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PROGRESS IN ASSESSMENT OF MORBIDITY DUE TO SCHISTOSOMA INTERCALATUM INFECTION: A REVIEW OF RECENT LITERATURE[1]

CONTENTS

[1] This review is issued as a challenge to clinicians and public health investigators in areas where Schistosoma intercalatum is endemic. Both clinical studies and data on the pathology of human disease are limited. It is hoped that in the near future new information will become available and our current concepts of disease due to S. intercalatum will then probably need to be revised.

The reader is also reminded that this bibliographic review is one of a series of WHO/SCHISTO documents (WHO/SCHISTO/83.68-69-70-71, 87.91, 88.95, 88.97) which have been prepared by the Schistosomiasis Unit of the WHO Parasitic Diseases Programme (PDP) and which are intended to provide up-to-date information on technical aspects of schistosomiasis control. According to the advances in technology and as experience accumulates in national control programmes, these documents will be revised. Inquiries and comments may be directed to Chief, Schistosomiasis and other Trematode Infections, Parasitic Diseases Programme, World Health Organization, 1211 Geneva 27, Switzerland.

1. INTRODUCTION

As compared with schistosomiasis due to the main species infecting man, i.e. Schistosoma haematobium, S. mansoni and S. japonicum, less is known about human infection with S. intercalatum. Infection with this parasite has been reported only from West and Central Africa. However, considering the wide distribution of its intermediate snail hosts, Bulinus forskalii and B. africanus, further expansion of the infection is a growing health concern. Generally, it is considered that the parasite is less pathogenic than the other Schistosoma that infect humans, but our understanding of the relationship between S. intercalatum infection and morbidity is still limited.

The first human infections probably were reported in 1918 (45). On the basis of Chesterman's report from Zaire in 1923 (9) this species was referred to as Schistosoma chestermani in older editions of the WHO Classification of Diseases.

S. intercalatum was described and its name proposed by Fisher (26) in a classic paper on the comparative morphological characteristics of the adult parasites and the eggs, the snail intermediate hosts, the epidemiological distribution and the clinical manifestations. This paper is recommended reading.

During the past 20 years, there have been few publications related to investigations on the parasitological characteristics of S. intercalatum or on the epidemiology, pathology and clinical sequelae of infection with this parasite. The present review of the literature covers relevant experimental and clinical studies since 1970 and is intended to give the reader a general overview of morbidity due to S. intercalatum infection.

2. EPIDEMIOLOGY

2.1 Epidemiological characteristics

Few community-based epidemiological studies have been reported (26,51). In general, it appears that the peak prevalence and the most heavy infections occur in the 5-14-year age-group. The intensity of infection tends to decrease with age. In different studies no persons over either 35 or 45 years of age were found to be infected (25,26,51).

Fisher (26) noted that the intensity of infection decreased sharply in the older age-groups. In 2 villages that were surveyed, no one over 30 or 35 years of age respectively was infected. At the same time in the village with the lower overall prevalence and intensity of infection and the lower assumed level of transmission, the intensity of infection did not vary with age. Fisher suggested that there was a significant difference between the immune status of individuals in areas where the prevalence and intensity of infection were high, as compared with areas where they were low. In the same paper he reports that 3 out of 6 fishermen between 35 and 45 years of age were found to be resistant to experimental challenge with S. intercalatum cercariae.

2.2 Distribution of S. intercalatum in Africa

The presence of S. intercalatum is confined to the forest areas of West and Central Africa and the island of Sao Tome. Infection with this parasite was reported from only 5 countries, i.e. Cameroon, the Central African Republic, Chad, Gabon and Zaire, as a result of a questionnaire survey conducted by WHO in 1981 (35). Isolated, unconfirmed cases of S. intercalatum have been reported from Angola, Burkina Faso, the Congo, Mali, Nigeria and Senegal, but no foci of transmission have so far been described in these countries (7,11,49).

In the Central African Republic, a focus of intestinal schistosomiasis due to S. intercalatum was discovered at Boyama by Becquet & Decroocq (1) in 1973. Among 92 persons examined, eggs of S. intercalatum were found in stool specimens from 13 persons (14.5%).

The first 2 cases of S. intercalatum infection in Chad were reported by Becquet et al. (3) in 1970. One of these persons was infected with 3 Schistosoma species: S. haematobium, S. mansoni and S. intercalatum identified by the specific characteristics of the eggs. In Spain a case of S. intercalatum infection was diagnosed in an individual who had been in Chad (23).

Endemic foci of S. intercalatum have been reported in Gabon, with the most important one being in Libreville (6,15,33,44). In 1971, it was found that in a series of 1644 persons infected with S. intercalatum from different areas in Gabon, 1278 were from Libreville (33). A WHO mission (15) visited Gabon in 1971 where it observed that 18 out of 91 (19.7%) schoolchildren between 5 and 12 years of age in Libreville were infected as assessed by stool examination. McCullough (44), who described several other

endemic foci, estimated that 20 000 persons were infected in Gabon in 1975. He also suggested that owing to the changes in socioeconomic conditions, such as forest destruction, water-resource development, expanding road and rail communication, etc., more endemic foci were likely to be discovered in the forthcoming years. Garin et al. (30) used the merthiolate-iodine-formaldehyde (MIF) concentration technique to examine 1548 stool samples collected from adults in 14 villages or towns in the interior of Gabon and found that 5.7% were excreting S. intercalatum eggs. In Okondja the prevalence was 24% among 140 people examined. A total of 275 infected persons were included in 3 reports on chemotherapy trials in Gabon (24,32,37).

