Health problems in the forested mountains of southern Viet Nam
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Chapter 7

Anemia, malaria and hookworm infections in a Vietnamese ethnic minority.

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Submitted
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ABSTRACT

Subject: to determine the prevalence of anemia and evaluate the relationship of malaria and helminth infections on anemia status in Phan Tien village - a mountainous ethnic minority community in southern Vietnam.

Methods: This longitudinal study was performed from April 1997 to 2000 by measuring the hemoglobin concentration of all people who participated in annual surveys at the end of the rainy seasons. Ferritin concentration was measured in 2000 to evaluate the proportion of iron deficiency anemia. The relation between malaria and intestinal helminth infections with anemia was investigated.

Results: 2767 blood samples were collected and measured for Hb concentration during six surveys. Anemia was always over 43% and mainly associated with iron deficiency (80.1%). Using generalized estimating equations, a small but significant decline of the anemia prevalence was detected (OR: 0.805; p < 0.0001). Malaria was significantly associated with anemia (OR: 2.408; p = 0.0006). There was no significant effect of the control of intestinal helminth infections on the time course of anemia (95% CI: -0.1548 to 0.1651).

Conclusion: It was concluded that, in ethnic minority communes in Viet Nam, anemia is highly prevalent but it cannot serve as a proxy indicator of malaria, and not of hookworm infections. This is probably caused by the marginal nutritional status of those who are at risk of malaria and helminth infections. Since micronutrient deficiency is common in the vulnerable populations of South-east Asia, infectious disease control programs should be accompanied by monitoring iron deficiency and, when needed, supplementation can be organized through the helminthiasis or malaria control programs.
INTRODUCTION

Anemia continues to be a major health problem worldwide. According to estimates of the World Health Organization (WHO), 2 billion people suffer from anemia in the world. (1) Anemia can lead to absenteeism, diminished learning ability, increased susceptibility to infection, growth retardation in children, reduced work performance and increased accident rate. (2-7)

The causes of anemia are multifactorial. Micronutrient deficiencies such as iron, folate, and vitamin B12 are important causes of anemia. (8) Iron deficiency (ID) is the commonest cause of nutritional anemia and is accountable for almost a million deaths annually (9-11) Sickle cell disease, other haemoglobinopathies and thalassaemia also contribute to anemia. (12) Anemia is often associated with parasitic diseases such as malaria and hookworm infections. (13-16) Hookworm infections may cause anemia because they induce iron deficiency by chronic intestinal blood loss. The association between chronic anemia and malaria in the highly endemic regions such as sub-Saharan Africa and Papua New Guinea, or with hookworm infections, may be so strong that anemia is often taken as a proxy indicator of malaria or hookworm control programs. However, in other regions, this relation is not so evident and other factors such as malnutrition and genetic factors may play a significant role.

To assess the rate of anemia in the ethnic minority population in Viet Nam and to investigate whether malaria control and control of hookworm infections decrease the rate of anemia, we followed the population of Phan Tien, an ethnic minority commune in southern Viet Nam, as a cohort, from before until after control of malaria and hookworm infections.

SUBJECTS AND METHODS

Study site and population

The study was conducted in Phan Tien village, an ethnic minority commune located in the mountainous area in Binh Thuan province, southern Viet Nam. Hidden in the forest, it took several hours to reach the village from the main road even in the dry season and it could not be reached by car in the rainy season. Before July 1994, there was no health care facility and water supply was from a small river next to the village. Electricity was introduced at the end of 2000.

The population of Phan Tien is composed of several ethnic minority groups. The number of individuals rose from 716 to 1088 in 2000 due to immigration of settlers of different ethnic minority groups and a high birth rate (3.2% per year). People lived family wise with 5 to 6 persons in one house, with clay walls and a thatched roof. They did not have knowledge of private sanitation, were often walked barefoot especially infants and young children. Humans shared their domestic area with animals. Human and animal excrements were disseminated in and around the
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village. People and cattle shared a small river as their water source for consumption, washing and agricultural irrigation.

