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Is ultrasonography useful for population studies on schistosomiasis mansoni? An evaluation based on a survey on a population from Kome Island, Tanzania

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Abstract

Background: Observation of characteristic alterations at liver ultrasonography in clinical schistosomiasis mansoni cases has initiated utilization of this examination method in population surveys in areas where this disease is endemic.

Purpose: To present results of liver ultrasonography and their relation to epidemiological data of a population in an area endemic for *S. mansoni*, to estimate the precision of classification of periportal anatomy changes known as periportal fibrosis (PPF), and to evaluate the relevance of ultrasonography in epidemiological studies on *S. mansoni*.

Material and Methods: A total of 459 inhabitants on Kome Island, Lake Victoria, Tanzania were examined by ultrasound with image documentation by locally trained personnel. A subsample of this population, 116 individuals, was subject to ultrasonography by two examiners independently. Separately, the images were classified for PPF according to the Managil protocol, twice for the subsample.

Results: PPF could be classified for 458 individuals; 64% and 36% were classified as I or II, respectively; none was classified as 0; only one as III. Results were similar for the subsample examined twice. Comparing the two separate classifications of all 232 sets of images of the subsample gave a Kappa (K) value of 0.50. When comparing the classifications of each of the two different examinations of the same individuals of the subsample, K values of 0.29 and 0.34 for the first and second classification, respectively, were obtained.

Conclusion: Ultrasonography does not appear to correlate well with disease stage. Presently, it should not be utilized for staging of schistosoma mansoni-related liver damage in population surveys.

Keywords

Schistosoma mansoni, ultrasonography, in-service training, mass screening, estimation reliability, population survey

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Introduction

Schistosomiasis is a chronic helminthic disease causing damage in different organ systems depending on parasite species. In schistosomiasis mansoni, the worms, which are mainly located in peripheral intestinal veins, release eggs that penetrate the vessel wall and pass into the bowel lumen to be excreted with the feces. This process represents the mammalian segment of the reproduction cycle of the parasite. A substantial number of eggs will, however, not follow this course but follow the blood stream of the venous drainage of the bowel, reach and penetrate the wall of a peripheral

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branch of the portal vein, and end up in the soft tissue space surrounding these vessels inside the liver. The deposited eggs generally induce a delayed type hypersensitivity reaction, resulting in granuloma formation, eventually followed by fibrosis of affected hepatic tissue. This condition, generally referred to as periportal fibrosis (PPF), causes narrowing of the portal branches eventually leading to alteration of the hepatic blood flow and localized atrophy, to be followed by hypertrophy of other parts of the liver (1). In advanced cases, portal hypertension develops, which leads to splenomegaly and appearance of portosystemic collateral veins in the upper abdomen. The end result is often upper gastrointestinal varices, which may ultimately lead to life-threatening hemorrhage.

The course of the disease, however, varies considerably and only a minor group of infected individuals develop PPF serious enough to cause complications of the kind mentioned above (2). However, due to the affection of the bowel, considerably more individuals present with symptoms, such as anemia, diarrhea, and/or bloody stools. At any rate, due to the systemic effect of the infection, most infected individuals experience a general impairment of their physical, as well as mental capacity that has made this infection a major health problem in the endemic areas in Africa and Brazil (3).

In order to assess the degree of liver involvement as a prognostic indicator for the development of PPF and further complications, ultrasound of the liver has been widely used in the clinical setting as a non-invasive alternative to liver biopsy (4). Thanks to the development of modern, mobile equipment, this technique has also been applied for epidemiological population studies in the field.

We performed abdominal ultrasound examination of a subsample of the study population participating in an epidemiological intervention study performed in a highly endemic area. The aim of the part of the study presented here is to report the results of the quality control of the data obtained and to discuss which structures that are depicted at ultrasonography. Based on this, the relevance of performing ultrasound examinations in epidemiological survey studies on schistosomiasis mansoni will be discussed.