In the Cameroon, van Wijk & Elias (58) reported that about 100 patients per year were diagnosed in an outpatient clinic of a general hospital in Mungo in the 1960s; most of these patients were from Loum, 100 km north of Douala. The prevalence rate of S. intercalatum in rectal scrapings was found to be as high as 54.2% in 500 schoolchildren aged from 4 to 15 years; 104 of these children were admitted to hospital for further evaluation of rectal and hepatic disease. In another survey, 32.6% (16 of 51) and 23.6% (13 of 55) of schoolchildren were found to have eggs in their stools in Eseka and Edea respectively (15). Deniau et al. (18,19) reported that out of a total of 50 patients in Loum, 5 excreted hybrid eggs in their urine. Hybridization between S. haematobium and S. intercalatum was also recorded in persons in Loum by other investigators (53).

Epidemiological data on the distribution of S. intercalatum in Zaire up to 1954 were reviewed by Gillet & Wolfs (34). Recently, de Clercq (16) reported the results of a survey in Zaire, at Brikin near Kinshasa, and showed the existence of an autochthonous focus of S. intercalatum in that area with a prevalence of 30% (i.e., 47 infected of 156 examined). The highest prevalence (58%) was seen in the 10-19-year age-group. S. intercalatum infections were found in an American family of 3 upon their return from residence in Kisangani, Zaire, to the United States (61).

Besides being the latest addition to the list of countries endemic for schistosomiasis (now 76), Equatorial Guinea is also the country from where S. intercalatum has been reported most recently. In 1989, Simarro (51) described 2 S. intercalatum endemic areas in Equatorial Guinea: Barrio de California, a suburb of the largest town, Bata, with an urban population of 380 persons, and a rural forest village, 400 km west of Bata, with a population of 850 persons. Among the 357 urban dwellers and the 755 villagers examined, S. intercalatum eggs were found in the stools in 31.9% and 4.6% respectively by the Kato-Katz technique. In addition, 4 cases imported from Equatorial Guinea reported in Spain by Escosa et al. (23), and another 2 autochthonous cases from that country reported separately (12,43), have all shown that S. intercalatum is endemic in several areas in Equatorial Guinea. The peak prevalence in these communities was in the 5-14-year age-group and the mean egg count decreased with age.

S. intercalatum infection was reported in a person who had never left the island of Sao Tome (13). Another person from the island was diagnosed to have S. intercalatum infection in Barcelona, Spain (23). No epidemiological surveys have been reported as yet.

Although the S. intercalatum endemic foci seem to be increasing gradually, the apparently restricted distribution of this infection is still puzzling. B. africanus and B. forskalii are widely distributed snails throughout Africa, south of the Sahara. Furthermore, both of these intermediate snail hosts from within, as well as outside, the present endemic areas have proved to be susceptible to S. intercalatum infection (63). In spite of these favourable conditions, S. intercalatum is still generally limited to the forest areas in a small part of Africa. Southgate (52) has suggested 2 hypotheses to explain this epidemiological situation. First, the cercariae of S. intercalatum tend to aggregate, a process which is initiated by the release of the adhesive post-acetabular gland secretion in response to the increase of temperature that occurs in nature. The aggregated cercariae have an impaired ability to invade the definitive host (63). Secondly, natural hybridization occurs between S. intercalatum and S. haematobium. As a

result of introgressive hybridization, a new strain of S. haematobium appears which supersedes the original S. intercalatum.

3. PARASITOLOGICAL CHARACTERISTICS RELATED TO MORBIDITY

Unlike the minimal intraspecific differences between the "strains" of S. haematobium and S. mansoni, the taxonomic and parasitological differences between the Cameroon and the Zaire strains of S. intercalatum require that all experimental, clinical and epidemiological studies should define the strain in question before drawing conclusions about pathogenicity.

3.1 Strains

There are apparently 2 different strains of S. intercalatum: the Cameroon (Lower Guinea) strain and the Zaire (Congo) strain. The former is found in Cameroon, Chad, Central African Republic and Gabon, and the latter occurs only in a restricted stretch of the Zaire/Lualaba river valley, in north-east Zaire (5,61). Both strains have marked intermediate snail host specificity: the Cameroon strain develops only in B. forskalii-group snails including B. crystallinus (36) and the Zaire strain only in B. africanus-group snails including B. globosus (27,28,63). Each strain is normally unable to develop in a snail which is compatible to the other strain (4,5,28,63). The integumental surfaces of adult S. intercalatum under the scanning electron microscope have been described (41); the teguments of the adult male worms from Cameroon and Zaire were morphologically quite different from one another. However, the teguments of the adult male worms from Gabon and Zaire were similar (48).