The economy of Phan Tien was and is still based on subsistence agriculture, mainly rice paddies, and on what the surrounding forests have to offer. In general, the local economy and living standards, including sanitation, are very poor. Nutritional intake is marginal with low protein and micronutrient intake.(17)

**Demographic surveillance**

A full census of Phan Tien was performed in 1994. Houses were numbered and all individuals were registered. A record was completed for each individual with name, unique identifier, age, sex, household and ethnic group. Over the period 1994–2000, surveys were always held at the end of the rainy season with a single additional survey at the end of the dry season in April 1997. During surveys, the demographic data were updated, including registering neonates, deaths, and population movement.

**Measurements**

Malaria was investigated during all surveys by on the spot microscopic examination of Giemsa stained thick and thin blood smears by experienced microscopists. The result was presented as positive/negative and specified by plasmodium species. Intestinal helminth infections were only investigated in children less than 17 years old starting in the survey of April 1997 and during the end of the rainy seasons from 1997 to 1999, as described elsewhere. Fresh stool samples were immediately examined by the Willis and Kato-Katz thick smear techniques and the agar plate technique for strongyloidiasis.(18-20) Intestinal helminth infections and helminth species were presented as positive or negative.

Hemoglobin concentrations (Hb) were measured in all surveys from 1996 to 2000. Blood was collected by finger puncture for measurement of Hb with a portable hemoglobinometer (HemoCue®, AB, Angelhom, Sweden).(21-23)

Anemia was defined per age group and a threshold of the Hb value: children < 5 years old (group A): Hb < 110 g/L; 5 – 12 years (group B): Hb < 115 g/l; boys of 12 – 15 years (group C) as well as girls of 12 – 15 years (group D): Hb < 120 g/l; non-pregnant females above 15 years (group E): Hb< 120 g/l and males above 15 years (group F): Hb < 130 g/l. Severe anemia was defined as Hb value <70g/l.(24)

Serum ferritin was only measured in 2000. 3ml of venous blood was collected of all participants and centrifuged immediately.. Sera were stored in -700C until measurement in the Academic Medical Center – the Netherlands. Iron deficiency in both sexes was defined as ferritin level < 12μg/l for children < 5 years old and < 15μg/l for the rest the people. Iron deficiency anemia (IDA) was anemia plus iron deficiency. (23)
Analysis

All data were entered into a computerized database with the repeated measurements of Hb, malaria and intestinal helminth infections specified for all inhabitants. Data were analyzed on the basis of repeated measures.

The association between anemia and malaria or intestinal helminth infections was investigated per year by Student's t-test for Hb values, using SPSS (version 11.0, SPSS Inc., Chicago, Ill.). For the longitudinal analysis, generalized estimating equations was applied with “anemia” as the repeated measure, using SAS (release 8.01, Sas Institute Inc, Cary, NC, USA). Since the value of Hb itself changes by age it was not analyzed in a repeated measures model. Statistical significance was accepted when p<0.05.

RESULTS

The results of the malaria control program in Phan Tien have been described elsewhere. (17) In brief, during the first survey in 1994, 41% of the general population carried malaria parasites, of which *Plasmodium falciparum* contributed 70%. Following the interventions with early diagnosis and treatment of malaria, distribution of insecticide treated bed nets and health education, the malaria prevalence decreased dramatically. Overall prevalence of malaria over the study period is shown in Figure 1. In 1998 no malaria was detected in the indigenous population of Phan Tien. Although malaria was reintroduced by new settlers, road and forest workers, the overall prevalence still remained low (3%) in 1999. There was no indication of local malaria transmission in the commune itself.

![Figure 1](image_url): The prevalence of malaria, intestinal helminth infections, and anemia in the population of Phan Tien.

The intestinal helminth infection control program is also described elsewhere (Le Q. Hung, Thesis, September 20 2004, University of Amsterdam). In brief, in
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April 1997, intestinal helminth infections were diagnosed in 28.6% of the children of Phan Tien. Hookworm infections were the most (23%), followed by Trichuris trichiura (1.9%), Hymenolepis nana (1.9%), Enterobius vermicularis (0.9%), Ascaris lumbricoides (0.5%), and multiple helminths infection (0.5%). Most of the mixed infections also involved hookworm. Strongyloides stercoralis was not detected. A control program, based on albendazole mass treatment, safe water supply and health education, started after this survey. Hymenolepis nana infections were treated with praziquantel in 1998 and 1999. To ensure safe water supply, wells were made available at the end of 1997. Improvements of the sanitary facilities were carried out simultaneously, supported by health education and promotion of personal and environmental hygiene.