Material and Methods

Study population

The study was performed in three villages, on Kome, an island in the southern part of Lake Victoria, Mwanza region, Tanzania. Water contact is frequent and the area is highly endemic for schistosomiasis. Choosing a sample from the population of an island was considered beneficial for a study planned to last several years because of the limited migration. The study participants were selected randomly from official census records. From a total population of about 4000 of the three villages, around 2000 individuals were invited to participate in the study. Blood and fecal samples were obtained from all participating individuals. From this group, every fourth individual according to order of appearance was selected for extended examination including ultrasonography. The decision to choose one of four individuals was based on the fact that only one ultrasound machine was available and that the examination required considerably more time than the lab test sampling only. The actual age and sex distribution of the sample examined with ultrasonography is given in Table 1 (one individual with inferior image material excluded). The data collection part of the study was performed in 1992.

Ethical clearance for the entire population study, including data collection for method precision analysis as well as the utilization of locally trained medical scientists for all examination methods including ultrasonography, was obtained from the ethical committee of

Table 1. Age and sex distribution among 458 randomly selected Kome villagers subjected to ultrasonography of the liver. The mean egg count for carriers (391 of 414 with data on egg count; 94.4%) is given for each category.

Age (years)	Women/girls	Mean egg count	Men/boys	Mean egg count	No note on sex	Mean egg count
0–9	24	663	38	735	0	0
10–19	36	627	88	977	1	44
20–29	51	238	57	626	0	0
30–39	27	254	45	568	0	0
40–49	13	118	21	438	0	0
50–89	10	84	17	290	0	0
Not known	15	356	10	851	5	290
Total	176		276		6	

the National Institute for Medical Research, Dar es Salaam, Tanzania.

Ultrasound examination

The ultrasonography examination was performed with a 5 MHz linear dynamic scanner (Toshiba SAL-32B, Otawara, Japan). Contact gel based on a concentrate from the provider (Stockholms Analytiska Laboratorium, Stockholm, Sweden) was prepared locally. Image documentation was performed on a thermal paper video printer (Toshiba Sonoprinter, Otawara, Japan). A portable generator powered the equipment during fieldwork.

The ultrasound examinations were done according to a protocol, which included image documentation and recording of data on measurements and other observations made during the examination procedure.

During the examination six standardized image projections of the liver, spleen, and the portal vessels were recorded for later evaluation of the portal vein and its intrahepatic branches as well as of the perivascular tissue (periportal tissue). Seven measurements were made and recorded during the examination: length of the left and right lobes of the liver, width and length of the spleen, inner width of the portal vein as well as the outer and inner diameter of the three separate portal vein branches anywhere between the first and the third branching.

Two specially trained biomedical scientists performed the ultrasonography examinations. Evaluation of the video printer records (Fig. 1) for periportal tissue alterations was done separately from the examination procedure at a later date by one of the authors (MA).

Training of technical personnel

A training course with the objective to find and train local biomedical scientists to perform ultrasound examinations for this study was organized. Out of several participants in an initial orientation part of the course, two were chosen for special training. Technical skill and spatial perception capacity, as estimated by the teacher, as well as proficiency in the local language and capacity to establish good relations with the examinees was considered most relevant for the selection procedure. The trainees were biomedical scientists with local college training. They were given a 4-week training session with the specific aim to perform successfully the ultrasound examinations and

