Measuring Schistosomiasis Morbidity

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Introduction

The World Health Assembly recognition of the public health problems caused by schistosome infections promotes efforts towards schistosomiasis morbidity control. The control strategy recommended by WHO is aimed at reducing the morbidity caused by schistosomiasis.

In order to make headway in the control of morbidity we must try to answer the following questions: what do we define as schistosomiasis related morbidity, how do we measure it, what is the impact of the detected morbidity on the health of affected communities, what other factors might influence the level of morbidity in an endemic setting, and how can we measure the impact of treatment or intervention on morbidity?

Another important question is what implications the ‘direct morbidity’ has at the community level and whether we are measuring anything relevant to the health and well-being of the population. It is of interest to know if people feel sick and unwell and if there is a direct relation between what we can measure and the well-being of people. In other words can we assess the ‘feeling sick’?

In order to control morbidity we need tools which can assist in monitoring the effect of an intervention on the level of morbidity. Preferably this should work both on a short-term and a long-term basis and be simple, non-invasive and non-expensive. It would be an added advantage if the risk of re-developing severe morbidity after an intervention could be predicted.

Morbidity assessment tools are essential in control but it is important to keep in mind that they are also needed as research tools. We need new tools that can tell us more about the pathogenesis of schistosomiasis including the mechanisms of both development and regression of morbidity in order to deliver chemotherapy and other interventions in the most rational, effective and safe way and to develop new tools for control.

Assessment of morbidity

Ultrasonography has proven its value as a safe, rapid and non-invasive technique for morbidity assessment in schistosomiasis. The technique has the invaluable advantage of directly visualizing the organ-specific schistosomiasis-associated changes seen in the liver and urinary bladder, as well as additional disease complications such as portal hypertension and hydrenephrosis [13, 27, 28]. Furthermore, WHO sponsored expert meetings have produced valuable standardized ultrasound
protocols for the quantification of morbidity in *S. haematobium* and *S. mansoni* infections, and the development of standardized protocols for evaluation of Asian schistosomiasis morbidity is in progress [24,28].

Urinary schistosomiasis, caused by *S. haematobium*, affects the genitourinary tract with egg deposition in the urinary bladder wall although the reproductive organs may also be involved. Late-stage consequences may include hydronephrosis and possible predisposition to urinary bladder cancer. Studies from different *S. haematobium* endemic settings in Kenya, Tanzania, Ghana and Niger using the standardized protocol have shown that reversal of urinary tract morbidity occurs within six months of treatment, and that the rate of reappearance of urinary tract morbidity depends on the level of re-infection [6,12,16,33].

Though classical autopsy studies in Brazil unequivocally linked the development of *S. mansoni* hepatosplenic schistosomiasis (HS), portal hypertension and its severe sequelae with gross periportal fibrosis, recent ultrasound and clinical studies in Africa suggest that HS can also be found in *S. mansoni*-infected children in the absence of gross hepatic fibrosis [31]. Many of the children presented with evidence of increased portal pressure, but none had ultrasound detectable peri-portal fibrosis. This combination does not currently feature in the diagnostic algorithm given by WHO [24].

Other studies have also reported evidence of portal hypertension in the absence of ultrasound detectable peri-fibrosis. In a study from Kenya and Egypt involving ultrasound examination of 3954 individuals and using the Niamey height-indexed criteria (Niamey Working Group, WHO, 2000) for portal vein enlargement, King et al. (2003) [17] found that 14% of Kenyans with a normal liver texture pattern met the criteria for portal vein enlargement. In Madagascar, ultrasonographic observations typical for portal hypertension but without any observable liver texture abnormalities or measurable peri-portal thickening were made in 37 individuals, representing 4.3% of the study cohort (Boisier et al., 2001). In contrast to the study by King et al. (2003) [17], Boisier et al. (2001) [2] used height adjusted reference values for portal vein diameter obtained from a Malagasy population. Together, these observations suggest that the current WHO guidelines may need revision.

