Using clinical signs to diagnose anaemia in African children

S.P. Luby,1 P.N. Kazembe,2 S.C. Redd,1 C. Ziba,3 O.C. Nwanyanwu,3 A.W. Hightower,1 C. Franco,3 L. Chitsulo,3 J.J. Wirima,4 & M.A. Olivar3,5

Anaemia is a serious and common problem among young children in sub-Saharan Africa. As a first step towards developing guidelines for its recognition and treatment, we conducted a study to evaluate the ability of health workers to use clinical findings to identify children with anaemia. Health care workers examined a total of 1104 children under 5 years of age at two hospital-based outpatient clinics in rural Malawi. Blood samples were taken to determine haemoglobin concentrations. Pallor of the conjunctiva, tongue, palm or nail beds was 66% sensitive and 68% specific in distinguishing children with moderate anaemia (haemoglobin concentration, 5–8 g/dl) and 93% sensitive and 57% specific in distinguishing those with severe anaemia (haemoglobin concentration, <5 g/dl). Even without laboratory support, which is often unavailable in rural Africa, clinical findings can identify the majority of children with anaemia.

Introduction

Paediatric anaemia is common throughout sub-Saharan Africa (1). Anaemic children have reduced exercise capacity (2, 3), slower growth (4, 5), impaired neurological (6, 7) and cognitive (8) development, delayed wound healing (9), and increased risk of dying (10). The main causes of anaemia in African children — dietary iron deficiency, malaria, helminth infection and malnutrition — are treatable.

The treatment of symptomatic anaemic children with a haemoglobin concentration of <5 g/dl by blood transfusion prevents death (10). The treatment of children with severe anaemia before they become symptomatic and of those with moderate anaemia before it becomes severe would probably prevent death, the risks associated with blood transfusion (e.g., human immunodeficiency virus (HIV)) and hepatitis B virus infection, and the sequelae of anaemia.

1 Epidemiology Branch, Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA. Requests for reprints should be sent to Dr S.P. Luby, Community Health Sciences, Aga Khan University, PO Box 3500, Stadium Road, Karachi 74800, Pakistan.
2 Kamuzu Central Hospital, Lilongwe, Malawi.
3 Community Health Sciences Unit, Ministry of Health, Lilongwe, Malawi.
4 The Medical College, University of Malawi, Blantyre, Malawi.
5 Deceased.

Reprint No. 5622

Diagnosing anaemia in African children is difficult because few rural areas can support laboratory facilities. Physical examination has been evaluated as a means of diagnosis; however, most of the studies have explicitly excluded Blacks (11-13), severely restricted (14) or excluded young children (11-13, 15, 16), or evaluated patients with a less severe spectrum of anaemia (11-16) than is typical among African children. Thus, the relevance of these studies to the diagnosis of childhood anaemia in Africa is unclear.

We have conducted a study to determine whether African children with severe and moderate anaemia could be identified using clinical signs and report our findings in this article.

Methods

The study was conducted in the outpatient departments of two hospitals in Malawi, Mangochi District Hospital and Nkhoma Hospital, both of which serve predominately rural areas. A systematic sample was recruited by approaching the parent or guardian of every fourth sick child brought to the clinic for under-5-year-olds in Mangochi between 17 April and 28 May 1993, and every second and third sick child brought to the paediatric clinic in Nkhoma between 28 April and 5 June 1993. Children aged over 5 years were excluded.

For patients whose parent or guardian consented, a fingerprick blood sample was collected and the haemoglobin concentration was measured by spectro-
photometry of a modified sodium azide/methaemoglobin reaction. The accuracy of this technique has been demonstrated in a variety of settings (17–19).

