Severity of anaemia in Nigerian children diagnosed with *Plasmodium falciparum* malaria in the first year of life

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Abstract

The prevalence and severity of anaemia was investigated in 450 Nigerian children aged 3-12 months, who were diagnosed with *P. falciparum* malaria. The children were grouped into 2 age groups: 3–6 mo and 7–12 mo. Four different Hb concentrations were used as cut-off points to categorise anaemia into mild anaemia (MA), Hb ≤10 g/dl; clear-cut anaemia (CCA), Hb ≤ 9.0 g/dl; severe anaemia (SA), Hb ≤ 7.0 g/dl and critically severe anaemia (CSA), Hb ≤ 5.0 g/dl. The mean Hb concentration of the 3–6 mo group (10.8 ± 1.45 g/dl) was not significantly different from the mean Hb concentration of the corresponding malaria-free controls (11.94 ± 1.4 g/dl), but while the mean Hb of the 7–12 mo group (8.7 ± 1.5 g/dl) was significantly lower than the mean Hb concentration of the corresponding malaria-free controls (11.74 ± 1.5). The prevalence of mild anaemia, clear-cut anaemia, severe anaemia and critically severe anaemia were 40%, 20%, 0% and 0% in the 3–6 mo group and 87%, 62.77%, 12.77% and 3.89% in the 7–12 mo group respectively. In addition, 4.16% had critically severe anaemia in the 7–12 mo group. The results suggest that a significant proportion of children who suffer from malaria in the first year of life develop iron deficiency anaemia despite the iron deposits acquired during uterine life. However, the severity of anaemia suffered is higher in the 7-12 mo group, when the bulk of the deposits would have been used up, and most children weaned from breast milk.

Key words: anaemia, malaria, infants, Nigeria, *Plasmodium falciparum*.

Introduction

Malaria-induced anaemia (MIA), characterised by low haemoglobin levels, has been identified as one of the life-threatening complications of childhood malaria (Newton et al 1997, Asobayire et al 2001), but the frequency and severity of MIA in children in their first year of life still needs to be studied in tropical malaria-endemic countries. Many investigators of malaria anaemia in children exclude children in their first year of life (Das et al 1999), while others lump this age group with much older children, sometimes up to 5 or 6 years of age (Biemba et al 2000, Stoltzfus et al 2000, Ekvall et al 2001). Although children of all ages growing up in malaria-endemic regions of the tropics face an increased risk of disease-associated anaemia, some physiological, developmental and nutritional peculiarities, which distinguish infants from older children of school age are likely to affect their vulnerability to anaemia, as well as their ability to recover thereafter. In our opinion, these differences justify the need for a separate investigation on the prevalence and severity with which MIA occurs in children in the first year of life.

Malaria-induced anaemia is a serious public health problem in the tropics. In addition to the many deaths caused by severe cases, a strong association has been established between anaemia and impaired development of physical, motor, cognitive, immunological and neurological functions in children, especially when it occurs in the very early years of life (Walter et al 1989, Eden, 2003). The possible long-term implications of childhood anaemia, which are thought to include permanent or irreversible psychomotor and mental retardation (Lozoff et al 2000, Gratham-McGreogor and Ani 2001), add to the health consequences of MIA in the long term. In this paper, we present the results of an investigation into the frequency and severity of MIA in Nigerian children diagnosed with *Plasmodium falciparum* malaria during their first year of life.

Materials and methods

The study was conducted at the Medical Diagnostic Unit of the Department of Biochemistry, University of Nigeria, Nsukka. The subjects were all residents of Nsukka, a semi-urban town in South-Eastern Nigeria. A total of 610 full-term, breast-fed infants aged between 3-12 months, who were referred to the laboratory between January and December 2005 for confirmatory malaria diagnosis, were used for the study. After securing consent from the accompanying parent, information on age, breast-feeding and haemoglobin genotype were obtained before haemoglobin tests on the children were performed. The infants were divided into two age groups: 3-6 months old (40.98%) and 7-12 months old (59.02%). Thick blood smears were prepared on glass slides within 6 hours of sample collection, and the malaria parasites were determined after staining with Giemsa buffer solution (WHO 1991, Asobayire et al 2001). Hb concentration was determined by the method cyanmethaemoglobin method within 12 hours of blood sample collection. Four different degrees of anaemia were defined as follows: moderate anaemia (MA) was defined as haemoglobin level below ≥ 10 g/dl, clear – cut anaemia (CCA) as Hb ≥ 9.0 g/dl; severe anaemia (SA) as Hb ≥ 7.0 g/dl and critically severe anaemia (CSA) as Hb ≥ 5.0 g/dl. These classifications are intended to remove the confusion caused by rather simplistic classification of anaemia into

mild or severe. This study received ethical clearance from the ethical committee of the Faculty of Biological Sciences of the University of Nigeria. Independence sample t-test and one sample t-test were performed with SPSS version 11. Differences were considered significant if $p<0.05$.