Detailed comparative studies between the 2 strains have been published (4,63). Apart from the differences in egg distribution mentioned in section 3.2, there were other differences such as worm length, egg morphology, prepatent period and liver and spleen weight of the infected animals (Table 1). There was no difference between the worm return of the 2 strains. In the hamster the adult worms of the Cameroon strain were 5-7 mm longer than those of the Zaire strain at 80 days after infection. In the mouse, these differences were not found (4). The shape of the eggs of the 2 strains differs slightly. The mean length of the eggs of the Zaire strain was longer than that of the eggs of the Cameroon strain (4). In contrast, in hamsters, the mean length of S. intercalatum eggs is slightly longer in the Cameroon strain than in the Zaire strain whereas the mean egg width in the 2 strains is similar (63). The prepatent period in mice for S. intercalatum of the Cameroon strain is 45-50 days whereas that for the Zaire strain is only 40-45 days. Both liver and spleen of the mice infected with the Zaire strain show a greater mean weight than those of mice infected with the Cameroon strain; the authors explained that this difference might be due to the greater egg load in the liver of the mice infected with the Zaire strain (4).

TABLE 1. COMPARISON OF SOME CHARACTERISTICS OF 2 STRAINS OF S.INTERCALATUM (4,63)

Characteristic	Experimental host animal	Cameroon (Lower Guinea) strain	Zaire (Congo) strain
Intermediate snail host		B. forskalii	B. africanus
Worm length (mm)	Mouse	Male: 8.2 ± 2.0 Female: 10.7 ± 2.7	Male: 7.7 ± 1.8 Female: 10.0 ± 1.4
Mean egg size (μm)	Mouse	166.3 ± 17.3 x 53.7 ± 5.4	187.2 ± 16.5 x 59.6 ± 7.1
	Hamster	172 ± 17 x 59.9 ± 9.8	167 ± 17.8 x 58.4 ± 8.8
Prepatent period (days)	Mouse	45-50	40-45

3.2 Egg output

In mice, 41 days elapsed from the time of exposure to S. intercalatum cercariae of the Zaire strain to the appearance of schistosome eggs in the stool, according to an early observation by Fisher in Zaire (26). In infected hamsters, about 15% of adult female worms had intrauterine eggs 43 days after cercarial (Cameroon strain) penetration. At 48 days after infection this proportion increased to 70% (63). In baboons infected with S. intercalatum cercariae of the Zaire strain, eggs appeared in the stool on the seventh week after infection (57).

The egg output varies with the experimental host. In hamsters experimentally infected with the Cameroon strain of S. intercalatum, 465 paired female worms produced an estimated daily mean of 207 eggs per worm pair (range 166-311). These calculations were based on the number of eggs in the host tissues as well as in the stools (63). In 2 baboons infected with 2000 cercariae of S. intercalatum (Zaire strain), the mean daily faecal egg outputs per worm pair were calculated to be 261 and 411 respectively, much higher than for S. mattheei whose mean daily faecal egg output in baboons is 27 and 149 faecal eggs per worm pair. The total tissue egg loads at 7 months after infection in the 2 S. intercalatum-infected baboons were 1.7 million and 1.6 million respectively and the tissue egg loads per worm pair amounted to 7053 and 7735 respectively, these being higher than the tissue egg burdens in the S. mattheei-infected baboons (57).

3.3 Worm and egg distribution in host body

3.3.1 Worms

In an experimentally infected goat, Wright et al. (63) found 91% of the paired S. intercalatum worms (Cameroon strain) in the small veins of the colon and the remainder in the superior mesenteric veins of the small intestine. In patas monkeys (Erythrocebus patas) 13 months after exposure to 500 S. intercalatum cercariae (Cameroon strain), 95.5% of the worms were found in the veins of the large intestine, whereas 1.8% and 2.7% of the worms were found in the veins of the small intestine and of the portohepatic system respectively (38). No worms were found in the lungs and urogenital system. It appears that E. patas might be an appropriate experimental host for S. intercalatum infection.

3.3.2 Eggs

The relative distribution of S. intercalatum eggs in organs varied according to the host species and the parasite strain, as shown in Table 2. In rabbits, all the eggs (Cameroon strain) were found in the liver digest and none were found in any other organ (63). In mice, the vast majority of the eggs (67.5% of the total recovery) (Zaire strain) were found in the liver (56) whereas in other animals, such as hamster, baboon and monkey, most of the eggs (61.9-96.4%) were found in the large intestine (38,40,56,57,63). In the infected opossum a higher proportion (40.0%) of the eggs (Cameroon strain) was discovered in the small intestine (63) than in other animals. A small proportion (<0.1-1.0%) of the eggs was deposited in the lungs and bladder in baboons and monkeys (38,40,57). Few eggs were found in other organs, such as the stomach, pancreas, spleen, genitals, and ureters in individual monkeys examined (38,40).

The Cameroon strain of S. intercalatum deposited a higher proportion of eggs in the liver and small intestine than the Zaire strain of the parasite (63). Another observation by Bjorneboe & Frandsen (4) in mice showed different egg distributions for the 2 strains of S. intercalatum in organs after an average period of infection of over 80 days. Although the total number of eggs recovered for the period of study for the 2 strains was very similar, the pattern of distribution was quite different. The Cameroon strain deposited about 25% of the eggs in the liver of the mice whereas with the Zaire strain about half the total egg output was found in the liver. The former strain deposited a higher proportion of eggs in the small intestine than did the latter.