Each child was given a standard physical examination, including measurement of rectal temperature, by one of three non-physician health workers, previously trained in physical diagnosis. To evaluate conjunctival pallor, the examiner gently everted the lower eyelid and directly inspected the ocular and palpebral conjunctiva. To evaluate tongue pallor, the examiner directed a pen-light and observed the superior surface of the tongue. To evaluate palmar pallor, the examiner opened one of the child’s hands by partially extending the child’s fingers and inspected the palm. To evaluate nail-bed pallor, the posterior surface of the child’s hand was gently rotated towards the examiner and the nail beds observed directly without applying any pressure to the nails.

The examiners were trained prior to the study for at least one day during which they evaluated children for pallor and were then told the children’s respective measured haemoglobin concentrations. To assess severity of pallor, the examiners were asked to use their own judgement and grade pallor as definite, probable, or absent.

During the study, the examiners were blinded to the measured haemoglobin level, though they were allowed to review the haemoglobin results of the children after their clinical evaluation was complete and recorded. This was permitted to allow the examiner to use the laboratory information in deciding how to treat the child. Each child was examined by only one examiner.

Statistical analysis of the data was carried out using the following: \( \chi^2 \) test, for comparing the observed differences in proportions between study groups; Student’s \( t \)-test, for comparing the means of two categories; one-way analysis of variance (Tukey–Kramer method), for pairwise comparisons of three or more means; multiple linear regression, to evaluate the relationship of measured haemoglobin concentration to various factors; and the \( \chi^2 \) test for trend, to evaluate changes in examiner sensitivity and specificity during the course of the study. Statistical significance was defined as \( P < 0.05 \). The calculations were performed using SAS and EpilInfo software.

Sensitivity was calculated as true positives/(true positives + false negatives), specificity as true negatives/(true negatives + false positives), positive predictive value as true positives/(true positives + false positives), and negative predictive value as true negatives/(true negatives + false negatives).

For children aged 6 months to 6 years anaemia was defined according to the WHO definition, i.e., a haemoglobin concentration of <11 g/dl (20). Severe anaemia was defined as a haemoglobin concentration of <5 g/dl since below this level hospitalized children are often transfused (10, 21). Moderate anaemia was defined as a haemoglobin concentration of 5–8 g/dl, a level that might be considered a reasonable point at which to intervene to prevent children from developing severe anaemia.

The study protocol was approved by the Malawi National Health Sciences Research Committee.

Results

Of 1225 eligible children, the parent’s or guardian’s consent to participate was obtained for 1139 (93%). Of these, 1104 (97%) underwent a physical examination of the conjunctiva, tongue, palm and nail bed and a blood test to determine haemoglobin concentration. Data were incomplete for the remaining 35 participants; these children were somewhat older (mean age: 23.5 months versus 17.5 months), but did not differ significantly from those with complete data in terms of their sex, chief complaint, prevalence of pallor or mean haemoglobin concentration. The analysis was restricted to the 1104 patients for whom complete data were available.

The median age of the enrolled children was 13 months (range, <1 month to 60 months); 580 (53%) were boys, and 590 (53%) were seen at Mangochi District Hospital. The common chief complaints were fever (60%), cough (12%), and diarrhoea (5%). The mean haemoglobin concentration of enrolled patients was 8.8 g/dl (range, 2.1–17.1 g/dl; standard deviation (SD) = 2.4 g/dl): 82% were anaemic according to the WHO definition; 35% had moderate anaemia; and 5% had severe anaemia.

For each anatomical site patients with definite pallor had significantly lower haemoglobin levels than those judged to have probable pallor, while the latter had significantly lower levels than patients without pallor (Table 1).

Probable pallor at each anatomical site and for each definition of anaemia was more sensitive but less specific than definite pallor in diagnosing anaemia (Table 2). The lower the haemoglobin threshold used to define anaemia, the more sensitive both definite and probable pallor were in identifying anaemic children (Table 2). Because of the small number of children with severe anaemia, excluding them from

\[ a \] HemoCue®, Mission Viejo, CA. Inclusion of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services or the U.S. Public Health Service.

