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Evaluation of ultrasonographic staging systems for the assessment of *Schistosoma mansoni* induced hepatic involvement

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Abstract

For the sonographic assessment and grading of hepatosplenic morbidity induced by *Schistosoma mansoni* infection, several quantitative and qualitative classification systems have been used. In an attempt to evaluate two staging systems, a study was performed as part of a schistosomiasis research and control programme in Richard Toll, Senegal. A total of 700 residents of the township N'diangué were parasitologically, clinically and sonographically examined in July 1993. Two ultrasound observers (M.D. and E.D.) applied the Cairo and the Managil classification (E.D. only) for the grading of periportal thickening of the liver. In spite of high prevalence and intensity of infection, severe hepatic morbidity was rare. According to the Cairo classification, there was a high percentage of subjects with grade I

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periportal thickening, with considerable inter-observer variability. In the Cairo classification, which is based on the diameter of peripheral portal vein branches, firm cut-offs are used, independent of body height. We show the relationship between body height and portal vein diameters and recommend the use of body height-dependent reference values to avoid falsely high percentages of periportal thickening, especially in children. To minimize inter-observer variability, a clarification of existing instructions for taking measurements for grading is suggested. These suggestions have been considered during the follow-up expert meeting on the Cairo classification in Niamey under the auspices of the World Health Organization in October 1996. © 1997 Elsevier Science B.V.

Keywords: Ultrasonography; Cairo classification; Liver lesions; *Schistosoma mansoni*

1. Introduction

The infection with *Schistosoma mansoni* is characterized by intestinal symptoms such as bloody stools, diarrhea and abdominal pain, often accompanied by liver and spleen enlargement. In advanced disease, periportal fibrosis of the liver may develop, leading to portal hypertension and oesophageal varices. Upper gastrointestinal bleeding is the major cause of death.

Hepatosplenic lesions related to schistosomiasis can be detected by sonography. For the grading of periportal thickening, several classification systems have been developed. Examples of quantitative grading systems are those described by Abdel Wahab et al. (1992) and by the Cairo Working Group (1991), i.e. 'Cairo classification', which are similar and grade according to the diameter of peripheral portal vein branches. A combination of quantitative and qualitative aspects has been introduced by Homeida et al. (1988). The 'Managil classification' has been developed for children and is based on the impression of an 'experienced ultrasound observer' of the thickness and the location of periportal thickening (Doehring-Schwerdtfeger et al., 1989). A panel of specialists (Cairo working group) recommended ubiquitous use of the Cairo classification in order to render studies from different endemic areas comparable.The aim of this study was to contribute to the evaluation of the Cairo classification, to compare it with the Managil classification and to assess inter observer variability.

2. Patients and methods

The survey was part of a comparative multicenter morbidity study and embedded into a multidisciplinary activity of many research groups in northern Senegal. It was conducted in N'diangué, a township of Richard Toll in Northern Senegal with about 5000 inhabitants, in July 1993. The area has been struck by an epidemic of *Schistosoma mansoni* infection in 1988, rapidly leading to high prevalences and intensities of infection (Talla et al., 1992). Details of the study area have been described elsewhere (Talla et al., 1992; Stelma et al., 1993, 1994).

A map of N'diangué was made, all households were numbered and 62 households were randomly selected. All people belonging to these households were invited to participate, resulting in 700 subjects with complete parasitological and ultrasonographical data. For the detection of *Schistosoma mansoni* infection, two Kato slides of 25 mg each were prepared from one stool sample (Katz et al., 1972; Polderman et al., 1985). In case of a negative result, a second stool sample was processed.

For sonography, two machines (Picker CS 9100 and SSD-500, Aloka Hellige, Freiburg, Germany) with convex probes (3.5 MHz) were used. Ultrasonographical examination was performed by two independent ultrasound observers (M.D. and E.D.). Fifty patients were examined by both observers who were not aware of the parasitological status nor the results of a potentially preceding examination. Observer M.D. is highly experienced in abdominal ultrasonography (instructor of the German Society for Ultrasound in Medicine, DEGUM, Deutsche Gesellschaft fuer Ultraschall in der Medizin), whereas observer E.D. has considerable experience in ultrasound examination of schistosomiasis patients in Africa with >4000 previous examinations at the time-point of the study. The procedure of examination was intentionally not discussed by the examiners during the whole study, but was obtained solely from the written instructions (Cairo Working Group, 1992). This ensured independent examinations which could then be compared to measure inter observer variability and assessed accuracy of written instructions.

