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Investigation of Pediatric Anemia in the Commonwealth of the Northern Mariana Islands

Tiffany F. Lin[1,2,3] · James N. Huang[1,2] · Haley L. Cash[4]

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Abstract
Objective To report on the prevalence and etiology of pediatric anemia in the Commonwealth of the Northern Mariana Islands (CNMI). *Method* A retrospective chart review was conducted that included patients up to 19 years of age who presented for well child care and whose hemoglobin or hematocrit was checked in the CNMI from 2014 to 2015. Lab values, diagnoses and treatment plans, patient reported ethnicity, and follow-up results were collected from eligible patients. *Results* The records for 1483 pediatric patients who had 1584 well child visits were reviewed. The prevalence of anemia amongst all eligible patients was 8.0% (5.4–10.7). This included 292 9 to 18 months old patients, which is estimated to be 40% of the total pediatric population of CNMI in that age group. Among the 9 to 18 months old patients, the prevalence of anemia is 5.5% (2.6–8.4). Etiology of anemia was investigated and of the patients treated with iron, 55.2% had a documented response. The majority of those without documentation of improvement with iron were patients who were lost to follow-up. In addition, a total of 10 patients were found to have an alpha or beta thalassemia variant discovered initially by anemia screening or sibling tracing. *Discussion* In this United States Commonwealth, prevalence of anemia appears lower than prevalence reported for other independent Pacific Island nations and closer to that of the US. Thalassemia is documented within this population. Limitations to this data were use of a convenient sample that may be hampered by lack of presentation to well-child care. This study will guide future public health studies on anemia prevalence and can guide public health intervention decisions to improve pediatric care in the CNMI.

Keywords Pediatric anemia · CNMI · Pacific Island · Anemia prevalence

Significance

The Pacific Islands face a unique challenge to public health as a set of disparately governed territories with differing populations and diets. Information about pediatric anemia prevalence and etiology will help drive public health interventions for prevention and treatment of anemia. This article contributes information about the Commonwealth of the Northern Mariana Islands' (CNMI) pediatric anemia prevalence.

✉ Tiffany F. Lin
tiffany.lin@ucsf.edu

[1] UCSF Benioff Children's Hospital, San Francisco, USA

[2] Department of Pediatrics, University of California San Francisco, 550 16th Street, Box 0434, San Francisco, CA 94143, USA

[3] Commonwealth Healthcare Corporation, Saipan, Northern Mariana Islands, USA

[4] Regional Epidemiology Unit, Pacific Island Health Officers Association, Honolulu, HI, USA

Introduction

The World Health Organization (WHO) defines anemia as a hemoglobin concentration less than 11.0 g/dl in children age 6 months to < 5 years, < 11.5 g/dl in children 5 to < 12 years old, and < 12.0 g/dl in children 12 to < 15 year olds (WHO 2011). The disease of anemia is most prevalent amongst children and women of childbearing age. Anemic pregnant women are at increased risk for delivering low birth weight and preterm infants (Rahman et al. 2016). In children, anemia of any etiology may lead to significant functional deficit because it can affect physical growth and educational success during childhood—a critical time period in development (Lozoff et al. 2000).

Anemia can arise from either nutritional or non-nutritional causes. Of the nutritional causes of anemia, iron deficiency is the most common. Deficiency of iron, even if not severe enough to cause anemia, can impact children and their academic performance (Lozoff et al. 2000; Halterman et al. 2001). Globally, however, roughly half the cases of anemia arise due to non-iron deficiency causes (WHO 2011). Other conditions leading to anemia include infections such as malaria, HIV, or parasitic infections and hemoglobinopathies such as sickle cell anemia or thalassemia.

In order to address the preventable sequelae of anemia of any type, both the etiology and prevalence of anemia in the community must be established to help guide measures for effective screening and treatment of the disease. Universal screening for anemia by testing of hemoglobin or hematocrit levels is recommended for infants aged 12 months in the US (Baker and Greer 2010). Anemia identified by routine hemoglobin screening in infants has been widely treated with a therapeutic trial of iron and a follow-up test, but this method of treatment can be challenging due to difficulty with adherence, especially in low-income and resource-limited settings (Geltman et al. 2009). In addition, a decline in iron deficiency anemia in the US is changing the predictive value of those initial screening tests. The decline in iron deficiency anemia globally and in the US has been attributed to increased iron fortification and nutritional supplementation via programs such as Women, Infant, and Children (WIC; Yip et al. 1987). As the prevalence of iron deficiency anemia decreases, the other causes of anemia make up a larger proportion of the overall cases. Identification of infectious and genetic causes of anemia can be delayed if a therapeutic trial of iron is tried first, and worse, morbidity of some of those diseases can be exacerbated by treatment with iron. For example, thalassemia patients are iron-avid secondary to their disease and exogenous iron exposure can lead to iron overload later in life (Gupta et al. 2018).