Results

Data on the haemoglobin levels of the two age groups of children infected with malaria and the uninfected controls are shown in Table 1. The Hb concentration in the 3-6 mo group ranged from 8.7 – 11.7 g/d (control = 11.3 – 13.7g/dl), while the range in the 7-12 mo group was 4.7 – 11.7 g/dl (control = 9.13 – 13.7). Similarly, the mean haemoglobin concentration of the children aged 3-6 mo group was 10.8 ± 1.6 g/dl, while the mean Hb of the children aged 7-12 mo group was 8.7 ± 1.5 g/dl. Comparatively, the mean Hb concentrations of the corresponding controls were 11.94 ± g/dl and 11.74 ± 1.5 g/dl, respectively. These values represent differences of 1.14 g/dl and 3.04 g/dl of Hb between the mean Hb concentration of the test subjects and the corresponding controls.

Table 1: Haemoglobin levels in children diagnosed with *Plasmodium falciparum* malaria and uninfected controls.

	3 – 6 month old group		7 – 12 month old group	
	Infected (n = 125)	**Uninfected (control) (n = 125)**	**infected (n = 180)**	**Uninfected (control) (n = 180)**
Mean (g/dl)	10.8 ± 1.6	11.94 ± 1.4	8.7 ± 1.5	11.74 ± 1.5
Mode (g/dl)	11.7	11.7	8.3	11.0
Median (g/dl)	10.5	12.5	8.2	10.65
Range (g/dl)	8.7 – 11. 7	11.3 – 13.7	4.7 – 11.7	9.3 – 13.7

Data on the prevalence of mild anaemia and the different degrees of severe anaemia in the two age groups are shown in Table 2. The prevalence of mild anaemia and the different degrees of severe anaemia in the 3-6 mo group were mild anaemia (40%), clear-cut anaemia (20%), severe anaemia (0.00%) and critically severe anaemia (0.00%). Similarly, the prevalence rates for the subjects in the 7-12 mo group were mild anaemia (87.00%), clear-cut anaemia (62.77), severe anaemia (12.77%) and critically severe anaemia (3.89%).

Table 2: Prevalence of the different degrees of anaemia in 3 - 6 and 7 - 12-month olds suffering from malaria. Mild anaemia (MA) was defined as Hb concentration ≤ 10.0 g/dl; clear-cut anaemia (CCA) as Hb concentration ≤ 9.0 g/dl, severe anaemia (SA) as Hb ≤ 7.0 g/dl and critically severe anaemia (CSA) as Hb concentration ≤ 5.0 g/dl.

Classes of anaemia	**Prevalence (%)**	
	3–6 mo group (n = 125)	**7–12 mo group (n = 180)**
Marginal anaemia (Hb ≤ 10.0 g/dl)	40.0 (32%)	156 (87.00%)
Clear-cut anaemia (Hb ≤ 9.0 g/dl)	20.00 (16%)	113 (62.77%)
Very severe anaemia (Hb ≤ 7.0 g/dl)	0.00 (0%)	23 (12.77%)
Critically severe anaemia (Hb 5.0 ≤ g/dl)	0.00 (0%)	7 (3.89%)

Discussion

The prevalence of anaemia in children has continued to be of interest to public health researchers in both developed and developing countries (Lartey et al 1999, Lehman et al 1992, Willows et al 2000, Male et al 2001, Kilinc et al 2002, Alberico et al 2003, Zetterstrom 2004), but it is often difficult to compare the prevalence rates reported from such studies. This is largely because of the variations in age, physiological state, socio-economic status and geographic origins of the subjects used in the studies (Asobayire et al 2001, Khusus et al 1999, Elhazim and Warsy 2001) as well as the apparent lack of uniformity in setting Hb levels as cut-off points for the definition of childhood anaemia, especially in the first year of life (Zetterstrom 2004, Domellof et al 2002). In the literature reviewed, 10.0 g/dl and 11.0 g/dl were the commonest cut-off points used for the definition of anaemia in infants (Antunes et al 2002), while 9.5 g/dl (Alberico et al 2003) 7.0 g/dl (Shresta et al 1994) and 5.0 g/dl (Biemba et al 2000) were used as cut-off points for severe anaemia.