The degree of schistosomiasis induced liver changes (periportal thickening/periportal fibrosis) was sonographically assessed, according to international proposals: The diameter of the portal vein was measured between its entrance into the liver and the bifurcation. A diameter of 12 mm or more was considered dilated. The diameter of three portal vein branches 'after the bifurcation [of the portal vein], between the first and the third branching point' was measured and the arithmetic mean taken for grading of periportal fibrosis: <3 mm, no fibrosis; 3–5 mm, mild (grade I); >5–7 mm, moderate (grade II); and >7 mm, severe thickening (grade III) (Cairo Working Group, 1991, 1992). Observer E.D. additionally applied the Managil classification system for grading ($n=319$). This is a rather qualitative method, which was developed for children. Details are described elsewhere (Doehring-Schwerdtfeger et al., 1989).

The results according to the various grading systems and the different observers (inter and intra observer variability) were compared (see Section 2.1).

All patients excreting *Schistosoma mansoni* eggs in their stools were treated with praziquantel, 40 mg/kg body weight, all patients found infected with intestinal parasites were treated with mebendazole and/or metronidazole. Pregnant women were asked to refer to the local health center after giving birth to receive treatment. Minor diseases, detected clinically or per ultrasound, were treated according to local standards, patients with severe diseases were referred to the local health center. All study subjects received health education. Ultrasound examinations were also offered to the patients presenting at the local health center. Training in ultrasound was a strong component of the study. The study was approved by the local health authorities, the Ministry of Health of the Republic of Senegal and the Ethical Committees of the Universities of Bonn and Hannover, Germany.

2.1. Statistical analysis

SPSS/PC 5 was used for analysis. Individual mean egg counts of infected subjects (eggs per gram stools, epg) were logarithmically transformed to obtain normal distribution. Group mean egg counts were calculated as geometric means of stool positive subjects only. For comparison of samples, t-test and Chi-square test were applied. The relation of portal vein diameters to age, body height, sex and egg output was investigated in multiple regression analysis, with backward elimination of independent variables (elimination criterion $p_F > 0.05$). The null-hypothesis was rejected at an error probability of $< 5\%$ ($p < 0.05$).

3. Results

The male/female ratio of study individuals was 324/376, 55% were < 15 years old. The overall prevalence of *Schistosoma mansoni* infection was 75% (525/700), the geometric mean egg count was 277 eggs per gram stools (epg). Prevalence and intensity of infection followed a typical age distribution with adolescents being the heaviest affected age group, prevalence declining slightly and intensity of infection declining sharply in higher age groups (data not shown).

Hepatic morbidity as detected by ultrasound was low and only four cases of moderate and none of severe liver involvement were seen. However, there was considerable variation of results between different classification systems and different ultrasound observers.

The portal vein was dilated in only 3/273 according to observer E.D. (two of them infected) or 10/260 cases according to observer M.D. (eight of them infected). All of them were adults.

The highest percentages of periportal thickening were detected when the cut-offs of the Cairo working group were used, resulting in 31% (84/268) for E.D. and 79% (200/253) for M.D., only two and four of these grade II, respectively. According to the Managil classification (only E.D.), 16% (51/319) had periportal thickening (48 grade I and three grade II). With either classification system, less than five persons (E.D. plus M.D.) had moderate changes (grade II), none had grade III (Table 1).

The frequency of periportal thickening according to either classification system and either examiner was higher in adults than in children (Table 2). Table 3 shows the sharp increase of periportal thickening with age only during adolescence for the Cairo classification and a steady increase with age through all age groups for the Managil classification.