Amongst the majority of the Pacific Islands for which pediatric anemia data are available, the prevalence of pediatric anemia is higher than 20%, qualifying it as a moderate public health problem (Lin et al. 2017). The CNMI is a US territory in the Pacific Ocean composed of three populated islands just north of the equator. The most populated of these islands is Saipan with a population of 48,220, followed by Tinian (3136) and Rota 2527) (US Department of Commerce 2012). The current CNMI response to anemia noted on screening is based on guidelines from the US. However, the CNMI population differs significantly from the continental US, in that the population is composed almost exclusively of Pacific Islander and Asian ethnicities. Of the persons who identified as being of one ethnic origin in the 2010 CNMI census, 39.9% identified as "Native Hawaiian or Other Pacific Islander" and 57.2% identified as "Asian" (US Department of Commerce 2012). In the continental US, Pacific Islanders and Asians experience decreased access and presentation to care in comparison with non-Hispanic Whites (Snyder et al. 2016). Moreover, CNMI pediatric anemia rates have not been reported, nor has the etiology been explored. We therefore undertook this study to determine the current coverage of patients screened for anemia and estimate the prevalence and underlying etiology of anemia in the CNMI.

Methods

A retrospective chart review was conducted that included Children's Clinic patients that were seen between October 2014 and October 2015. The Children's Clinic at the Commonwealth Healthcare Corporation (CHCC) is the only exclusively pediatrician staffed clinic in the CNMI. The clinic treats any patient from birth to age 18 years. CHCC is the only hospital in the CNMI and is located on the most populated island of Saipan. Eligible patients for chart review were those who had presented for well child visits. The time period selected was used because of the ready availability of all the data in the electronic medical record during those dates. Prior to that date, records were kept by hand and were not reliably complete. Eligible visits were defined as those coded in ICD9 or ICD10 for well child checks, physical examination, immunization update, or general health examination as their primary diagnosis.

Each eligible visit was reviewed to exclude duplicate patient data that were collected within the study period. If a unique patient had multiple visits within the study period, the first visit with a hemoglobin or hematocrit tested was the only visit that was included. If no lab results were available or ordered, the patient was only counted once towards the total number of patients evaluated.

Data Collected

Of those eligible visits identified on chart review, patient demographics were recorded including age, unique patient identifier, and family-reported ethnicity. Data on whether hemoglobin and/or hematocrit tests were ordered by the provider, whether tests were performed, whether follow-up found evidence of iron deficiency or thalassemia, and follow-up lab results were all recorded. Recording any available hemoglobin electrophoresis result, newborn screen result, or globin gene mutation analysis for all eligible patient charts was done to collect evidence of thalassemia.

Screening and Testing Protocols for Anemia

In the CNMI it is routine practice for patients to be seen for well child checks whenever they receive their routine

immunizations, which includes multiple visits in infancy, at 12 months, and 15–18 months. After age 2 to 4, routine practice is to see the patient annually for their well child care. Screening for anemia during the included study period followed American Academy of Pediatrics (AAP) guidelines. Namely, routine anemia screening with hemoglobin or hematocrit levels was recommended for all patients seen for well child visits between age 9 and 15 months and a second screen was performed between 2 and 4 years of life. Testing for anemia is recommended later at other times by provider discretion only. Lab testing occurred at the CHCC Lab in the same building as the Children's Clinic.

Data Interpretation and Standard Practice for Anemic Patients

The counts of patients who qualified as anemic, received follow-up, responded to iron therapy, or were lost to follow-up were recorded. The presence of anemia was identified on the basis of positive screens for anemia based on the age-appropriate cutoffs as recommended by the US Preventative Services Task Force (USPSTF) and the WHO. If a patient was found to have anemia, the family was called to discuss the results and based on the history and physical, iron was prescribed or dietary changes were recommended and follow-up testing was planned. Documentation of any contact or attempted contact with the family for that follow-up was recorded. Families unable to be contacted after two attempts were deemed lost to follow-up. No patients declined therapy. Any complete blood counts, hemoglobin or hematocrit levels, reticulocyte counts, iron or ferritin levels that occurred within 6 months after the initial positive anemia screen were also recorded. Response to iron supplementation was defined as a documented increase in 1.0 g/dl of hemoglobin within 6 months of initial diagnosis if iron supplementation or dietary changes were prescribed.