Table 1: Mean haemoglobin levels, according to physical signs of pallor, by anatomical site, among 1104 paediatric outpatients, Mangochi and Nkhoma, Malawi, 1993

<table>
<thead>
<tr>
<th>Pallor</th>
<th>Conjunctiva</th>
<th>Tongue</th>
<th>Palm</th>
<th>Nail bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>4.9 ± 1.5</td>
<td>4.3 ± 1.4</td>
<td>4.8 ± 1.6</td>
<td>5.0 ± 1.7</td>
</tr>
<tr>
<td>Probable</td>
<td>7.8 ± 2.0</td>
<td>7.4 ± 2.2</td>
<td>7.9 ± 2.1</td>
<td>8.0 ± 2.1</td>
</tr>
<tr>
<td>None</td>
<td>9.2 ± 2.2</td>
<td>9.2 ± 2.2</td>
<td>9.6 ± 2.1</td>
<td>9.5 ± 2.1</td>
</tr>
</tbody>
</table>

* For each anatomical site, the mean haemoglobin concentration was significantly different, by level of pallor (\(P < 0.05\)); one-way analysis of variance with Tukey-Kramer adjustment for multiple comparisons.

the analysis had only a slight effect on the sensitivity of probable pallor at any site to identify children with moderate anaemia.

For probable pallor at any site there was an inverse relationship between sensitivity and specificity according to the definition of anaemia that was used (Table 2). In general, nail-bed and palmar pallor were more sensitive and less specific than pallor of the conjunctiva and tongue. Definite pallor at any of the four sites had a specificity \(\geq 97\%\) for each of the anaemia definitions.

We developed a composite definition for pallor by combining the physical examination findings. Children were classified as having definite pallor if they had such pallor in at least one anatomical site; probable pallor if they had no signs of definite pallor and had probable pallor in at least one site; and no pallor if they had neither definite nor probable pallor at any site. Composite definitions for definite and probable pallor were slightly more sensitive and slightly less specific than definite or probable pallor in individual sites (Table 3). Probable pallor at any anatomical site was \(70\%\) sensitive, \(68\%\) specific, and had a \(54\%\) positive predictive value in diagnosing a haemoglobin concentration of <8 g/dl.

To evaluate test performance throughout the population, we constructed multiple linear regression models predicting haemoglobin levels. The sensitivity and specificity of pallor did not vary with age or according to rectal temperature. Thus, the diagnostic performance of pallor was independent of age and temperature.

Since each examiner evaluated different children, the distribution of haemoglobin concentrations varied according to the examiner. Despite this variation, children with definite pallor had significantly lower haemoglobin concentrations than children with probable pallor, and those with probable pallor had significantly lower concentrations than those without pallor (\(P < 0.05\) for each comparison, Table 4).
S.P. Luby et al.

Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of definite or probable pallor at any site in predicting anaemia among 1104 paediatric outpatients, Mangochi and Nkhoma, Malawi, 1993

<table>
<thead>
<tr>
<th>Anaemia definition (haemoglobin conc.)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 g/dl</td>
<td>59</td>
<td>93</td>
<td>97</td>
<td>57</td>
</tr>
<tr>
<td>&lt;8 g/dl</td>
<td>17</td>
<td>70</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>5–8 g/dl</td>
<td>10</td>
<td>66</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>&lt;11 g/dl</td>
<td>7</td>
<td>51</td>
<td>100</td>
<td>83</td>
</tr>
</tbody>
</table>

* PPV = positive predictive value.
* NPV = negative predictive value.
* c, d See footnotes b and c, Table 2.

We evaluated each examiner’s sensitivity and specificity in diagnosing moderate anaemia for each week of the study using the χ² test for trend. Neither sensitivity nor specificity significantly improved for any of the health workers during the course of the study.

Discussion

Among the study children, 82% had haemoglobin concentrations <11 g/dl and were therefore anaemic according to the WHO definition; in principle, these children would benefit from diagnosis and treatment of their condition. It is currently impractical to consider treating all cases of anaemia among African children, so that focusing upon those most in need of therapy would appear to be a reasonable strategy.

