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Health implications of chronic hepatosplenomegaly in Kenyan school-aged children chronically exposed to malarial infections and *Schistosoma mansoni*

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ABSTRACT

Hepatosplenomegaly among school-aged children in sub-Saharan Africa is highly prevalent. Two of the more common aetiological agents of hepatosplenomegaly, namely chronic exposure to malaria and *Schistosoma mansoni* infection, can result in similar clinical presentation, with the liver and spleen being chronically enlarged and of a firm consistency. Where co-endemic, the two parasites are thought to synergistically exacerbate hepatosplenomegaly. Here, two potential health consequences, i.e. dilation of the portal vein (indicative of increased portal pressure) and stunting of growth, were investigated in a study area where children were chronically exposed to malaria throughout while *S. mansoni* transmission was geographically restricted. Hepatosplenomegaly was associated with increased portal vein diameters, with enlargement of the spleen rather than the liver being more closely associated with dilation. Dilation of the portal vein was exacerbated by *S. mansoni* infection in an intensity-dependent manner. The prevalence of growth stunting was not associated with either relative exposure rates to malarial infection or with *S. mansoni* infection status but was significantly associated with hepatosplenomegaly. Children who presented with hepatosplenomegaly had the lowest height-for-age *Z*-scores. This study shows that hepatosplenomegaly associated with chronic exposure to malaria and schistosomiasis is not a benign symptom amongst school-aged children but has potential long-term health consequences.

1. Introduction

In endemic areas, school-aged children bear the greatest burden of infection with *Schistosoma mansoni* and this is associated with subtle morbidities that are distinct from the severe manifestations of hepatic periportal fibrosis, for which the peak prevalence occurs in much older age

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groups than the peak in *S. mansoni* infection intensities.[1] Although many of these subtle morbidities and their consequences are difficult to assess or attribute to a single causative agent, they are thought to be major contributors to the disability-adjusted life-years associated with *S. mansoni* infections.[2] One manifestation of the high infection intensities carried by school-aged children is chronic hepatosplenomegaly in which these organs have a firm to hard consistency when palpated, often being extensively enlarged beyond the costal line,[3,4] but not associated with ultrasound-detectable hepatic fibrosis.[5,6]

Chronic exposure to malaria can also cause overlapping physical signs of hepatosplenomegaly of a firm consistency in school-aged children,[7,8] which contributes to what has been described as an epidemic of hepatosplenomegaly in children throughout the tropics.[9] *Plasmodium*-associated hepatosplenomegaly has been reported as a confounder of *S. mansoni*-associated hepatosplenomegaly,[3,10] however there is evidence that chronic exposure to malaria and infection with schistosomiasis may interact in childhood hepatosplenomegaly.[11,12] Studies in Kenya have shown that, as well as being associated with higher *S. mansoni* infection intensities,[6,13] *S. mansoni*-associated hepatosplenomegaly is more severe in areas where malaria is a greater public health problem, although it is not associated with concurrently detectable parasitaemia.[13] High levels of IgG_3 against *P. falciparum* schizont antigen (Pfs-IgG_3), a marker of relative exposure to malaria and therefore frequency of infection,[14] are also associated with hepatosplenomegaly.[12,15,16] Thus, in sub-Saharan Africa hepatosplenomegaly is common amongst school-aged children who are yet to develop immunity to infection with *Plasmodium* spp. or *S. mansoni*, and where exposure to the two infections overlaps geographically hepatosplenomegaly is both more prevalent[13] and more severe.[12,16]

The adverse effects of this hepatosplenomegaly are not well studied, although it is most prevalent during a critical age in terms of human growth and intellectual development.

Here we present data from a Kenyan school-aged cohort in which hepatosplenomegaly was (a) highly prevalent even in the absence of detectable *S. mansoni* infection, (b) associated with Pfs-IgG_3 levels and (c) clearly exacerbated in children who were infected with *S. mansoni*.[16] This allowed us to test whether or not childhood hepatosplenomegaly, in the presence or absence of detectable *S. mansoni* infection, was associated with dilated portal veins and/or stunting of growth. A school feeding programme, introduced in 1999, ensured that the study was not confounded by current poor protein and micronutrient intake.

2. Materials and methods

2.1. Study area and population

The study area in Makueni District, Kenya, in which *S. mansoni* transmission was restricted to the east owing to habitat availability for the *Biomphalaria* snail intermediate host but where *P. falciparum* was transmitted throughout, as well as the selection of school-aged children (4–17 years) from two primary schools who participated in the study are described in detail elsewhere.[16] Informed consent was obtained from parents or guardians. Five stool samples were collected from participating children and two 50 mg Kato–Katz slides[17] were prepared from each stool sample. A child was considered free of *S. mansoni* infection if all 10 slides were negative for *S. mansoni* eggs. All *S. mansoni* infections were treated with a single dose of praziquantel 40 mg/kg body weight. Pfs-IgG_3 levels were measured by ELISA as described previously.[14] Malaria transmission is considered to be mesoendemic due to highly seasonal rains, with prevalence amongst schoolchildren of microscopy-detectable *P. falciparum* infections being recorded as 15.3% at the end of the long dry season, rising to 51.8% during the high transmission season.[14] At the time of the study, the prevalence of microscopy-detectable *P. falciparum* infections was 21.0% at one primary school and 19.6% at the other and was not associated with hepatosplenomegaly.[16] The field work was carried out in May–June 2002.

2.2. Clinical examination

Children were examined clinically for palpable, enlarged livers and spleens of a firm consistency and were classed into groupings of (a) no organomegaly, (b) splenomegaly only, (c) hepatomegaly only and (d) hepatosplenomegaly, as described previously.[16] This variable is referred to as 'clinical group'. Clinical measurements of the left liver lobe and spleen were also classed as an ordinal variable for extent of organomegaly. The first category was no enlargement of the organ. The left liver lobe was considered moderately enlarged if palpable 3–5 cm and substantially enlarged if palpable >5 cm below the costal margin in the liver mid-sternal line. The spleen was considered moderately enlarged if palpable 3–4 cm below the costal margin in either the mid-clavicular or mid-axillary line or substantially enlarged if palpable >4 cm below the costal margin in either line.

2.3. Ultrasound examination

A randomised cohort of 272 children aged 4–17 years was selected from two primary schools in the area, Yumbuni Primary to the west and Matangini Primary to the east, to participate in ultrasound examinations. The children were examined using an Aloka SSD-500 portable ultrasound machine with a 3.5 MHz curvilinear (60%) probe (Imai, Tokyo, Japan). Ultrasound examinations were conducted according to the Niamey protocol[18] and included measurements of the portal vein diameter (PVD), taken in the right oblique view, at the point of entrance into the porta hepatis at the ventral lower end of the caudate lobe; the measurement taken was the distance between the inner sides of the walls. Ultrasound measurements of PVD required height standardisation prior to analysis. As no data are available from a suitable reference population, standardisation was carried out internally by linear regression. The appearance of the liver parenchyma was assessed in the substernal transverse and subcostal transhepatic views,