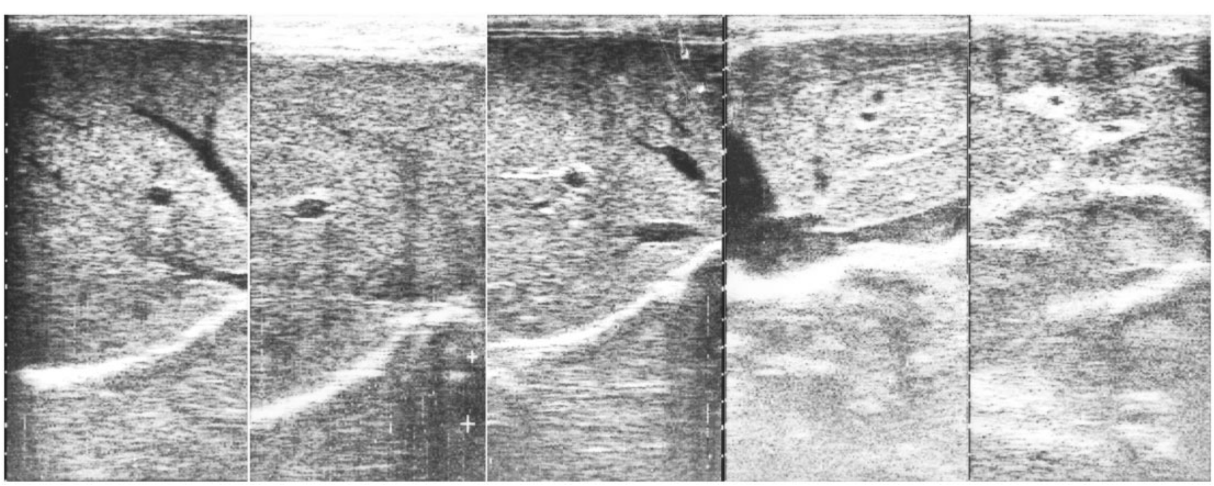

Fig. 1. Varying appearance of portal space as seen at ultrasonography in a population survey.
There are five panels in this figure (a–e). All images were obtained with the equipment used in the survey. (a) A non-infected individual for comparison; (b–e) all infected individuals from the survey. All images are depicted on the same scale. Scale, best seen to the left, 1 cm between markers. (a) Oblique projection of the right lobe of the liver, through the main liver veins, seen as vascular non-echogenic structures without any structure delineating them from adjoining parenchyma. In the middle of the image the superior branch of the right portal vein is seen in cross-section. A minimal amount of echogenic material surrounds the vessel, mainly above and to the right, most probably a biliary duct. This is a normal finding. (b) Projection similar to (a). Portal vein branch surrounded by some echogenic material, representing PPF, degree I. (c) Projection similar to (a, b). Portal vein branch surrounded by some more echogenic material, still representing PPF, degree I. (d) Sagittal projection of the medial segments of the left lobe of the liver, through the inferior vena cava and the left liver vein. To the right of the liver vein there are two similar vascular structures, both branches of the left portal vein. Both are surrounded by a considerable amount of echogenic material, representing PPF, degree II. (e) Projection similar to (d), slightly more to the left. Two portal vein branches seen in left lobe of the liver surrounded by a substantial amount of echogenic material, still representing PPF, degree II.

evaluations specifically required for this study. The training was supervised by one of the authors (MA), a radiologist/clinical teacher, experienced in clinical ultrasonography for more than 15 years at the time of the study. The final part of the training was supervised practical work in the field. The training was finished with the teacher convinced that the examiners had acquired the necessary skills. This appraisal agrees with the suggestion made in a previous World Health Organization technical report on the introduction of new imaging technology in developing countries (5).

Quality control

In order to perform quality control, one-quarter of the individuals examined with ultrasound were selected to form a subgroup ($n = 116$), which was subject to a second, independent ultrasonography examination performed by the other examiner. The second examination was done in a manner identical to the previous. The two examinations of each participant were finished in less than 1 h. The two separate records made possible independent and repeated evaluation of the images obtained, permitting estimation of the inter-observation as well as the intra-observer variation of evaluations.

MA did the evaluation of all the images later and independently from the examination. The complete set of images from the duplicate examinations (116 + 116 examinations) was evaluated in random order at two separate sessions with an interval of about 1 month amounting to 464 evaluations in total.

Classification protocol

For classification of the portal vein branches and surrounding tissue at this separate evaluation, measurements were made according to the Managil protocol (6). Contrary to the earlier Cairo proposal (7), where measurement of "periportal thickening" is advocated, this method takes measurements of the combined thickness of the vessel wall and the perivascular portal tissue into consideration. Thickness of vessel wall and surrounding highly echogenic tissue in the area of the *porta hepatis* in the 4–10 mm interval is classified as grade I, thickness >10 mm as grade II. Thickness >10 mm in combination with extension of changes towards peripheral vein branches and the liver surface is classified as grade III. Thickness <4 mm is considered non-pathological and is classified as grade 0. For each participant, a portal vein branch of the second to third order with surrounding high echogenicity tissue is measured. Our measurements were performed with a calibrated ruler with markers for 4 and 10 mm, respectively. The measurement procedure was then repeated on a separate occasion. In this way, a set of four separate classifications for each participant was obtained separately from the examination procedure.

