Methemoglobinemia and Consumption of Vegetables in Infants

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ABSTRACT. Objective. To assess clinical and epidemiologic data of 7 infants diagnosed with acquired methemoglobinemia at the pediatric emergency department between 1993 and 1998. All cases were attributed to the consumption of mixed vegetables.

Methods. Medical records were reviewed to collect anamnestic data; history of food ingestion; and results of physical examination, pulse oximetry, gasometry, cooximetry, urinalysis, and outcome. Local health authorities provided information on nitrate concentration in running water and in vegetables of common consumption in the area.

Results. The mean age of the patients was 8.14 months (range: 7–13). None of the infants was undernourished, had diarrhea, or was given any drug. Drinking water showed a nitrate concentration of 3 to 6 ppm. All were fed homemade purée of mixed vegetables, prepared in advance and kept in the refrigerator for 12 to 27 hours. Silver beets were a common ingredient. No case showed metabolic acidosis. Methemoglobin level ranged between 10% and 58%. Three cases had nitruria. Silver beets in our area were the vegetables with the highest nitrate concentration (mean: 3200 mg/kg).

Conclusions. Consumption of silver beets and incorrect storage of homemade purées of mixed vegetables were potential causes of methemoglobinemia in this series. The disease may occur in children older than 6 months of age. Nitruria in a cyanotic infant may suggest the diagnosis of methemoglobinemia.

METHODS

The clinical records of 7 infants diagnosed with methemoglobinemia at the pediatric emergency department of Hospital de Cruces in Barakaldo, Bizkaia (Basque Country, Spain) over a 5-year period (1993–1998) were retrospectively reviewed. Our institution is an acute care teaching hospital with 90 beds for children. Approximately 40 000 pediatric emergencies are attended per year.

For each case, the following data were recorded: date of admission to the emergency department, age, sex, weight, place of residence, reason for consultation and associated symptoms, feeding characteristics in the last days, foods ingested in the previous 24 hours, exposure to drugs, results of laboratory investigations, treatment, and outcome. Data from physical examination and laboratory tests included pulse rate and oxygen saturation (SaO₂) measurements using a Ohmeda Biox 3740 pulse oximeter (Ohmeda, Madrid, Spain); blood pH, oxygen partial pressure, SaO₂, and bicarbonate by capillary gasometry; urine nitrite using a reagent strip (Multistix 10SG, Bayer, Elkhart, IN); and in the presence of a blood specimen that remained a chocolate brown color, plasma concentrations of total hemoglobin (Hb), oxidized Hb, and methemoglobin using an Instrumentation Laboratory IL-682 Cooximeter (Lexington, MA).

At the time of performing this study, family members of the 7 patients were contacted by phone to assess the occurrence of additional episodes of cyanosis. In addition, the Health Department of the Basque Country provided information on the concentration of nitrates in the drinking water as well as results of chemical analyses in different groups of foods for the period from 1990 to 1995. Nitrate and nitrite ions were determined by the rapid strong anion exchange high-performance liquid chromatography/ultraviolet procedure described by Dennis et al. This method has a quantification limit of 5 mg/kg with a coefficient of uncertainty of ±5%.
RESULTS

Data of the 7 infants with methemoglobinemia are shown in Table 1. The mean age of the patients was 8.14 months (range: 7–13 months). The 7 infants lived in different urban populations in which nitrate concentration in the running water varied between 3 and 6 ppm (mg/L). Three of the cases occurred in August 1997 and the remaining 4 cases in different months (July, November, December, and February). At the time of consultation, none of the patients was undernourished and all of them showed a body weight above the 10th percentile for age and sex. Exposure to drugs in the days before admission was not recorded either. In all patients, milk formulas had been prepared with tap water. On the day of admission, all children were fed a homemade purée of mixed vegetables in which in addition to silver beets, carrots were included in 4 cases and pumpkin and green beans in 3 cases. In all cases, the purée had been prepared in advance and kept refrigerated for 12 to 72 hours.

All patients presented to the emergency department because of cyanosis of the lips associated with vomiting in 2 infants and irritability in 1. None of the patients had diarrheal disease before hospitalization or during his/her stay in the hospital. On admission, tachycardia (between 150 and 195 beats/min) was present in all patients together with tachypnea in 1. Initial \( \text{Sa}_2 \) levels measured by pulse oximetry ranged between 82% and 96% and were higher than those measured by cooximetry. Although blood gas measurements were performed by capillary extraction, oxygen partial pressure values did not correspond to \( \text{Sa}_2 \) concentrations detected with the cooximeter. No case presented with metabolic acidosis. All infants had total Hb levels within normal limits. The methemoglobin fraction ranged between 10% and 58.2%. The highest level of methemoglobin was registered in the patient with tachypnea. Urine nitrite was positive in 3 cases (42.8%), although a correlation with methemoglobin levels was not found. Treatment consisted of 100% oxygen therapy and intravenous administration of methylene blue. In cases 3 and 5 with methemoglobin levels of 17% and 10%, respectively, only 100% oxygen was given. All patients recovered promptly and were discharged from the hospital between 12 and 24 hours after admission. The telephone survey confirmed that none of the patients showed additional episodes of cyanosis. The content of nitrate ions of some vegetables frequently consumed in our geographical area and expressed as mg/kg (ppm) is shown in Figs 1 and 2.