TABLE 2. MEAN PERCENTAGE OF EGG DISTRIBUTION IN ORGANS OF DIFFERENT EXPERIMENTAL ANIMALS

Animal/strain	Liver	Small intestine	Large intestine[a]	Lung	Bladder	Reference
Mouse/ZS[b]	67.5	11.9	20.6			Taylor & Andrews (56)
Hamster/ZS	34.4	3.7	61.9			
Hamster/						Wright et al. (63)
CS[c]	21.1	11.4	67.5			
ZS	16.9	1.7	81.2			
Opossum/CS	31.5	40.0	15.5[d]			
Rabbit/CS	100.0					
Sheep/CS	0.6	29.9	69.5			Christensen et al. (10)
Baboon/ZS	1.8	0.6	96.4	1.0	0.2	Taylor et al. (57)
Patas monkey/CS	7.6	0.9	91.3	<0.1	<0.1	Kuntz et al. (38)
Cynomolgus monkey/CS	4.0	10.3	85.3	0.1[e]		Kuntz et al. (40)

[a] Including the caecum.

[b] Zaire strain.

[c] Cameroon strain.

[d] The authors did not mention the remaining 13% eggs.

[e] 0.3% in the spleen.

3.4 Hybridization

Natural hybridization between *S. intercalatum* and *S. haematobium* was discovered in 1974 among a group of children in Loum, Cameroon, by Wright et al. (64), who observed the characteristic eggs of *S. intercalatum* in the urine. Burchard & Kern (6) reported from western Gabon that 20 children had eggs resembling those of *S. intercalatum* in their urine and no eggs in their stools. However, 19 other children had *S. intercalatum* eggs in their stools and 10 of those excreted eggs with a similar morphology in their urine. It was suggested that the eggs found in the urine might be hybrids between male *S. haematobium* and female *S. intercalatum*. The male worms determine the localization (i.e., the bladder), hence the site of mating and egg deposition. The egg shell is the product of the vitelline cells of the female worm, and consequently the morphology of the egg is determined by the *S. intercalatum* female. A range of *Bulinus* snails including *B. rohlfsi* (*B. truncatus* group), *B. forskalii* and *B. wrighti* was experimentally exposed to miracidia hatched out from the eggs recovered from children in Loum. *S. intercalatum* recovered from these children developed in *B. forskalii* but failed to infect *B. rohlfsi*, an intermediate host of *S. haematobium*. This *S. intercalatum* parasite infected *B. wrighti* (6,54).

In experimental studies carried out in hamsters, hybrids were derived from male S. haematobium and female S. intercalatum as well as from reciprocal mating (male S. intercalatum and female S. haematobium) (62). The hybrids (male S. haematobium and female S. intercalatum) were studied longitudinally for up to 7 generations in snails, mice and hamsters (47). Male S. haematobium crossed with female S. intercalatum gave hybrid offspring that were fully viable but the reciprocal mating produced only a few eggs with very low viability (53,62). Although the viable eggs resembled morphologically those of the maternal species, those resulting from male S. haematobium and female S. intercalatum pairing were slightly larger than normal S. intercalatum eggs whereas those from the reciprocal mating were smaller than the normal eggs of their maternal species, S. haematobium (62). The hybrid parasites both in snails and hamsters had the characteristics of rapid maturation and greater egg-production than the parent species, but they had reduced infectivity for B. forskalii, while their capacity to infect B. wrighti was not affected. Southgate (52), Southgate et al. (53) and Wright & Southgate (62) have suggested that a new strain of S. haematobium is appearing in some endemic areas where formerly only S. intercalatum was present, and is gradually replacing the latter.

In Loum, Cameroon, among the children passing hybrid eggs in both their urine and their stools, the hybrid eggs in the stools resembled those of S. haematobium. Further studies revealed that the eggs in the stools (suggestive of hybridization between male S. intercalatum and female S. haematobium) were not viable implying that successful hybridization in both humans and animals occurs only between male S. haematobium and female S. intercalatum (54).

Hybridization between S. mansoni and S. intercalatum has also been reported (38). An E. patas monkey from Nigeria was experimentally infected with S. intercalatum cercariae; subsequently, S. mansoni eggs, along with those of S. intercalatum, were found in tissues at autopsy. However, no S. mansoni eggs were present in the stools. At autopsy, 4 pairs of adult S. mansoni and 27 S. mansoni males, most of which were clasping S. intercalatum females, were observed in the blood vessels of the large intestine of the monkey. Intrauterine eggs in female S. intercalatum mating with male S. mansoni were similar to those in female S. intercalatum mating with S. intercalatum males.

3.5 Reservoir hosts

Several species of animals have been experimentally infected with cercariae of S. intercalatum (63). Variable adult worm recoveries, that were greater than 10% of the infective cercarial dose, were seen in the rhesus monkey, hamster, opossum, gerbil, goat and sheep. In contrast, in several other hosts, rat, guinea-pig and rabbit, all the adult worms were stunted and no intrauterine eggs were present in the female worms found in the rat or guinea-pig. Furthermore, cats, pigs, calves and deer mice were resistant to the infection. Other reports have shown that mice (4,27,56), hamsters (20,22,56), sheep (10,29), baboons (57), gibbons and chimpanzees (39) can be infected, develop pathological changes, and excrete viable eggs in the stools.