Parasitological examination

The Kato-Katz test (8) was performed on one fecal specimen from each individual. Single cellophane thick smears, approximately 42 mg, were prepared and all intact eggs and shells in the sample were counted. Counts were converted to eggs per gram feces by multiplying by 24.

Statistical analysis

Mean (M) and standard deviation (SD) were calculated according to standard procedures. Variation between measurements of continuous variables on the same individual is expressed as the standard deviation of the difference between results of repeated measurements of the same object as a percentage of the mean of the measurements.

The reliability of estimation concerning categorical variables is described by the value of Kappa (K), which represents the agreement between estimates exceeding that, which would be expected by chance only. K can vary between 1 and zero. A low value indicates chance as being the major factor of variation with zero indicating chance only. A value of 1 indicates complete agreement between the estimates (9).

Results

Considering that around 2000 individuals were invited, 1840 participants indicate an attendance rate of approximately 90%. In total, 459 individuals were subject to extended examination with ultrasonography. Images from one were excluded from evaluation due to inferior quality, not permitting classification. A total of 116 individuals were subject to duplicate ultrasonography.

The prevalence of egg-excreting individuals in this part of the Kome population was found to be 95% (391/414, 44 individuals with missing egg data). The mean egg count distribution for sex and age groups (Table 1) shows the typical distribution pattern for age groups in an endemic area.

The distribution of PPF classification according to the Managil protocol is shown in Table 2. Approximately the same distribution of classification was obtained from the four different evaluations of the subsample of 116 individuals together. It should be noted that the PPF classification for the entire sample with one single exception was I or II.

A cross-tabulation of PPF classification and egg count classes for the entire sample is presented in

Table 3, illustrating that there is no evident relationship between these two parameters.

The results of measurements made by the examiners and the estimated measurement variations for five continuous variables from the 232 evaluations in the duplicate part of the study are presented in Table 4. The measurement variations for all parameters amount to approximately 20%. These measurements appear at the same level as those corresponding with European/American populations.

The evaluations by an experienced radiologist (MA) are presented in Tables 5 and 6. A cross-tabulation of the first reading of 116 record pairs with findings classified according to the Managil protocol is presented in Table 5. The K value for the first reading is 0.29, representing some intra-rater agreement as well as agreement between the two examinations on the same individual. The corresponding figures for the second reading are presented in parentheses. The K value for this dataset is 0.34. A cross-tabulation of figures from both readings is given in Table 6. The K value for this dataset was 0.50 representing intra-rater agreement only.

Table 2. Distribution of PPF classes at single evaluations in the complete study group and in the selected subsample summarized as evaluated at four different occasions together (464 evaluations).

PPF class	Whole sample (n = 458)	Whole sample (%)	Subsample (n = 116)	Subsample (%)
I	293	64	283	61
II	164	36	180	39
III	1	0.2	1	0.2
Total number of evaluations	458		464	

Discussion

Egg counts vary considerably between specimens from the same individual (10). Detection of schistosome eggs in feces samples only indicates ongoing infection by the worm. Egg level does not allow for classification of pathology level.

Ultrasonography has been suggested for this purpose (11). The utilization of ultrasonography in this

Table 4. Ultrasonography measurement values for five parameters in the selected subsample of 116 Kome individuals. All measurements were done twice and accordingly means were calculated on 232 values and the SD of measurement differences were calculated on 116 values. The measurement error is expressed as the SD in % of the mean.

Parameter	Mean (mm)	SD of measurement differences	Measurement error (%)
Size of left liver lobe	73.4	15.6	21.3
Size of right liver lobe	126.3	23.0	18.2
Inner diameter of portal vein	11.6	2.1	18.3
Width of spleen	49.5	10.8	21.8
Length of spleen	112.0	16.1	14.4

Table 5. Distribution of duplicate classifications of 116 Kome villagers according to the Managil system. First reading, K = 0.29; second reading (numbers in parentheses), K = 0.34.