The prevalence of intestinal helminth infections decreased significantly during the program, despite a delay during the first 6 months caused by using inappropriately formulated albendazole tablets. By the end of 1999, the overall prevalence of intestinal helminth infections had decreased to 3.3% and hookworm infections to 0.8%. The prevalence of intestinal helminth infections is shown in Figure 1.

Hb was measured in a total of 2767 blood samples, collected at 6 surveys. The prevalence of anemia and severe anemia in the first survey, in 1996, was 66.1% and 2.1% respectively. The prevalence of anemia observed in the consecutive surveys is shown in Figure 1, along with malaria and intestinal helminth infections. Figure 2 presents all Hb values in the first survey (1996), stratified by age and gender. The Hb values and anemia rates, specified by age group and survey, are shown in Table 1. During the consecutive six surveys, the mean Hb values of children in group A were often the lowest.

![Figure 2: Distribution of hemoglobin concentrations in the population of Phan Tien in 1996, stratified by sex and age.](image-url)
The prevalence of anemia in Phan Tien was very high, but variation from year to year was considerable, ranging from 43% to 77% (Table 1) and severe anemia ranged from 1.2 to 3.0%. This is considered a severe significance from the perspective of public health.(24)

The mean Hb values of subjects with and without malaria were compared with Student’s t-test, for every age group in every survey. Hb values were not different between parasitamic and non-parasitaemic subjects in the surveys of 1996 through 1997 (data not shown). Hb values of parasitemic subjects were lower in group A (t=3.49; p=0.001) and group B (t=2.99; p=0.02) in 1999 and in group B (t=2.61; p=0.01) in 2000. There was no significant association between malaria and anemia rates among the different age groups. By analysing the repeated data with generalized estimating equations (GEE) a significant decline of the anemia prevalence was detected (OR: 0.805; 95% CI: 0.761 to 0.850, p < 0.0001) with an independent significant effect of the malaria prevalence (OR: 2.408; 95% CI: 1.458 to 3.796, p = 0.0006). In the subgroup of children younger than 17 years with available stool examination results, the same findings were confirmed but there was no significant effect of the intestinal helminth infections on the time course of anemia (95% CI: -0.1548 to 0.1651).

Table 1: The mean Hb values and prevalence of anemia in Phan Tien from 1996 to 2000, stratified by age and gender.

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;5</th>
<th>5 - 12</th>
<th>12-15 boy</th>
<th>12-15 girl</th>
<th>&gt;15 male</th>
<th>&gt;15 female</th>
<th>Proportion of anemia/ severe anemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>99.7 (1.3)</td>
<td>105.4 (1.4)</td>
<td>121.3 (3.8)</td>
<td>112.7 (2.6)</td>
<td>110.9 (1.2)</td>
<td>128.3 (1.6)</td>
<td>66.1 / 2.1</td>
</tr>
<tr>
<td>Apr '94</td>
<td>103.8 (1.7)</td>
<td>111.8 (1.2)</td>
<td>110.6 (3.0)</td>
<td>118.6 (2.5)</td>
<td>112.0 (3.5)</td>
<td>112.2 (6.5)</td>
<td>62.6 / 1.2</td>
</tr>
<tr>
<td>Nov '97</td>
<td>98.1 (2.2)</td>
<td>105.3 (1.1)</td>
<td>110.7 (2.2)</td>
<td>108.6 (2.1)</td>
<td>107.8 (1.4)</td>
<td>122.1 (1.9)</td>
<td>76.8 / 3.0</td>
</tr>
<tr>
<td>1998</td>
<td>104.2 (1.7)</td>
<td>116.9 (1.1)</td>
<td>118.8 (3.5)</td>
<td>126.5 (1.6)</td>
<td>118.3 (1.6)</td>
<td>129.9 (3.2)</td>
<td>43.0 / 2.2</td>
</tr>
<tr>
<td>1999</td>
<td>104.6 (2.5)</td>
<td>115.6 (1.1)</td>
<td>119.8 (4.5)</td>
<td>121.0 (3.6)</td>
<td>119.5 (1.6)</td>
<td>129.3 (1.7)</td>
<td>47.8 / 1.3</td>
</tr>
<tr>
<td>2000</td>
<td>100.0 (1.3)</td>
<td>108.8 (1.1)</td>
<td>116.9 (3.2)</td>
<td>119.8 (2.8)</td>
<td>117.1 (5.0)</td>
<td>104.5 (6.5)</td>
<td>64.9 / 2.4</td>
</tr>
</tbody>
</table>