Although many animals can be infected in the laboratory, and will pass viable eggs in the stool, natural infections with S. intercalatum have only been reported in 1 species of wild rodent, Hybomys univitatus, by Schwetz in 1956 (cited in Wright et al. (63). Zoonotic S. intercalatum infection has not yet been shown to play a role in the transmission and epidemiology of human disease.

4. PATHOLOGY

4.1 Experimental animals

Pathological changes due to experimental S. intercalatum infection have been investigated in various animals including the hamster (20,22,63), sheep (10), chimpanzee and gibbon (39), and monkey (8). As expected the major histopathological changes occur in the lower bowel.

4.1.1 Intestine

The intestine is the organ which is the most involved in S. intercalatum infection, especially the colon, rectum and caecum. In hamsters, congestion of the mucosa and petechial haemorrhages with sandy patches have been observed macroscopically (22). In 1 hamster, the intestinal wall was perforated below the sigmoid loop. Eighty days after the infection thickening of the intestinal wall was marked in the ileum, caecum, colon and rectum of the animals (63).

In sheep infected with as many as 5000 cercariae, gross pathological change was limited to the colon and caecum with slight thickening of the wall and with occasional petechiae in the mucosa. No lesions in the small intestine could be found (10).

In 2 chimpanzees and 2 gibbons exposed to 1000 cercariae per animal, mild intestinal pathology developed which included granulomatous inflammation and oedema in the colonic mucosa and enlarged lymphoid follicles in the colon (39).

4.1.2 Liver and spleen

In light infections in hamsters exposed to 35 cercariae, no obvious macroscopic changes were found. With up to 1500 cercariae, the hamsters showed a variable degree of congestion, enlargement and darkening of the liver. Multiple, small white-grey spots corresponding to the granulomatous lesions were present on the liver surface, whereas fewer numbers were observed in deep liver parenchyma. No ascites or marked splenomegaly was observed in a group of animals each infected with 1500 cercariae (Cameroon strain). Only the spleen was darkened. None of the heavily infected animals died (22).

In another report, however, 59% of the infected hamsters died between 40 and 120 days after infection with 200 cercariae each of the same strain of S. intercalatum. At 50 days most of the hamsters showed enlargement of the liver and spleen (63). After the eggs began to be deposited in the liver, an exudative stage with either an acute or chronic inflammatory infiltrate was seen. Later, true granuloma formed with an inner zone of epithelioid cells and histiocytes, a central zone of fibroblastic histiocytes and an outer zone of lymphocytes, plasma cells and eosinophils. Slight periportal vein fibrosis was observed occasionally in the affected livers, in sharp contrast to the finding in hamsters infected with the same number (1500 each) of S. mansoni cercariae. In the latter, fibrotic granulomas developed after a relatively short period of infection, as early as 48 days (20,21,22). Other changes included accumulation of fine to coarse granular pigment in the Kupffer and endothelial cells observed by the electron microscope (20).

Liver lesions in infected sheep were very mild. A few greyish egg-granulomas were seen scattered over the liver surface and in the parenchyma. No changes in the size or colour of the liver were reported (10).

Pathological changes in the liver in the chimpanzee and gibbon were also mild. Degenerated eggs of S. intercalatum with surrounding granulomas were demonstrated, schistosomal pigment was present, and fibrous connective tissue was increased in the periportal regions of the liver (39).

Eggs deposited in the spleen were seen in 1 out of 6 infected monkeys (40). Adult worms were found in the spleen in a chimpanzee exposed to 1000 cercariae (39).

4.1.3 Lung

The lung is rarely affected in experimental S. intercalatum infection. In most of 50 experimentally infected hamsters no pulmonary lesions were observed. From the lungs of 2 different animals, 37 encapsulated and 29 encapsulated but decaying adult S. intercalatum were recovered (63). In another study, moderate oedema and congestion

were observed in the lungs of several infected hamsters and were associated with pleural effusion in 1 animal. In another hamster, 2 worms were found in a pulmonary vessel without local inflammatory reactions (22).

No eggs, worms or pathological changes could be found in the lungs of infected sheep (10). Schistosomal granulomas were seen in the lungs of 2 infected baboons. Pulmonary arterial thrombosis was observed in 1 infected chimpanzee (39).

4.1.4 Genitourinary tract

The genitourinary tract is not usually affected in experimental infections with S. intercalatum. Minimal pathological changes in the genitourinary tract were observed in 50 infected hamsters (63). In 3 hamsters, the kidneys were pale and enlarged and the kidney cortex was haemorrhagic. The significance of this observation, however, was not discussed by the authors. A very small portion of the eggs were found in the bladder and/or the kidney (63). Neither the parasite nor the eggs could be demonstrated in the genitourinary tract in sheep infected with S. intercalatum (10).

A few eggs of S. intercalatum have been discovered in the bladders of experimentally infected baboons (57), monkeys (8,38) and gibbons (39), in the ureters of 3 monkeys (8), in the testes of a chimpanzee and in the prostates and seminal vesicles of a gibbon and a chimpanzee (39). Generally, the pathological effects on those organs were negligible (39).

However, Cheever et al. (8) reported that 3 out of 5 cynomolgus monkeys infected with S. intercalatum had eggs in the bladder. In 1 animal nodules of atypical epithelial cells interpreted as superficially invasive undifferentiated bladder cancer were found at 23 weeks after infection. No eggs were detected in the urine. The relationship between the presence of eggs and bladder cancer in this experimental infection was discussed.