The main problems concerning the use of ultrasonography in control programmes are the relatively high cost of the equipment, the need for well trained examiners preferably with a medical, radiography or similar qualification, and the need for adequate quality control procedures.

There is still a need for simple and inexpensive tools for morbidity assessment. One way of assessing morbidity may be simply to ask subjects about the presence of signs and symptoms of morbidity associated with schistosomiasis. Generally this works very well for haematuria associated with *S. haematobium* infection among schoolchildren, but in a Tanzanian study that examined schistosomiasis-related perceptions, attitudes and treatment-seeking practices, it was found that the perceived causes and symptoms were incongruous with the biomedical perspective. In this study, a number of respondents reported schistosomiasis to be a shameful disease [22], an attitude that may lead to underreporting of symptoms. This approach of directly questioning subjects is more problematic for intestinal schistosomiasis, where symptoms such as diarrhoea and blood in the stool are often also associated with conditions other than schistosomiasis [14,30].

Enlargement of the liver and/or spleen is commonly detected with schistosomiasis mansoni [14], and has recently been reported to occur even in the absence of periportal fibrosis [31]. Assessment of the degree of organ enlargement by simple clinical examination may be a useful tool. A standardized method of clinical scoring that takes organ consistency into account has recently been described [31] and has proven useful in post-treatment assessment of regression of organ enlargement [32].
Genital schistosomiasis in women is now viewed as a disease with important individual and public health consequences [20], while *S. haematobium* eggs can be detected in semen samples from men with *S. haematobium* infection indicating that the genitals are a common site of egg deposition [20]. Genital schistosomiasis is receiving increased attention because it is potentially a risk factor for a number of sexually transmitted diseases including HIV [18]. Genital schistosomiasis poses a problem for proper diagnosis and it is worth noting that urine examination is not very valid since egg excretion in urine is often very low or absent in adults with genital schistosomiasis [25].

In *S. haematobium* infection, detection of eosinophil cationic protein (ECP) in urine has proven to be a valuable marker for urinary bladder inflammation with the potential to reveal signs of early inflammation and morbidity [26]. ECP has been evaluated as a morbidity marker for female genital schistosomiasis (FGS); increased levels of ECP were detected in vaginal lavage samples from women with FGS compared to endemic controls. However, the sensitivity of this diagnostic method was reported to be low [21]. Studies that assessed ECP in faecal samples as a marker of intestinal morbidity in *S. mansoni* infection have yielded promising preliminary results [C.M. Reimert, personal communication].

**Factors influencing the level of morbidity**

When measuring the level of morbidity, it is important to know to what extent the results can be generalized within the community as well as to a larger geographical area, since a number of factors such as degree and length of exposure [3], intensity of infection [14], and co-infections with malaria [4], may influence both the development and the level of morbidity in an exposed population.

Geographic information system (GIS) technology is increasingly being applied to the study of schistosomiasis. This powerful tool for mapping the spatial distribution of infection and disease is now starting to generate important data for use in both basic morbidity research and the development of more effective and efficient national control programmes [7,11,15], and can provide valuable information about risk of exposure and co-infection on a micro-geographical scale. This is important in view of the very focal nature of schistosomiasis infection and disease.

Malaria and schistosomiasis are often geographically co-endemic in sub-Saharan Africa, and co-infections with these parasites are common in school-age children, the main target group for schistosomiasis control programmes. Both infections may cause enlargement of the liver and/or spleen, and an exacerbating effect of relatively high exposure to both malaria and *S. mansoni* infections on splenomegaly has been demonstrated in a study in which GIS spatial analysis was combined with detailed clinical and ultrasound examination [4]. IgG3 responses to malaria schizont antigen, a proxy for exposure to malaria, were higher in Kenyan children with *S. mansoni* infection and hepatosplenomegaly compared with infected controls [23], and results from a study in Kenya indicate that the benefits of treating hepatosplenomegaly with praziquantel (PZQ) will depend on the level of exposure to malaria [5].