For patients found to have thalassemia based on testing results, sibling tracing and testing were routinely performed as part of standard of care and to complete genetic counseling.

Population Data

We gathered information on population from two sources. Using the data from a local public health report on annual local birthrate in 2014 (Dela Cruz 2015), we estimate that 725 children residing in the CNMI should have turned 1 year of age during the study period. Of note, birthrate population data are separated into tourist and non-tourist births in the CNMI. For the purpose of this calculation, we used only the non-tourist births due to the fact that tourist birth children will more than likely stop receiving well-child care in the CNMI after infancy. As of the 2010 census, the CNMI had 18,611 individuals under the age of 19 (US Department of Commerce 2012). Calculations of percentage of population seen used the aforementioned population data as denominators. A confidence interval of 95% was calculated for each prevalence data point.

Approval for a retrospective chart review was obtained via University of California San Francisco's (UCSF) Institutional Review Board. The CHCC and the CNMI Department of Public Health gave UCSF proxy rights in light of a lack of a Local Institutional Review Board.

Results

There were a total of 1584 visits that met our coding definitions of well child checks during the study period that encompassed 1483 unique patients. The 1483 unique patients evaluated within the year-long study period therefore comprise approximately 8.0% of the expected pediatric (< 19 years) population of the CNMI.

There were 432 orders for blood tests that included hemoglobin and/or hematocrit levels with 402 of those orders actually drawn. Of the 402 hemoglobin or hematocrit levels checked, 238 were done in the subset of children 9–18 months old.

Those meeting the age-appropriate criteria for anemia were identified. The prevalence of anemia amongst all the pediatric patients included in the study was 8.0% (95% CI 5.4–10.7; Table 1). Of the individual patients with anemia

Table 1 Well child visits, anemia screening, and anemia prevalence from October 2014 to October 2015 at CHCC's Children's Clinic

Age groups	Documented well child visits	Hemoglobin/hematocrit levels tested, N	Anemia, N	Prevalence within patients tested in age group (95% CI)
Birth to under 5 years	1382	373	30	8.0% (5.3–10.8)
5 years to under 10 years	53	14	0	0.0%
10 years to under 15 years	21	7	1	14.3% (0–40.2)
15 years to under 19 years	27	8	1	12.5% (0–22.9)
Total	1483	402	32	8.0% (5.4–10.7)

identified for this study, the vast majority (93.2%) were between the ages of birth and 5 years.

Of the anemic patients found during the study period, three patients were found to harbor thalassemic globin mutations. One of the three patients was started on iron supplements prior to receiving the results of the mutation studies. Seven additional patients were found to have thalassemic mutations based on sibling tracing, newborn screen results, or microcytosis without anemia. Thus, a total of 10 patients were diagnosed with having a thalassemic variant during the time period of data collection—eight with alpha globin mutations and two with beta thalassemia mutations (Table 2). The majority (8 out of 10) of the patients with these diagnoses identified as Filipino but one of the patients with alpha thalassemia trait (heterozygous for –/SEA deletion) identified as Chamorro and one of the patients with alpha thalassemia trait (heterozygous for total deletion) identified as both Chamorro and Carolinian.

Of the remaining patients with anemia not identified as having a thalassemia variant, 23 of the 29 (79.3%) were treated with iron for presumptive iron deficiency anemia (Fig. 1). Six were unable to be contacted in order to recommend iron supplementation. Of the 23 treated with iron, 16 responded to iron and the remaining were lost to follow-up. Overall, 55.2% of all children with presumed iron-deficiency anemia both received iron supplementation and were followed up to verify a response to treatment.