In the study, health workers with a minimum of additional training successfully identified a subgroup of African children at high risk for complications of anaemia. Screening for probable pallor of the conjunctiva, tongue, palm or nail bed proved to be a good test for anaemia among these children. This approach identified 66% of children with moderate anaemia (haemoglobin concentration, 5–8 g/dl) and, as has been reported previously (13, 15), was more sensitive (93%) in distinguishing patients with severe anaemia.

In contrast to prior studies of White adults, our study suggests that, in settings where paediatric anaemia is highly prevalent, signs detected on physical examination are useful in identifying those children who are most anaemic. Our results differ from previous studies primarily because we used a more extreme definition of anaemia (haemoglobin concentration <8 g/dl, rather than <11 g/dl); as a result, pallor proved a more sensitive sign for identifying anaemia than had previously been reported (14, 15). Furthermore, the high prevalence of anaemia in the study population resulted in a higher positive predictive value for pallor than that reported by previous workers (14, 15). Of note is that the prevalence of anaemia in the study population is comparable to that in other locations in Africa (1), and hence the test performance should be similar in those settings.

In our study, evaluating all four anatomical sites — conjunctiva, tongue, palm and nail beds — was the most sensitive technique for recognizing anaemia. Previous investigators have evaluated palmar-crease pallor (11–13), but we rejected this approach because of the normally increased pigmentation in the palmar creases of Blacks. Although some researchers have

Table 4: Mean haemoglobin concentration, by physical signs of pallor and examiner, among 1104 paediatric outpatients, Mangochi and Nkhoma, Malawi, 1993

<table>
<thead>
<tr>
<th>Mean haemoglobin conc. ± SD (g/dl): a</th>
<th>Examiner 1</th>
<th>Examiner 2</th>
<th>Examiner 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children seen by this examiner</td>
<td>8.7 ± 2.6</td>
<td>9.2 ± 2.1</td>
<td>8.8 ± 2.0</td>
</tr>
<tr>
<td>Children with at least one sign of definite pallor</td>
<td>4.7 ± 1.6</td>
<td>6.3 ± 1.3</td>
<td>5.1 ± 1.3</td>
</tr>
<tr>
<td>Children with at least one sign of probable but no sign of definite pallor</td>
<td>7.5 ± 2.1</td>
<td>8.9 ± 2.0</td>
<td>8.1 ± 1.6</td>
</tr>
<tr>
<td>Children with no signs of pallor</td>
<td>9.6 ± 2.3</td>
<td>9.9 ± 1.9</td>
<td>9.7 ± 1.6</td>
</tr>
</tbody>
</table>

* a For each examiner, mean haemoglobin concentration was significantly different, by level of pallor (P<0.05); one-way analysis of variance using Tukey–Kramer adjustment for multiple comparisons.
concluded that nail-bed evaluation is not useful (11–13), in our study nail-bed pallor performed almost as well as combined evaluation of all four sites. However, the examiners assessed nail beds for pallor at the same time as the other anatomical sites, and it is therefore unclear whether assessment of nail-bed pallor alone would be as diagnostically useful. If further study demonstrates that evaluation of nail-bed pallor independently is nearly as sensitive and specific as the composite findings from all the anatomical sites, this simpler approach could be taught to rural health workers.

Many investigators have documented substantial inter-observer variation in the use of pallor as a diagnostic test for anaemia (11, 13, 15, 22). The present study was not designed to measure such variation. In the clinical setting, validity is a more important criterion, and we found that children who had pallor, as determined by any of the three examiners, had lower haemoglobin concentrations than children without pallor.

Although anaemia causes substantial morbidity and mortality in Africa, guidelines for managing the condition are rudimentary. Our study demonstrates that physical examination is sufficient to diagnose moderate and severe anaemia. In this setting, probable pallor at any site was a sensitive and specific measure for identifying children with moderate anaemia, and definite pallor had high specificity in distinguishing those with severe anaemia.