Ferritin concentration was only measured in 2000. The mean (± SE) ferritin values were 8.9 µg/l (± 9.1) and 8.2 µg/l (± 5.2) for children ≤ 5 years old and the remaining population, respectively. In girls and females ferritin values were lower...
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than in boys and males but this did not reach statistical significance (data not shown). Prevalence of iron deficiency was very high: 86.3% of the overall population. Iron deficiency was found in 85.7% of anemic subjects.

DISCUSSION

This study uncovered a high frequency of anemia in an ethnic minority commune in Viet Nam. Anemia in developing countries is often related to malaria and hookworm infections. In this commune anemia was not easily redressed by controlling both infections. Understanding the dynamics of anemia, malaria and hookworm infections as a public health problem may benefit public health intervention programs.

The prevalence of anemia varied during the study period, but nearly half of population always suffered from anemia. Initially, malaria was considered the most significant cause. It is evident that malaria causes hemolysis and that both symptomatic and asymptomatic malaria are strong risk-factors for anemia.(25;26) In this study, we did not detect an association between malaria and hemoglobin concentrations, or even anemia, when analyzing the respective surveys on it self, except in 1999. Not until the repeated dataset was analyzed with GEE, the relationship between anemia and malaria became clear. Similarly, Stoltzfus did not detect any association between malaria and haemoglobin concentration on Pemba Island, off the East African coast, except in children below 30 months of age with a high parasite density, probably because the statistical power of analyzing a single cross sectional survey is limited.(27;28).

In our study, eventually in 1999, when local malaria transmission had been interrupted for approximately two years, Hb levels were lower in malaria-infected subjects. This may suggest a possible role of malaria immunity also protecting against anemia. An arithmetic, but more plausible, explanation is that in hyperendemic areas, such as Phan Tien in the early nineteen nineties, malarriometric surveys only measure the point prevalence of parasite carriers. They underestimate the total force of infection and thus obscure the association with the chronic effects of repeated infections, such as anemia. In fact, the number of malaria cases during the survey of 1999 was small to draw sound conclusions. When the improvement of anemia did not substantiate, we postulated that hookworm infections were a significant contributor to anemia. This was confirmed when a high frequency of hookworm infections was demonstrated, but no association between hookworm infection and anemia was found. And also, control of hookworm infections did not improve the rate of anemia, despite the fact that most of the anemia was explained by iron deficiency. Worldwide, hookworm infections are an important cause of iron deficiency, especially the infections with high worm densities.(14;28-30) In our study we did not count egg loads and so we cannot exclude the possibility that worm densities were low and thus did not contribute significantly to iron deficiency anemia.
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The most likely explanation for the high rate of anemia in this population is therefore insufficient dietary intake of micronutrients, especially iron. It may explain a delayed recovery of iron deficiency anemia after control of hookworm infections. In another study we showed that the Phan Tien inhabitants had a marginal nutritional status throughout the study period. Previously we observed some reversal of stunted growth in Phan Tien, probably related to the control of malaria. This suggests that macronutrient deficiency was not critical but that micronutrients, especially iron, were deficient. Iron supplementation through existing control programs such as the malaria control program should be considered.

Hemoglobinopathies and thalassemia may also contribute to anemia. Thalassemia and hemoglobin E occur in Vietnamese subjects, but the prevalence in Viet Nam is not known.(31) Attempts to investigate this in Phan Tien have not been successful thus far.

CONCLUSION

In conclusion, in ethnic minority communes in Viet Nam, anemia is highly prevalent but it cannot serve as a proxy indicator of malaria, and not of hookworm infections. This is probably caused by the marginal nutritional status of those who are at risk of malaria and helminth infections. Since micronutrient deficiency is common in the vulnerable populations of South East Asia, infectious disease control programs should be accompanied by monitoring iron deficiency and, when needed, supplementation can be organized through the helminthiasis or malaria control programs.
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