DISCUSSION

Clinical features of methemoglobinemia are well known and have been frequently reported in the pediatric literature. Acquired methemoglobinemia is the most common cause and has been related to different conditions, such as diarrhea (of infectious origin or secondary to cow milk protein intolerance)
and acidosis\textsuperscript{8–12}; consumption of high-nitrate water (contaminated or well water that is mixed with infant formula),\textsuperscript{4,5,13} or high-nitrate food (spinach, carrots, beets),\textsuperscript{3–5,14,15} food-borne nitrates and nitrites (used as food preservative because they inhibit the growth of \textit{Clostridium botulinum})\textsuperscript{16,17}; exposure to certain drugs\textsuperscript{1,4,18} including topical anesthetic agents (benzocaine, eutetic mixture of local anesthetics, procaine, lidocaine) and silver nitrate, chloroquine, sulfonamides, dapsone, phenacetin, sodium valproate, phenazopyridine, inhaled nitrous oxide, amyl nitrite, as well as acute nitrite toxicity resulting from accidental exposure to aniline dyes, coloring compounds or cleaning solutions.\textsuperscript{19}

In the cases reported here, the rare causes of hereditary methemoglobinemia (methemoglobin reductase deficiency, hemoglobinopathies) can be excluded because of the absence of an additional episode of cyanosis. In the group of acquired methemoglobinemias, those caused by exposure to drugs or domestic products were excluded by anamnesis. Acute toxicity resulting from consumption of high-
nitrate water seems highly improbable because all children lived in urban populations in which composition of potable water was strictly controlled (nitrate concentration in the running water of 3–6 ppm was clearly below the maximum tolerated limit of 45 ppm). Moreover, unexpected contamination of running water would have been followed by outbreaks of toxic methemoglobinemia—a fact that was not observed. In contrast, the relation between methemoglobinemia and diarrhea is well known with or without some degree of metabolic acidosis in infants, particularly in those with weight at or below the 10th percentile for age. However, none of these circumstances occurred in our patients.

Therefore, alimentary methemoglobinemia seems the most plausible cause. Methemoglobinemia associated with consumption of high-nitrate infant food has been reported frequently. However, it should be noted that all our children were >6 months old (mean age: 8.14 months). Infants younger than 6 months old are particularly susceptible to nitrate-induced methemoglobinemia because of low gastric pH, persistence of fetal Hb, large numbers of nitrite-reducing bacteria, and immaturity of the reduced nicotinamide adenine dinucleotide-reductase system, so that it is likely that some of these factors may persist beyond this age. Second, although the amount of nitrate of each vegetable given to the children was not analyzed, in all cases, the puree of mixed vegetables was made of silver beets. As shown in Fig 1, silver beets showed the highest mean nitrate ion levels (3200 mg/kg) compared with the other vegetables that were analyzed, reaching up to 6300 mg/kg in samples analyzed in the month of August (Fig 2), when 3 of the 7 cases of methemoglobinemia occurred. The other 4 cases occurred in February, November, July, and December, with nitrate ion concentrations in silver beets >2000 mg/kg. As a reference, mean nitrate ion content of spinach was 2700 mg/kg with only 200 mg/kg in the month of August. In contrast to that found in other countries, carrots in our area have a low nitrate concentration. Other authors have already reported differences in nitrate composition of greens even in different areas of the same country. This may be related to characteristics of soil composition, farming, and especially to the use of nitrogenous fertilizers. Therefore, it is important to know which are the vegetables with high nitrate concentration in each particular region for appropriate counseling on infant feeding during the first year of life.

Although alimentary methemoglobinemia caused by consumption of commercial infant food of mixed vegetables has not previously been reported (eg, enzyme complexes in spinach able to reduce nitrites to nitrites are destroyed in the food production process), an increase in nitrate concentration may occur in purees of greens prepared in advance and stored in the refrigerator. Changes in the biochemical composition of some vegetables associated with an increase in temperature and poor ventilation during storage, transport, and canning have been described. Accordingly, purees of mixed vegetables kept in cold (refrigerated) storage is not advisable.

This type of infant food should be prepared for immediate use or should be kept frozen when consumption is delayed for more than 24 hours. Nitrituria in the 3 of the 7 cases was another interesting finding. After ingestion, nitrites are rapidly absorbed from the intestine and may be detected early in the urine because of their extrahepatic metabolic pathway (60%–70% of nitrites are excreted in the urine in the first 24 hours after ingestion). Although nitrituria has a low sensitivity (as in the case of infection of the urinary tract), given the high specificity of this parameter it may be useful in the diagnosis of methemoglobinemia, particularly in the extrahospital setting.

CONCLUSION

Consumption of silver beets and incorrect storage of homemade purees of mixed vegetables were identified as potential causes of acquired infantile methemoglobinemia; age at risk is not limited to the first 4 to 6 months of life; and detection of nitrituria in a cyanotic infant may suggest the diagnosis of methemoglobinemia.

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REFERENCES


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**IT’S OFFICIAL: EVALUATIVE RESEARCH MUST BECOME PART OF ROUTINE CARE IN THE NHS**

“The recently published *National Health Service (NHS) Plan* sets out some core principles on which the NHS is to be based. One states that the NHS “will work continuously to improve quality services and to minimize error,” and that “healthcare organizations and professions will establish ways to identify procedures that should be modified or abandoned and new practices that will lead to improved patient care.” Another states that the NHS will “provide open access to information about services, treatment, and performance,” and that it will ”continue to use information to improve the quality of services for all and to generate new knowledge about future medical benefits.” These are important and welcome statements of principle, both for those who agree with Archie Cochrane that the results of rigorous evaluative research should inform policies and decisions in the NHS, and for those who have argued that secrecy about the effects of licensed drugs is incompatible with a professed commitment to promoting the health of the public.


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