In an effort to isolate patients who had hemoglobin checked based on routine screening recommendations rather than clinical judgment, we analyzed the subset of patients from ages 9 to 18 month old. For this subanalysis, an upper limit of normal of 18 months was chosen to be inclusive of as many patients as possible that would have been sent for screening in the 9 to 15 month age period. A total of 292 9 to 18 months old children were part of the subanalysis

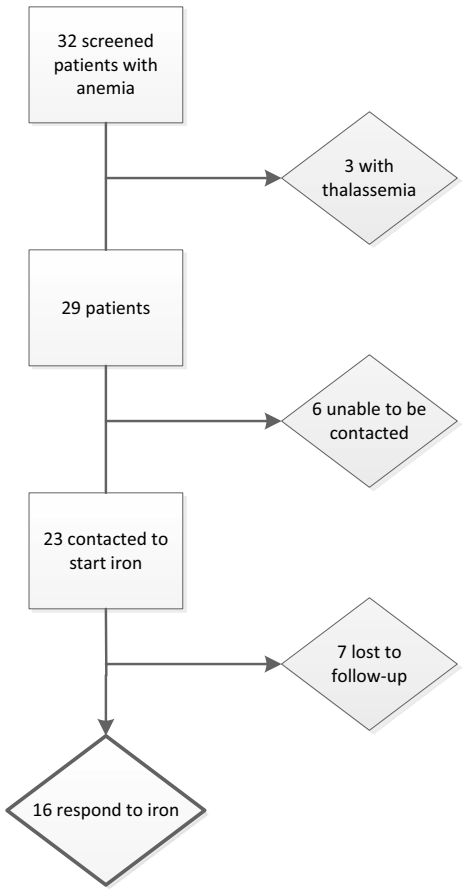

Fig. 1 Identification of iron deficiency anemia—treatment responses in patients without thalassemia

(Table 3). Of those, 238 (81.5%) patients had their hemoglobin or hematocrit levels tested. Using the data from a local public health report on annual local birthrate in 2014 (Dela Cruz 2015), we estimate that we covered approximately 40.3% (292/725) of the children in CNMI who should have turned 1 year of age during the study period. Amongst those 238 patients who had hemoglobin screens

Table 2 Hemoglobinopathy findings in from October 2014 to October 2015 at CHCC's Children's Clinic

Hemoglobinopathy diagnosis	Number of patients	Mutation result or method of diagnosis
Beta thalassemia trait	2	Consistent hemoglobin electrophoresis result
Alpha thalassemia trait	3[a]	–SEA/αα
	2[b]	–/αα
	1	$-\alpha^{3.7}\alpha/-\alpha^{3.7}\alpha$
Silent alpha thalassemia carrier	2	$-\alpha^{3.7}\alpha/\alpha\alpha$

[a]One of these patients identified as Chamorro

[b]One of these patients identified as both Chamorro and Carolinian

Table 3 Well child check anemia screening results for 9 to 18 month old patients from October 2014 to October 2015 at CHCC's Children's Clinic

Age	2014 Non-tourist CNMI birthrate	Unique patients seen for well child visits (% of 2014 births)	Patients with hemoglobin/hematocrit levels (% of well visits)	Positive screens for anemia	Prevalence among those screened (95% CI)
9 to 18 months	725	292 (40.3)	238 (81.5)	13	5.5% (2.6–8.4)

sent between age 9 to 18 months, 13 screened positive for anemia. Therefore the prevalence of anemia was found to be 5.5% (95% CI 2.6–8.4) amongst the 9 to 18 months old children seen during the study.

Discussion

Guidelines for anemia screening in pediatric patients were made with the intention to appropriately diagnose and treat anemic patients at an early age. In the US, anemia screening through hemoglobin/hematocrit testing has been recommended for high-risk pediatric patients, although there are now differing opinions due to the decreasing prevalence of iron deficiency anemia (Yip 1998). For example, the AAP currently recommends universal screening at age 12 months (Baker and Greer 2010). The USPSTF concluded that there is insufficient evidence to assess the risks and benefits of screening for iron deficiency anemia universally secondary to the lower prevalence of anemia (McDonagh et al. 2015). High-risk patients are often defined as patients who come from populations with high rates of iron deficiency anemia or populations who are at high risk for nutritional deficiencies of any kind. Examples include preterm infants, children with special healthcare needs, or breastfed infants who do not receive iron rich foods after 6 months of life. Whether CNMI should recommend universal screening for anemia is unclear because the rate of anemia had not been known. The CNMI population differs from US general population and this difference makes it imprudent to extrapolate recommendations from the US directly to the CNMI. Importantly, the reported prevalence of anemia in Pacific Islands is high (Lin et al. 2017). In this study we attempted to establish the baseline prevalence of anemia to guide screening recommendations in the CNMI population.

Using a convenient clinical sample of the pediatric population from October 2014 to October 2015 at CHCC's Children's Clinic, the prevalence of anemia was 8.0%.