The frequency of periportal thickening according to the Managil classification was 16% in infected and 17% in uninfected subjects (Chi-square $= 0.9$; $p > 0.76$). According to the Cairo classification, periportal thickening was more frequent in infected than in uninfected for M.D. (83 versus 67%; Chi-square $= 8.3$;

Table 1
Periportal cuffing and thickening of patients with *Schistosoma mansoni* infection in Richard Toll, Senegal

	E.D.		M.D.
	Managil	Cairo	Cairo
Grade 0	84%	69%	21%
Grade I	15%	30%	77%
Grade II	1%	1%	2%
Total	319	268	253

Results of the Managil classification (only observer E. D.) and the Cairo classification (both observers, E.D. and M.D) are presented.
Please note that grade III did not occur in the study area at the time-point of examination.

Table 2
Percentages of individuals with periportal thickening in the study area

	Children (%)	Adults (%)	Chi-square/p	Total
Cairo E.D.	21	46	$19.6/p>0.001$	84
Cairo M.D.	70	92	$17.2/p<0.001$	200
Managil E.D.	6	34	$41.8/p<0.001$	51

Percentages refer to subjects with periportal thickening (sum of grades I and II), in children and adults according to the Cairo and the Managil classification (Managil only E.D.).
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Table 3
Periportal thickening in relation to age

Age (years)	Managil (E.D.)	Cairo (E.D.)	Cairo (M.D.)
<5	0	2.9	29.7
5–9	4.8	9.8	71.4
10–19	9.7	36.9	94.9
20–34	27.5	42.5	87.8
≥ 35	39.7	48.6	95

Numbers are percentages of subjects positive (grade I or higher) according to the respective classification system. While there is a steady increase of subjects with periportal thickening according to the Managil classification, a plateau is reached after puberty according to the Cairo classification.
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Table 4a
Inter-observer variation regarding measurements of portal vein diameter in study patients

M.D.	E.D.		
	PV normal	PV dilated	Total
PV normal	43	3	46 (92%)
PV dilated	3	1	4 (8%)
Total	46 (92%)	4 (8%)	50

The definition of normal portal vein diameter versus dilated refers to the value of 12 mm laid down by the Cairo working group in 1990.

$p < 0.005$), but not for E.D. (30% in infected versus 37% in uninfected; Chi-square = 1.0; $p > 0.3$; the two patients with grade II were infected).

The inter- and intra-observer variation is shown in Tables 4a & b The portal vein was regarded normal in 43/50 cases and dilated in one case by both observers, in 6 cases the observers disagreed (Table 4a).

Regarding periportal thickening, 31 (86%) of the subjects graded negative by E.D., had grade I periportal thickening according to M.D. All those graded I or II by M.D. were also grade I or II according to E.D. In general, M.D. tended to measure higher values. This is confirmed by a t-test comparing the mean portal vein branch diameter in the double examinations ($n = 50$). The means are 2.5 mm (2.22–2.74; E.D.) versus 3.7 mm (3.48–3.88; M.D.), the mean difference between the two observers (1.2 mm) is statistically significant ($p = 0.005$). This difference may explain the comparatively better fit between the Managil and the Cairo classification obtained by observer E.D. (Table 4b).

Table 4b shows the grading of 216 subjects examined by E.D. according to both the Managil and the Cairo classification. In 68% of the cases, the grading was congruent, the differences concerned mainly grade 0 and I.

Table 4b
Intra-observer variation

Cairo	Managil		
	Grade 0	Grade I	Grade II
Grade 0	122	23	–
Grade I	44	25	2

Managil (columns) versus Cairo classification (rows). Data of patients who were examined by E.D. and graded according to both classifications are shown.
Only E.D. Absolute numbers of subjects are given.

To examine the influence of different variables (age, height, sex, egg excretion) on the diameter of the portal vein branches, variables were tried in multiple regression models alone and in combination, separately for each observer. The results were similar for both observers. Body height was the variable with the strongest influence on the portal vein branch diameter (for E.D.: $p < 0.0001$; $R^2 = 0.18$; $B = 0.094$; for M.D.: $p < 0.0001$; $R^2 = 0.29$; $B = 0.116$).