4.1.5 Other sites

S. intercalatum eggs were found in the gastric mucosa in both of 2 infected gibbons and in the pancreas of a chimpanzee (39) and a monkey (40).

4.2 Human pathology

Few papers have dealt with pathological studies of human disease due to S. intercalatum as the disease is comparatively mild and has not yet been reported as a cause of death. In this respect van Wijk & Elias (58) appear to be the only investigators who have described some aspects of rectal and hepatic pathology caused by S. intercalatum in humans, based entirely on biopsy specimens.

4.2.1 Intestine

Rectoscopy was performed in 85 hospital inpatients with S. intercalatum infection in Mungo, Cameroon (58). The mucosa was abnormal in 47 patients; 41 had only rectal lesions and in 6 others the sigmoid colon was also involved. The lesions were nonspecific: oedematous or granular mucosa, petechiae, plica inflammation, polyps or pseudopolyps and granulomatous ulcer.

Microscopic examinations of the biopsies revealed S. intercalatum eggs in the submucosa. The lesions can be generally classified as those with inflammation and those without. The diffuse inflammatory lesions included congestion, oedema, bleeding, ulceration and cellular infiltrate in mucosa, or granuloma surrounding the eggs as those seen in other forms of intestinal schistosomiasis. In the non-inflammatory type of reaction, the submucosa was thickened and contained many eggs. Formation of fibrous tissue, hyalinization and calcification of the eggs differed between patients. In these latter lesions, cellular infiltrates were absent around the eggs.

4.2.2 Liver

Needle biopsy has its inherent limitations in the study of liver pathology. However, in the absence of autopsy or wedge-biopsy materials, it is the only source of data on the hepatic lesions due to S. intercalatum infection. The following description was based on 49 liver biopsies from the same group of hospital patients as mentioned above in section 4.2.1 (58).

The granulomatous lesions were limited to the portal triads and eggs were only infrequently found elsewhere. The large size of the eggs may be the reason for the limitation of the affected areas. The diameters of the granulomas varied from 200 to 350 μm, a smaller size than for the granulomas in S. mansoni infection (59). The tissue reaction to the eggs was slight or absent in 5 patients. Exudative inflammatory reactions were found in half of the biopsy specimens, but the inflammation was strictly confined to the portal areas.

The parenchymal changes in the liver were nonspecific, such as cloudy swelling of the liver cells, a considerable degree of anisocytosis and anisonucleosis, differences in glycogen content in hepatic cells and the presence of multinuclear cells. Hepatic cell necrosis was never seen. Many eosinophils were present in the periphery of the portal areas as well as in the sinusoid spaces.

Profound vascular changes as seen in S. mansoni infection could not be demonstrated. No obstructive lesions of the presinusoidal portal venules and medium-sized portal veins have been observed; these lesions are usually associated with portal hypertension in S. mansoni infection. Vasculitis with endothelial proliferation and perivascular inflammation were present but to a lesser extent than observed in S. mansoni infection. In all patients the Kupffer cells were hypertrophied and increased in number. Pigment formation was more extensive in S. intercalatum than in S. mansoni infection. A fine or coarse granular, refractory pigment was present in abundance in the Kupffer cells and in the histiocytes of the portal area, but not in the parenchymal cells of the liver. The pigment varied from golden-brown to dark-brown and black depending in part on the conditions (such as light) of the examination.

As a whole, the hepatic pathological change was mild. No portal hypertension was observed in these patients. It was suggested that the differences between the hepatic lesions of S. intercalatum and S. mansoni infections in humans might be due to a lower immune response to the antigens of S. intercalatum eggs.

5. CLINICAL PRESENTATION

5.1 Symptoms

Generally, the clinical manifestations of disease due to S. intercalatum infection are milder than those due to either S. haematobium or S. mansoni infection (26,63). According to the current literature, most of the infected persons are asymptomatic. Among 56 patients who were diagnosed by the finding of S. intercalatum eggs in their stool specimens (42 persons) or in the rectal snip specimens (14 persons), 75% (42 persons) were asymptomatic (65). The infection has little effect on the health of infected schoolchildren; their attendance at school is no less than that of children in the same school but without the infection (26). In some endemic areas, schistosomiasis due to S. intercalatum is not perceived as a specific health problem and those infected may not recognize any benefit from treatment (51).

In those who are symptomatic, the typical clinical picture is that of large intestine enteritis. Lower abdominal pain with dysentery is the major complaint (51,63). There was a positive association between increasing intensity of the infection as assessed by stool egg count and the presence of the symptom of diarrhoea and a history of blood in the stools (51). Fever, as is seen in other schistosome infections in the acute phase, has not been reported in S. intercalatum infection.

As with other schistosomal infections, S. intercalatum may be associated with severe Salmonella infection. Gendrel et al. (31) reported from Libreville in Gabon that among 42 children hospitalized for typhoid septicaemia, S. intercalatum was confirmed in 76% by rectal biopsy whereas in the control group of 55 children of the same age living in the same district but without Salmonella infection, S. intercalatum was observed in only 38% by the same method ($P < 0.001$). Salmonella infection associated with S. intercalatum infection is prolonged with severe clinical deterioration and resistance to the classical antibiotic treatment of salmonellosis. Simultaneous treatment with antibiotics and antischistosomal drugs for Salmonella and S. intercalatum infections is effective (2,31).