	Examination 1				
	Class	I	II	III	Σ
Examination 2	I	54 (50)	21 (15)	0 (0)	75 (65)
	II	17 (22)	23 (29)	0 (0)	40 (51)
	III	0 (0)	1 (0)	0 (0)	1 (0)
	Σ	71 (72)	45 (44)	0 (0)	116 (116)

Table 3. Cross-tabulation of PPF classification and egg count classes for 458 individuals. Egg classes based on egg number/g feces. Percentage for egg distribution in PPF classifications I and II is presented in parentheses.

	Egg class						
PPF classification	No eggs	< 10/g	10–100/g	101–1000/g	>1000/g	Missing	Total
I	14 (4.8%)	4 (1.4%)	66 (22.5%)	137 (46.8%)	48 (16.4%)	24 (8.2%)	293
II	9 (5.5%)	3 (1.8%)	34 (20.7%)	71 (43.3%)	27 (16.5%)	20 (12.2%)	164
III	–	–	1	–	–	–	1
Total	23	7	101	208	75	44	458
Part of sample (%)	5.0	1.5	22	45	16	10	

Table 6. Distribution of duplicate classifications of 232 duplicate examinations of 116 Kome villagers according to the Managil system. K = 0.50. Cross-tabulation of data from both readings.

	Classification 1				
	Class	I	II	III	Σ
Classification 2	I	114	32	0	146
	II	23	62	0	85
	III	0	1	0	1
	Σ	137	95	0	232

context is based on the assumption that PPF is detected and that the images can be classified in a manner that reflects the extent of the disease (12). The high prevalence of egg-excreting individuals, despite the fact that only one fecal sample was analyzed, in combination with the typical age versus egg load relationship, shows that the sample studied is representative of a population living in an area highly endemic for schistosomiasis mansoni. All age and sex groups are sufficiently represented. The most important conclusions are made by comparing results from the same individual.

Our study is the first where the precision of the method has been estimated continuously in a field setting. Furthermore, this is the first study presented where examiners have been trained locally. Nevertheless, the precision figures expressed as Kappa values compare favorably with those presented in other studies (13–15). In several of these studies, the precision data were obtained from small homogenous groups of individuals separate from the main population subject to the study. Generally, in previously presented studies the ultrasound examinations were performed by researchers from outside the country or trained abroad. Our data directly reflect the achievements of locally trained biomedical scientists. Moreover, the precision data obtained on PPF in our and other studies are similar to those presented when other radiological methods are studied (16).

Our data were collected with equipment that nowadays would be considered out-of-date. Modern equipment most certainly should give images with higher linear resolution and dynamic range. The structures studied in this context are large and present with high contrast against surrounding tissue. Modern equipment would probably have supplied us with images that would be nicer looking but not contributing further with respect to dealing with the task of depicting, classifying, and measuring the vascular structures of the liver according to established protocols.

The use of ultrasonography of the liver and the portal vessels for population studies in schistosomiasis has previously been based on the assumption that PPF can be detected and that the images can be classified in a manner that reflects the extent of this aspect of the disease. Furthermore, it has been assumed that there is a linear correlation between different classes of PPF as estimated by ultrasound investigation and the various levels of gravity of liver damage caused by the parasite.

Several systems for classification of the findings at ultrasonography in population studies have been presented (6,17,18). They have, to a considerable extent, been based on findings made at clinical ultrasonography. In earlier presentations, linear measurements of changes with regard to certain structures were often utilized. This was later exchanged for classifications that were based on a general impression of the images observed, the Niamey classification (19). This classification protocol is often presented as the method most suitable for population studies (12). No substantial support for such a consideration has been presented. The observation that a method is used widely is not sufficient to confirm its reliability. There are studies presenting precision figures that make the Niamey classification appear more reliable. They are either based on a homogeneous population group (20) or on hospital patient groups with a wider range of findings (21).

The gold standard for estimation of the extent of PPF is histopathological examination. Some studies have compared clinical and histopathological findings with ultrasonography findings made in patient groups (22). Data from these studies hardly give any information on early or subclinical stages of disease with respect to ultrasonography findings. Nevertheless, all classification systems presented include several levels considered low or early activity/infection. In population studies presented, the levels in fact utilized to a very large extent are limited to two only, these two representing stages without any known histopathological correlation (6,23).