The regression equations were:

D (1/10 mm) $= 0.094 * BH$ (cm) $+ 13$ for E.D. and

D (1/10 mm) $= 0.116 * BH$ (cm) $+ 19$ for M.D., where $D =$ diameter of portal vein branches, $BH =$ body height, reflecting the above described difference between observers.

4. Discussion

In late stages of schistosomiasis mansoni it has been well demonstrated that the thickened cuffing around portal vein branches can be easily detected by ultrasound as hyperechogenic streaks and that in those cases the picture is highly characteristic (Homeida et al., 1988; Cerri et al., 1984). However, the doubts mentioned by other authors (e.g. Nooman et al., 1995; Kardorff et al., 1994) about the usefulness of ultrasonography in the detection of early lesions were confirmed by this study. We will discuss potential explanations and solutions for this problem.

The inter-observer variation in our study was considerable. Results stratified according to age and regression analysis indicate a linear relation between portal vein branch diameters and body height which was similar for both observers, despite inter-observer variation: The comparison of the regression equations for the two observers shows almost identical slopes (0.09/0.12), with only the y-intercept being different, resulting in discordant absolute values. This indicates a systematic error which could have several sources:

Firstly the inter-observer variation may indeed be the result of the measurement of two different vein branches since the instructions given by the Cairo working group on which branch is to be measured ('between the first and the third branching point') are potentially misleading.

Secondly the use of different ultrasound machines may be responsible for diverging results, e.g. it is not clear whether the machine includes the space occupied by the cross/calliper arrow into its measurement. This may result in a difference of no more than 0.5 mm, though. However, even if these sources of error can be eliminated, an important point remains: The cut-off value between normal and slightly abnormal (grades 0 and I) is 3 mm. The precision required for the application of a grading system based on these millimeter differences is not necessarily met by the resolution capacities even of modern ultrasound machines. The object to be measured is barely greater than the point of the calliper arrow and

the arrow moves in steps of 0.5 mm in the Aloka machine (E.D.) and of 0.1 mm in the Picker machine (M.D.). This problem is demonstrated by the fact that the difference in the mean portal vein branch diameter as measured by the two observers is just around 1 mm, a value being of questionable biological significance, as most clinicians will agree.

Thirdly, a potential source of error could be inexperience of the observers in measurements of low size. This, however, was not the case in the present study.

In addition to the points made above, it seems that the cut-off values used are too low to adequately describe periportal thickening in schistosomiasis endemic areas. We found periportal thickening mainly of grades I and II, but we did not detect other signs indicating advanced schistosomiasis (e.g. splenomegaly shrinking of the right liver lobe, enlargement of the left liver lobe). In fact, as might have been expected after an only short duration of the disease, morbidity was low and the Cairo classification obviously led to falsely high percentages of periportal thickening.

The main problem with the Cairo classification in its present form seems to be the differentiation between grades 0 and I periportal thickening. This has already been suspected in previous examinations providing similar results with periportal thickening (mainly of grade I) in endemic populations and controls with regards to the Cairo classification (Nooman et al., 1995; Yazdanpanah et al., 1997; and with regards to the Managil classification: Kardorff et al., 1996). Reference values of portal branch sizes of Schistosoma uninfected individuals in a non-endemic area in Senegal have been published by Yazdanpanah et al. (1997).

Summarizing our results, the Cairo classification needs revision, especially for the use in areas with expected or confirmed low hepatic morbidity. We suggest the following modifications:

(1) To avoid systematic errors: the points of measurement should be clarified. The scope and limitations of different ultrasound machines in measuring very small distances have to be assessed.

(2) To correct the differentiation between normal and slightly abnormal (grades 0 and I): findings should be related to body height dependent reference values instead of using absolute cut-offs. In case local reference values are still lacking, in the meantime until they will be established, the above mentioned reference values from Senegal (Yazdanpanah et al., 1997) could be used as they show at least good fit with similar values gained in Europe.

(3) When the state of morbidity in an area needs to be assessed with ultrasound with respect to public health aspects, it may be useful for that purpose to use grade II onwards in order to gain more reliable information until final recommendations from the Niamey workshop are available.

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