5.2 Signs

Few physical signs have been associated with S. intercalatum infection. In a series of 56 patients reported by Zwingenberger et al. (65) from Gabon, hepatomegaly up to 3 cm below the right costal margin was found in 28%, and ≥4 cm below the costal margin in 20 of the patients. Enlargement of the spleen was found in 22% of the patients. The intensity of the infection as measured by stool egg count was low. No control data from uninfected local persons were given, however.

A population-based study from Equatorial Guinea reported that enlargement or tenderness of the left lobe of the liver was more frequent in persons with heavy infections, i.e., more than 400 eggs per gram of faeces (51). Hepatomegaly was found in 3 of 7 cases with S. intercalatum infection reported by Escosa et al. (23).

Other investigators (26,61), however, could find no association between the infection and hepatomegaly. On the contrary, in a classic field survey in 411 schoolchildren in Zaire, Fisher (26) found that the higher rate of liver enlargement was seen among those with negative stools (178 children examined) as compared with those with eggs in their stools (233 children examined). Similarly, spleen enlargement was not associated with the infection.

Portal hypertension and/or collateral circulation have not been reported in any of the published reports reviewed.

5.3 Laboratory findings

Data of laboratory findings based on a large series of patients are not available in the recent literature.

According to the few case reports, the only change in haematology is peripheral eosinophilia. Six of 7 patients with S. intercalatum showed eosinophilia ranging between 9% and 39% of the total leukocyte count (23). In another report of 3 cases only 1 had eosinophilia, i.e., 11% (61). The leukocyte count is usually within normal limits. Mild to moderate anaemia may be observed (13,23,24); however, the anaemia may not be attributable to S. intercalatum infection, as some of the general uninfected population in the same areas were anaemic (24).

In heavily infected sheep, the only significant finding was eosinophilia at 9 to 11 weeks after the infection, followed by a gradual decline. All other blood parameters, including peripheral leukocyte count, erythrocyte count, packed cell volume and haemoglobin level were almost unaffected as compared with uninfected control animals.

No abnormal urinalysis results or liver and renal function tests in infected persons have been reported (24,61). Serum IgG and IgE were found to be higher in patients with the infection than in control subjects (65).

6. DIAGNOSIS

6.1 Stool examination

Diagnosis of S. intercalatum infection is indicated by the detection of typical terminal-spined eggs in the stools. The mean length of S. intercalatum eggs is between

that of S. haematobium and that of S. bovis eggs but there is overlap of a small proportion of S. intercalatum eggs; the smaller eggs are close in size to those of S. haematobium whereas the larger eggs have a length similar to that of the animal schistosome, S. bovis. The mean length measured in 430 eggs (Zaire strain) by Fisher (26) was 175 μm and their mean width was 60 μm, whereas in 196 eggs (Cameroon strain) measured by Dazo & Biles (15) the mean length was 160 μm and the mean width was 58 μm. Typical S. intercalatum eggs are rhombic with a long, slightly curved spine whereas S. haematobium eggs are usually smaller in size, oval shaped with a straight, short, slender spine (6,26,37). The biloculation of the intra-ovular miracidium is morphologically characteristic and is different from that observed in S. haematobium eggs. It was seen in 77.2% of the 196 S. intercalatum eggs measured (15).

Various stool concentration methods have been used. The Kato-Katz technique has been successfully applied in epidemiological surveys (51). Its relatively low sensitivity limits its use in clinical studies. The merthiolate-iodine-formaldehyde (MIF) concentration technique was significantly less sensitive than a modified stool filtration technique which used 2 cylindrical nylon mesh filters and in which the filtration process was facilitated by suction with a water jet pump (25). For 22 patients passing S. intercalatum eggs in their stools, the modified filtration technique failed to find the eggs in 1 sample, whereas the MIF concentration technique detected only 13 of the 22 positive samples. Furthermore, when egg counts were compared, the median number of eggs/gram stool was 7.0 by the modified filtration and 1.5 by the MIF concentration technique. The difference was significant ($P < 0.01$).

6.2 Serological tests

Serological reactions are probably less marked in S. intercalatum infection than in infections with S. mansoni, S. haematobium and S. japonicum. S. intercalatum may have low antigenicity in man and induce lower antibody response (58,61).

In a family of 3, originally from a non-endemic area and with active infection, only fluorescent antibody tests were positive in all three, whereas the skin, complement fixation and slide flocculation tests for schistosomiasis with unidentified antigens were all negative before treatment in the 2 persons examined (61). Using S. haematobium antigen for the indirect fluorescent antibody test, Lapierre et al. (42) found that 83% of 66 patients with S. intercalatum eggs in their stools were positive, whereas only 33% of the 66 patients were positive when S. mansoni antigen was used.

The concentrations of IgG- and IgE-containing circulating immune complexes (CIC) were higher in infected persons compared with uninfected controls (65).

Recently, a circulating anodic antigen (CAA) has been identified in S. intercalatum infected patients using an enzyme-linked immunosorbent assay (ELISA) with an anti-S. mansoni CAA mouse monoclonal antibody (17).