To facilitate the comparison of our results to prevalence figures published elsewhere (Shresta et al 1994, Biemba et al 2000, Antunes et al 2002, Domellof et al 2002, Alberico et al 2003), we used four cut-off points (10.0 g/dl, 9.0 g/dl, 7.0 g/dl and 5.0 g/dl) in our study. To eliminate potential confusion caused by the rather over-simplified classification of anaemia into either mild or severe, we grouped anaemia into four categories namely, marginal anaemia (Hb ≤10.0 g/dl), clear-cut anaemia (Hb ≤ 9.0 g/dl), severe anaemia, (Hb ≤ 7.0g/dl) and critically severe

anaemia (Hb ≤ 5.0 g/dl). This classification is required to distinguish borderline cases of anaemia (moderate anaemia) from clear-cut cases which would require different interventions. Amongst the clear-cut cases there is also a need to distinguish non-life threatening and life-threatening cases that usually require urgent and multiple blood transfusions.

Anaemia in children aged 3 – 6 months

Data on the Hb concentration of the subjects are shown in Table 1, while data on the prevalence of the different degrees of anaemia are shown in Table 2. The mean Hb level (10.8 ± 1.45 g/dl) observed in children infected with malaria in this age group was lower than the mean Hb level (11.94 ± 1.12 g/dl) recorded in the malaria-free controls, but this difference was not significant. In addition, no cases of severe anaemia (Hb ≤ 7.0 g/dl) and critically severe anaemia (Hb ≤ 5.0 g/dl) were recorded in this age group, but the prevalence of clear-cut anaemia (Hb ≤ 9.0 g/dl) and mild anaemia (≤ 10.00 g/dl) were 20% and 40%, respectively. Although the absence of the severe forms of anaemia in this age group is comforting, the number of infants within this age group whose Hb levels fell below 9.0 g/dl is enough cause for concern. Although these apparently moderate or mild forms are unlikely to result in fatality, such children are at risk of developing severe anaemia if exposed to further physiological challenge (Soh et al 2004). More importantly, mild forms of anaemia are capable of adversely affecting cognitive development of affected infants (Rowland et al 1988). This observation is remarkable because in countries like Nigeria where breast-feeding is common, iron deficiency anaemia is considered unlikely in normal children younger than 6 months because the iron deposits accumulated during uterine life augment the iron needs of infants when dietary intake is low until about 4 to 6 mo of life (Oski 1993). Furthermore, healthy breast-fed babies are expected to meet their daily dietary iron needs at this stage of their development from breast milk alone (Duncan et al 1985, Butte et al 2002, Casey and Hambidge 1983). This is because although haeme iron is only present in breast milk in low concentrations, usually below 0.5 mg/l (Casey and Hambidge 1983, Saarinen et al 1977), its relatively high bioavailability ensures that babies are able to meet their daily dietary iron requirements through breast milk alone (Oski 1993, Saarinen et al 1977). These factors may explain the relatively high mean Hb levels and the non occurrence of the more severe forms of anaemia observed in this test group despite being infected by malaria. Worthy of note however, is that despite these factors, the blood Hb levels of a significant number of the children in this age group fell below the cut-off point for clear-cut anaemia (9.0 g/dl). This is because the rich iron deposits of full-term infants are stored as haemoglobin in the red blood cells, and these are therefore vulnerable to destruction by *Plasmodium falciparum* parasites, which are equipped with haemoglobin-specific, proteases, known as falcipain (Sijwali and Rosenthal, 2004). The severity of anaemia caused by malaria at this stage of development is dependent on, amongst other factors, the status of the iron deposits in the child at the time of infection. Thus, low weight, pre-term babies (Iwai et al 1986), and children born to anaemic mothers (De Pee et al 2002), who have lower iron endowment at birth, would be the most vulnerable. The increasing numbers of HIV-positive and HIV-negative infants born to HIV-positive mothers, who are not breast-fed from birth, represent another vulnerable group (Miller et al 2003, Buskin and Sullivan, 2004). Other factors, which may determine the severity of anaemia due to malaria, include the severity of infection (parasite load), duration of infection and, may be, strain of *Plasmodium* involved in the infection (Ekvall et al 2001, Song et al 2003). The severity of anaemia could also be increased by cases of prolonged illnesses due to infection by drug-resistant strains of *Plasmodium* (Erah et al 2003), the presence of such common co-infections, like helminthiasis and giardiasis, which are associated with additional blood losses or iron malabsorption in the gastrointestinal tract (De Vizia et al 1992). However, these infections, which are largely food- or water-borne, occur rarely at this stage of development when majority of infants are still exclusively breast-fed.

Anaemia in children aged 7 – 12 months.