Outside of the under 5 age group, 28.7% of these well child visits had hemoglobin/hematocrit level tested (N = 29 of the 101 total patients seen that were greater than 5 years old). Patients who presented for well-child care in the CNMI in the older age group were likely to have chronic medical conditions, which are a known risk factor for anemia and could have falsely skewed the data (Weiss and Goodnough 2005). By contrast, a larger proportion of those younger than age 5 are likely to present to care and receive screening due to their need for mandatory immunizations. The lack of sufficient pediatrician availability contributes to the low rate of presentation to medical care in well children above the age of 5 and the preferential care provided to those with chronic medical diseases. Hence, the prevalence of anemia in patients seen at CHCC above the age of 5 years is likely not representative of the pediatric population as a whole.

In order to attempt to remove the selection bias for including chronically ill children, we analyzed the subset of patients aged 9–18 months and found that the prevalence of anemia among this age group in the CNMI is 5.5%. This prevalence estimate still has limitations due to the potential bias of our convenient clinical sample. While there were no specific exclusion criteria, eligible patients may have been automatically excluded if their visit diagnosis was coded incorrectly. The 9–18 month sample comprised an estimated 40.3% of all patients who should have been screened if universal screening were fully implemented during the 1-year period of evaluation. In this age group, it is likely that those patients who had the resources to present to care have a higher socioeconomic level or improved food security. Those factors which are associated with lower risks of anemia, so 5.5% likely represents a low boundary for the prevalence of anemia in this infant and toddler population in the CNMI.

Well-child care is one of the main avenues by which public health screening and monitoring of ones' pediatric population occurs. The convenient sample here comprised 40.3% of that expected well-child population and suggests room for improvement in compliance with well-child care. If there is an increase in that compliance in the future, this study should be repeated to validate or confirm the accuracy of this study's convenient sample.

One additional strategy to more comprehensively screen for anemia and to include children in lower socioeconomic strata is to partner with organizations that also serve high-risk patients. More high-risk infants and toddlers may be captured by collaborating with the WIC program (the special supplementation nutrition program for WIC). In calendar year 2016, 41% of the mothers with live births (N = 1017) were on Medicaid, a surrogate for eligibility for the WIC program. As WIC can perform point of care testing for anemia, the prevalence of anemia in their population would be a useful comparison and help provide a more complete view of the overall prevalence of anemia in children of this age group. We sought to partner with the WIC program for this study but their anemia data was not available for review.

Historically, anemia in Pacific Islander populations has been attributed to nutritional deficiencies because prior reports noted that alpha thalassemia in Oceania is 'exceedingly rare' (Origa et al. 2013). However, we found alpha thalassemic mutations in eight patients amongst the limited pediatric population seen for well child checks. This may be due to new migration patterns from Southeast and East Asia as a large source of the workforce in the CNMI. Eight of the 10 patients with thalassemic mutations identified as Filipino, whereas 49.9% of the CNMI population identifies as Asian (US Department of Commerce 2012). Nevertheless,

we found thalassemic mutations in two patients who identify as local Pacific Islander. In addition, these mutations may have been identified at a higher rate because thorough sibling tracing was performed. Because of this ascertainment bias, the prevalence of hemoglobinopathies cannot be established in this study, but our identification of the presence of thalassemic mutations should at least cue providers into the possibility of this disorder in anemic patients. In the future, the prevalence of hemoglobinopathies should be more accurately determined in order to guide recommendations for empiric treatment of anemia since the correct management of anemic hemoglobinopathy patients is not nutritional fortification.

Another limitation of this study was the lack of investigation or data collecting regarding the potential for infectious processes as a cause of confounder of the anemia data. Hookworm, for example, can lead to iron deficiency anemia from blood loss related to the parasite, and treatment of the parasite would be the preferred therapy over iron therapy. While there are other helminthes that may cause anemia, hookworm is one of the known causes and has been reported in the Pacific Islands concurrent with anemia in children (Hughes et al. 2004). The rate of helminthiasis in the CNMI has not been reported.

Despite these limitations, this paper provides novel data on pediatric anemia in the CNMI and estimates prevalence based on a clinical convenient sample. The prevalence reported here is in line with previously reported prevalence within the developed world in locations with access to iron fortified foods. If this prevalence is an accurate representation of the pediatric population on CNMI, then the US recommendations regarding anemia screening in patients only at high-risk may apply. Our study represents a first step to address the lack of anemia data amongst Pacific Islanders and we hope to spur further study into the prevalence and etiologies of anemia in this population to help guide clinicians on screening needs and treatment decisions.

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