Many studies on the diagnostic reliability in medical imaging have been noted. Considerable inter-observer and intra-observer variation has been noted, even for common radiological procedures, e.g. chest X-rays (24). In a later study on the results achieved by experienced radiologists when interpreting plain radiographical images, a precision (mean accuracy) of 77% was reported (16). The K values for inter-observer agreement improved from 0.31 to 0.58 for all radiographs, from 0.40 to 0.70 for abnormal radiographs, and from 0.24 to 0.43 for normal radiographs when clinical details were known to the radiologist, indicating the considerable contribution of bias.

Measurement is not only a matter of precision. An issue of equal importance is the identification of the structures to be measured. As mentioned above, comparisons between histopathological findings and ultrasonographic ones have been made. Such direct comparisons are dubious.

When discussing the structural appearance of the tissues surrounding the portal vein and its intrahepatic branches, one also has to consider the basic image forming properties of the imaging modality used. It is a general opinion in medical imaging that highly echogenic structures with ordinary soft tissue attenuation, observed during ultrasonography, usually have a high fat content. Solid proof for this assumption applied to ultrasonography of the liver in schistosomiasis mansoni was, however, not available at the time of our collection and initial analysis of data. However, in a more recent report on 54 patients with schistosomiasis mansoni, high echogenicity thick margins of intrahepatic portal vein branches were recorded by ultrasonography. These structures, which also were visualized using magnetic resonance imaging (MRI), were found to correspond to fatty tissue (25). Thus, it appears reasonable to belive that the increased volume of perivascular portal tissue observed at ultrasonography on individuals with probable schistosomiasis mansoni might indeed, to a considerable extent, consist of fat.

In fact, the development of fibrosis is a continuous process with gradual introduction of collagen elements in the tissues and subsequent late scar formation. In periportal fibrosis, there is also the element of vascular compromise with obstructed flow from peripheral portal vein branches leading to atrophy of hepatic subsegments and hypertrophy in areas with preserved portal perfusion. "Fissure widening" has also been described as a finding at MRI in patients with schistosomiasis mansoni (26). The volume of the portal soft tissue is, therefore, to a considerable extent, an indirect sign of the transformation of the shape of the liver and should not be considered as a direct sign of local disease processes in schistosomiasis mansoni.

Besides the problems of limited precision at measurement as well as the difficulties in identifying the structures that are observed, there is the matter of time. A reason to estimate the stage of disease is the ambition to follow its development under different circumstances. This means repeated examination and classification. Unless image classification is blinded, not only regarding the individual examined, but also regarding the occasion when the examination was done, the risk of optimism bias cannot be escaped (27). No follow-up study of PPF in *S. mansoni* infection considering this risk has yet been presented.

Ultrasonography of the liver and the portal vessels for population studies of liver damage induced by schistosomiasis mansoni has been used for more than 20 years. There are many population studies, some reported recently (28).

There are still proponents for the use of ultrasonography in population studies on schistosomiasis mansoni. In a recent review of the Schistosomiasis Control Initiative (SCI) concerning evaluation and application of potential schistosome-associated morbidity markers within large-scale mass chemotherapy programs, ultrasonography is described as a method to "... document such morbidity, and its reduction following treatment ..." and that it has been proven to be valuable in this context (29). In a recent review on ultrasonography according to the Niamey protocol applied on population studies as well as on patient studies, "the practical usefulness of the pictorial approach of the WHO protocol is confirmed by its wide acceptance" (12).

The gold standard for disease stage classification in schistosomiasis mansoni is a classification based on histopathological findings in a tissue specimen. Tissue specimens will not be available, especially in early stages of the infection, and certainly not in population surveys. Staging based on ultrasonography classification as well as on fecal microscopy egg counts has been suggested. It appears from several studies, including our own results, that there is no correlation between these two methods of classification and that both are marred by low precision.

In conclusion, considering the low precision estimated in our and other studies, the uncertainty of what kind of tissue is depicted and measured, as well as the risk of optimism bias, ultrasonography is not found to be useful for follow-up studies on PPF in schistosomiasis mansoni.

Declaration of conflicting interests

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