The mean Hb concentration observed in children within this age group infected with *Plasmodium falciparum* malaria (8.7 g/dl ± 1.5 g/dl) was significantly lower than the mean Hb concentration of the control group (11.74 ± 1.5 g/dl), made up of children in the same age group, who were not infected by malaria. The prevalence of different degrees of anaemia (defined by the different cut-off points) were 87% (≤ 10.0 g/dl), 62.77% (≤ 9.0 g/dl), 12.77% (≤ 7.0 g/dl) and 3.89% (≤ 5.0 g/dl). Thus, children in this age group showed much higher prevalence values of all five degrees of anaemia and lower mean Hb concentration than the children in the 3-6 mo group. This implies that the impact of malaria on the Hb levels of the subjects is more pronounced in the 7-12 mo age group. Iron deficiency anaemia is considered more likely in this age group for a number of reasons. Firstly, the rapid physiological changes, which occur at this stage of development, necessitate a huge increase in the daily iron requirements of children (Eden 2003, Butte et al 2002). Thus, while the RDA for iron in children below 6 months is 0.27 mg per day, the RDA for children aged between 7 and 12 months is up to 11.0 mg per day (Brabin et al 2001). Secondly, the iron deposits accumulated during uterine life are usually used up by the sixth month of life resulting in an increased dependence on the diet for the supply of iron (Brabin et al 2001, DeMaeyer and Adiels-Trgman 1985, FAO/WHO 1992). Thirdly, at about the same time, most children are

weaned from breast milk, a relatively good source of iron, and are placed on a variety of substitutes namely, infant formula, cow milk and a variety of cereal-based preparations. Of all these, only the brands of formula fortified with iron are likely to provide sufficient iron to meet the dietary needs of children at this stage of development. Although some of the brands of infant formula on sale in Nigeria are reportedly fortified with iron, a good number of them are not (pers. obs.). However, owing to the relatively high cost of such fortified brands, and lack of education on the part of the parents, only a low percentage of babies are fed iron-fortified brands. In a recent survey (unpublished), only 16 (9%) out of the 200 literate and high-income-earning mothers interviewed in a Nigerian city mentioned iron content as a factor that would influence their choice of which baby formula they fed their babies. Cow milk, the other common breast milk substitute, is a poor source of dietary iron, and has been associated with iron malabsorption and the increased faecal losses of iron when given to children below one year of age (De-Vizia et al 1992, Soh et al. 2004). Its consumption at this stage, therefore, further predisposes the children to iron deficiency anaemia. The other plant-derived meals, which are the major components of infant diet in Nigeria, for example, soybean, rice, maize extracts, tea, etc., contain non-haeme iron, which is poorly absorbed. In addition, these foods contain significantly high amounts of phytic acid, polyphenols and tannin, which further reduce the bioavailability of whatever iron may be present in the diets (Wharf et al 1997).

Considering the high RDA of iron for children aged 7-12 mo (which is comparable to those of adult males, who often fail to meet their daily iron needs despite their more varied diet), it is difficult for them to meet their dietary requirements and maintain healthy iron deposits on such a restricted diet. In the absence of such deposits, malaria infection rapidly results in the further depletion of any iron deposits, leading to severe forms of anaemia observed in this study. More severe cases of anaemia may also be observed when other parasitic or bacterial infections affecting the gastrointestinal tract run concurrently with malaria. In the developing countries of the tropics, where drinking water is often contaminated and poor sanitary conditions prevail, the risk of exposure to these infections is increased at the 7-12 mo stage by the introduction of bottle-feeding and the consumption of a number of other home-prepared dishes.

Another factor, which may have an adverse effect on the iron status of children in this age group, is the fact that many of the children would have suffered previous attacks of malaria or helminthiasis in early life, and these may have depleted their iron status, leaving them clearly or marginally anaemic. Typically, these children are often not allowed enough time to re-build their iron deposits before a second infection strikes to further deplete the iron stores.

The prevalence of the mild and severe forms of anaemia observed in this study, especially in the 7-12-month group deserve an urgent attention in the management of malaria not only because of the risk of impaired cognitive development, but also for the risk of death, which increases significantly when haemoglobin concentrations fall as low as 5.0 g/dl. Whereas it is common practice for doctors to recommend iron supplements in addition to antimalarials when treating malaria especially in children, compliance with the iron supplements is often low. However, because of poor access to standard hospitals, many families indulge in the home management of malaria. As a consequence, the associated anaemia is not diagnosed, and is, therefore, not properly managed. A program that encourages iron intake in children within appropriately defined risk groups is urgently needed to reduce the prevalence and severity of anaemia in children with or without malaria. In addition, other workable strategies aimed at improving the iron status of pregnant women, promoting breast feeding up to the sixth month, the fortification of all breast milk alternatives and a number of other staple foods must be explored.

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