6.3 Proctosigmoidoscopy

Since the parasite resides in the vessels of the lower part of the intestine, examination of rectal snips through proctosigmoidoscopy has proved to be a sensitive technique in the diagnosis of S. intercalatum infection. Rectal biopsy was significantly more sensitive in demonstrating the presence of eggs of S. intercalatum than the stool modified filtration technique ($P < 0.0001$). However, when the 2 techniques were compared in terms of sensitivity in detecting viable eggs, no statistically significant difference could be found ($P = 0.22$) (25).

Muller & Taylor (46) demonstrated the value of the Ziehl-Neelsen staining technique to differentiate eggs of S. intercalatum in tissue from terminal-spined eggs deposited by other schistosomes. Egg shells of S. intercalatum were found to stain red, while those of S. haematobium, S. mattheei and S. bovis were not. Use of this technique, combined with studies on egg morphology, can provide unequivocal differentiation of S. intercalatum from other species with terminal-spined eggs. On the other hand,

Burchard & Kern (6) found that not all eggs with a typical S. intercalatum morphology stained red and some eggs from S. haematobium also stained red. However, other investigators considered that the Ziehl-Neelsen staining technique was valuable in the differentiation (12,25,57,63), and that proper processing of the tissue material was necessary, otherwise misleading results might be obtained (63).

7. TREATMENT

Praziquantel, the current drug of choice, is safe, easily administered and very effective against all species of schistosomes, including S. intercalatum.

Before praziquantel was available for the treatment of S. intercalatum, different kinds of antischistosomal drugs had been used including trivalent antimonials (26,50) and niridazole (24,50,55). Niridazole was found to be less effective against S. intercalatum than against S. mansoni in infected mice given a daily dose of 50 mg/kg bodyweight for 10 consecutive days (55). In a comparative clinical study between niridazole and praziquantel, niridazole was given in a daily dose of 25 mg/kg for 7 consecutive days and praziquantel was given in 2 doses of 30 mg/kg administered at a 4-hour interval. Six weeks after the treatments, 9 (53%) of 17 patients in the niridazole-treated group still excreted viable eggs of S. intercalatum in the stools compared with only 3 (16%) of 19 patients in the praziquantel group. The difference was significant ($P < 0.025$) and praziquantel was proven to be superior to niridazole in the treatment of S. intercalatum infection. Other reports showed that a single dose of 40 mg/kg of praziquantel was also very effective for S. intercalatum infections (18,19) and in 5 children excreting hybrid S. intercalatum-shaped eggs in their urine, praziquantel treatment was curative (18). The high efficacy of praziquantel against S. intercalatum infection was also reported in infected hamsters (60). Comparative studies of an experimental antischistosomal drug, oltipraz (35972 RP), versus praziquantel showed that the high cure rates of the 2 drugs were not significantly different (32,37). However, owing to the late onset of toxicity in a few oltipraz-treated patients, clinical trials with oltipraz were suspended in 1984 and its development was terminated (14).

8. CONCLUSIONS

Endemic foci of S. intercalatum have been found in forest areas of 6 countries in West and Central Africa: Cameroon, the Central African Republic, Chad, Equatorial Guinea, Gabon and Zaire. Isolated cases have been reported from a few other countries and epidemiological surveys are needed to determine whether transmission occurs in these areas. In laboratory studies, various animals can be infected with the parasites. However, natural infection with S. intercalatum has been reported in only 1 species of wild animal. The wide distribution of its intermediate snail hosts contrasts to the restricted distribution of the disease. In the few population-based epidemiological studies which have been reported, the peak prevalence and intensity of infection are observed in the 5-14-year age-group. After 35-40 years of age, few, if any, persons are infected.

In experimental animals, most of the eggs are found in the large intestine as the adult parasites reside mainly in the small veins of the colon. A portion of the eggs are deposited in the small intestine and liver, whereas few eggs are seen in the lung and bladder. Two geographical strains of S. intercalatum, the Cameroon strain and the Zaire strain, have been described. Each has different intermediate snail hosts and different patterns of the egg distribution in the host body. Experimental hybridization in animals and natural hybridization in humans have been demonstrated. If S. intercalatum-like eggs are found in the urine, this is probably owing to hybridization between male S. haematobium and female S. intercalatum.

Morbidity due to S. intercalatum infection is lower than that due to S. mansoni or S. haematobium infection. The large intestine is the target organ with egg granulomas, inflammation and, occasionally, bleeding. Abdominal pain and bloody diarrhoea are the major symptoms. Pathological change of the liver is usually limited to the portal

triad. Exudation and infiltration are mild, granulomas are smaller than those seen in S. mansoni infection and parenchymal changes in the liver are nonspecific. No hepatic cell necrosis has been reported. Presinusoidal portal obstruction is not evident. Periportal fibrosis, if it exists, is slight. Accumulation of fine-to-coarse granular pigment in the Kupffer and endothelial cells is common. As a result, hepatomegaly is not a prominent sign, splenomegaly is rare, and portal hypertension has never been reported. No death due to S. intercalatum infection in humans was found in our review. Most people in the endemic areas are asymptomatic. Clinical diagnosis can be appropriately made by a stool concentration technique. The Kato-Katz technique, although less sensitive, is useful in epidemiological surveys. Seroreactivity to S. haematobium or S. mansoni antigens is low. Rectal biopsy is a sensitive clinical diagnostic procedure. Praziquantel is the drug of choice in the treatment of the disease.

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