68$ (6 to -8) ^a
Mean pH	7.25 ± 0.09	7.34 ± 0.07	$P = .25$ (0.13 to -0.29) ^a
Mean hemoglobin (g/dL)	10.3 ± 1.2	11.8 ± 2.2	$P = .13$ (0.7 to -3.7) ^a
Mean chloride (mEq/dL)	114 ± 11	106 ± 5	$P = .033$ (15 to 1) ^a
Total	3	24	

^aThe 95% CI of the difference in the means.