Résumé

Utilisation de signes cliniques pour diagnostiquer l'anémie chez les enfants africains

L'anémie pédiatrique est courante dans toute l'Afrique subsaharienne. Il serait probablement possible de prévenir la mortalité due à l'anémie et les séquelles qu'elle entraîne chez les survivants en traitant les enfants atteints d'anémie grave avant qu'elle ne devienne symptomatique et en traitant ceux qui présentent une anémie modérée avant qu'elle ne devienne grave. Le diagnostic de l'anémie chez les enfants africains est difficile car peu de régions rurales peuvent disposer d'installations de laboratoire. L'examen physique a déjà été évalué comme moyen de diagnostic de l'anémie; toutefois, la plupart des études excluaient les Noirs, limitaient très strictement ou excluaient les jeunes enfants, et portaient sur des patients présentant des tableaux d'anémie moins graves que ceux que l'on rencontre couramment chez les jeunes enfants africains. Nous avons réalisé une étude visant à déterminer si des enfants africains atteints d'anémie modérée à grave peuvent être identifiés au moyen de critères cliniques.

Trois agents de santé non médecins déjà formés au diagnostic clinique ont été recrutés et ont reçu une formation d'au moins une journée sur la reconnaissance de la pâleur, avec accès à postérieur aux taux d'hémoglobine mesurés chez les enfants examinés. L'étude a porté sur 1104 enfants de moins de 5 ans recrutés dans deux services de consultations externes d'hôpitaux situés en zone rurale au Malawi. Les agents de santé ainsi formés ont recherché les signes de pâleur en examinant la conjonctive, la langue, les paumes et les orteils des patients et ont classé les résultats en pâleur nette, probable ou absente. Les taux d'hémoglobine ont été mesurés par spectrophotométrie sur prélèvement de sang capillaire au bout du doigt.

Le taux d'hémoglobine moyen des sujets recrutés dans l'étude était de 8,8 g/dl. Pour chacun des quatre sites anatomiques examinés, les patients ayant une pâleur nette avaient des taux d'hémoglobine significativement plus bas que ceux chez qui la pâleur avait été classée comme probable, lesquels avaient à leur tour des taux plus bas que ceux chez qui la pâleur était notée comme absente. Par exemple, pour la pâleur des orteils, le taux d'hémoglobine moyen était de 5,0 g/dl chez les enfants ayant une pâleur nette, de 8,0 g/dl chez ceux ayant une pâleur probable et de 9,5 g/dl lorsque la pâleur était absente. En général, la pâleur des orteils et des paumes était un signe plus sensible et moins spécifique que la pâleur de la conjonctive ou de la langue. La pâleur nette de l'un quelconque de ces quatre sites avait une spécificité ≥97% pour chacune des définitions de l'anémie. La pâleur probable de la conjonctive, de la langue, des paumes ou des orteils avait une sensibilité de 66% et une spécificité de 68%, une valeur prédictive positive de 48% et une valeur prédictive négative de 82% pour l'identification des enfants atteints d'anémie modérée (hémoglobine 5–8 g/dl), et une sensibilité de 93%, une spécificité de 57%, une valeur prédictive positive de 10% et une valeur prédictive négative de 99% pour l'identification des enfants atteints d'anémie grave (hémoglobine <5 g/dl). La sensibilité et la spécificité de la pâleur étaient indépendantes de l'âge et de la température rectale de l'enfant.

Il est actuellement impossible en pratique d'envisager de traiter tous les enfants africains anémiques, aussi semble-t-il raisonnable d'axer les interventions sur ceux qui ont le plus grand

References

13. Nardone DA et al. Usefulness of physical examination in detecting the presence or absence of anemia. Archives of internal medicine, 1990, 150: 201–204.