**Post-intervention assessment**

The key tool in schistosomiasis morbidity control is treatment with PZQ, and, with the major ongoing control initiatives [9], this drug will be used extensively in many schistosomiasis endemic countries in the coming years. In a comprehensive review, Utzinger and Keiser [29] described the current drugs available for morbidity control and covered aspects of therapeutic efficacy and adverse events in clinical schistosomiasis.
Several studies have examined the effect of treatment on *S. mansoni* related organomegaly, periportal fibrosis and other ultrasound detectable parameters \([2,8,10]\), and one study has compared ultrasonography and detailed clinical examination in measuring morbidity regression \([32]\). In this study a steady decrease of the organomegaly among children with HS was demonstrated up to three years after treatment with PZQ. There was however a significant difference in the rate of organ regression between children who became egg negative after treatment as compared to children who remained egg positive, but where intensity of infection decreased markedly (own unpublished results).

Most previous studies have assessed the effect of treatment over a relatively short follow-up period and often among children only. It is therefore important to assess the long-term effect of PZQ treatment with follow-up studies more than five years after treatment among populations living in areas of intense transmission in order to assess the impact of PZQ on the severe consequences of schistosomiasis mansoni such as portal hypertension and oesophageal varices.

**Conclusions**

The increased focus on conditions such as malaria, AIDS and tuberculosis, that cause either severe acute disease or high levels of mortality, has resulted in relative neglect of infections such as schistosomiasis. With the Schistosomiasis Control Initiative, focus has been redirected towards schistosomiasis control. However, control strategies should be evidence-based and field research is necessary to determine the impact of an intervention on the morbidity level. Scientific evidence that allows accurate evaluation of what works, what does not work, and the reasons why, is crucial for the development of efficient and cost-effective strategies to ensure long-term reduction in disease levels in target populations.

Significant advances have been achieved in our understanding of the epidemiology of schistosomiasis and the various factors that may influence the morbidity level. However, there is need for greater understanding of the morbidity mechanisms and for better tools for morbidity assessment. Good research is vital to sustainable disease control, and advances in the laboratory, even if not immediately applicable to control efforts, are needed to improve our understanding of the disease and develop new tools for morbidity assessment and control.

It is also important to strengthen research capacity in endemic countries and to support the many good scientists from these countries. One of the advances in morbidity assessment has been the increase in number of ultrasonographers from endemic countries trained in assessment of schistosomiasis morbidity. It is vital for the sustainability of control efforts that local capacity is created, and that this capacity participates in the control programmes and assists in the training of new people. Any support for further training and exchange between ultrasonographers from endemic areas would be very valuable.

**Main points and conclusions**

- The absence of gross or ultrasound detectable fibrosis does not exclude the possible presence of severe morbidity in *S. mansoni* infected patients.

- Chronic co-exposure to schistosomiasis mansoni and malaria may influence both the level of morbidity and the measurement of morbidity:
  - by affecting the severity of HS morbidity
  - by affecting the regression of morbidity after PZQ treatment
by confounding the assessment of morbidity.

- There is geographical variation (at the macro and micro-geographical levels) in the severity of schistosomiasis associated morbidity, and it is likely that many external environmental factors have important roles in determining the severity of morbidity associated with schistosomiasis.

- Inflammatory markers may prove to be important parameters for the assessment of a variety of schistosomiasis associated morbidities.

- Ultrasonography is useful as a tool for morbidity assessment of several different schistosomiasis-associated conditions. However, the capacity to apply this technique locally in schistosomiasis endemic countries needs to be developed as a priority in order to make full use of its potential.

- Other types of pathology may be of significance in populations living in endemic areas, e.g. intestinal morbidity associated with schistosomiasis mansoni and japonicum remains almost completely unstudied and is likely to be of significance, particularly in situations where other factors such as co-exposure to intestinal parasites and/or malnutrition are present.

References


