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REVIEW

Considering treatment of male genital schistosomiasis as a tool for future HIV prevention: a systematic review

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Abstract
Objectives Male genital schistosomiasis (MGS) is a neglected manifestation of Schistosoma haematobium infection with ignored implications on reproductive health and a differential diagnosis to sexually transmitted infections in endemic regions. MGS may have associations with HIV transmission and acquisition, and treatment could be a neglected chance of HIV prevention. This review summarizes current knowledge on epidemiology, clinical manifestations, diagnosis and treatment of MGS as a hypothesized risk factor for HIV transmission. Future research areas of global interest are suggested.
Methods PubMed published literature was reviewed based on the MOOSE guidelines. All publications on MGS were included regardless of publication year and study design. Furthermore, all publications were searched for information on possible HIV association.
Results The 40 identified publications related to MGS were dominated by case reports and observational studies. No randomized clinical trials have been conducted to date, and very scant information related to possible associations with HIV transmission was presented.
Conclusions Clinical, randomized studies and epidemiological studies covering the possible association between MGS and HIV are urgently needed. Furthermore, field diagnostic tools should be developed and future mass treatment programs should include adults to reduce morbidity and prevent HIV acquisition.
Systematic review registration number CRD42015016252.

Keywords Male · Genital · Schistosomiasis · HIV · MGS

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Introduction

Epidemiology

Schistosomes are prevalent in sub-Saharan Africa, regions of South America, the Middle-East and Asia (Shebel et al. 2012), and a proposed 8 % of the world's population is infected. According to the World Health Organization (WHO) fact sheet #115, there were 249 million people who needed preventive therapy for schistosomiasis in 2012. Approximately, 90 % of these individuals live in sub-Saharan Africa. Prevalence surveys yield considerable underestimation due to insensitive schistosome detection assays. More recent estimates suggest that 400 million people are infected and an additional 779 million people are at risk of acquiring schistosomiasis.

Life cycle and pathology

Schistosomes are blood-dwelling flukes. The infective cercariae are hosted by intermediate host snails in vegetation of slow-flowing waters and enter the human body through the skin during fishing, bathing and other household activities. Evasion mechanisms render the worms refractory to immunological defence mechanisms and clearance. Clinical manifestations of the infection reflect the schistosome subspecies, the developmental stage of the parasite, and the host's immunological response. For example, approximately 6 weeks after infection with SH, the adult worms start to excrete eggs, which penetrate the bladder wall and venous plexuses of the urogenital organs, inducing tissue granulomas around deposited eggs. Adult worms can survive in the human host for two decades and cause a variety of symptoms from acute Katayama fever to chronic lesions as seen in genital schistosomiasis. Eggs induce inflammatory reactions, whilst the presence of adult schistosomes and mating pairs induces moderate protection against re-infection (Shebel et al. 2012).

Female genital schistosomiasis (FGS)

Many unanswered questions remain regarding the pathogenesis of FGS. Researchers have worked intensively to turn the eyes of policy makers in Africa towards the problem (Mbabazi et al. 2011; Ndeffo Mbah et al. 2013a). Kjetland et al. found that 75 % of women with urinary schistosomiasis have genital egg-induced inflammation (Kjetland et al. 2005; Norseth et al. 2014). No correlating studies have been conducted in males, but the same mechanism can be assumed to cause lesions in males accordingly. Mucosal hyperplasia, erosive lesions and epithelial ulceration are typical findings and have recently been officially classified as granules, sandy patches and rubbery nodules (Jourdan et al. 2011b). Schistosomal endometritis and placental involvement have been associated with premature deliveries and intrauterine growth retardation, respectively (Poggensee and Feldmeier 2001). In a clinical survey, eggs in the cervical region were found in 23 % of Tanzanian women without schistosome eggs in their urine (Poggensee et al. 1998). They found that 32 % of infected women had genital disease, and that only 43 % of all SH-infected subjects had haematuria (Poggensee et al. 1998). Over the last decade, numerous reports have found an association between FGS and HIV, suggesting that inflamed genitals are more readily infected by HIV versus non-inflamed genitals. This is due to genital sores and immunological changes favouring HIV establishment when women with FGS are exposed genitally to HIV (Kjetland et al. 2014a).

MGS and association with human immunodeficiency virus (HIV)

HIV prevalence is high in many SH-endemic regions, especially in sub-Saharan Africa where more than 24 million HIV-infected individuals live within the well-established geographic overlap of the two diseases (Ndeffo Mbah et al. 2013b; Secor 2012) The growing acknowledgment of schistosomiasis as a cause of considerable genital morbidity in females and its possible connection to HIV acquisition led to the 1997 inclusion of schistosomiasis on the list of high-priority scientific areas of the "Gender Task Force of the WHO's Tropical Disease Research Program" (Kjetland et al. 2014a). Schistosomiasis has traditionally been regarded as a childhood disease, causing visible organomegaly, growth retardation and male "menstruation" among boys in endemic areas. Consequently, haematuria, caused by schistosomal bladder infiltration, has been regarded as a common sign that adolescent males have reached adulthood. During the acceleration of the HIV epidemic in Africa in the last two decades, genital involvement of urogenital schistosomiasis infection has attracted the interest of medical researchers because of characteristic pathologies observed in reproductive organs (Poggensee and Feldmeier 2001). In line with the emerging awareness of a possible association between schistosomiasis and HIV transmission, there is now increased interest in MGS as an HIV risk factor, particularly in the highly affected young adult population. The hypothesis is that the mechanical breach of the genital mucosa renders schistosomiasis-infected individuals more prone to contracting or transmitting HIV during intercourse. The local recruitment of CD4+ cells in the genitals during genital schistosomiasis may also facilitate uptake of HIV virions and establishment of infection. In co-infected individuals, a higher viral load can result in intensive HIV

shedding (Feldmeier et al. 1999; Kjetland et al. 2012). Recent data suggests that sexually transmitted infections STIs and genital inflammation may partially override the suppressive effect of antiretroviral therapy (ART) on seminal HIV shedding (Politch et al. 2012). Genital schistosomiasis results in increased genital vascularity (Kjetland et al. 2014b), which is associated with higher white-blood-cell frequencies. If these include HIV-infected CD4+ lymphocytes, cells could be directly deposited with semen or could increase seminal HIV viral load. Either outcome could result in HIV transmission.

Data suggest that praziquantel (PZQ) treatment of SH in HIV co-infected subjects reduces HIV replication and increases CD4 cell count in the absence of ART (Kallestrup et al. 2005). However, the effect of MGS on genital HIV-1 shedding in co-infected men has not been investigated (Kjetland et al. 2012). WHO has requested increased research awareness towards the role of genital schistosomiasis in HIV transmission across sub-Saharan Africa (Mbabazi et al. 2011) and clinical studies testing the potential of PZQ to reduce HIV shedding and HIV transmission rates.

Objectives

The review focuses on the following:

1. Is MGS a major health problem in SH-endemic areas?
2. Does MGS increase HIV shedding in co-infected individuals?
3. Obstacles for MGS diagnosis.
4. A summary of current knowledge on clinical manifestations, long-term complications and treatment of MGS.
5. Future research aims.

Methods

We followed the PRISMA and MOOSE consensus guidelines (Stroup et al. 2000). Accordingly, this review is registered with Prospero: CRD42015016252. Between October and December 2014, Pubmed and Medline databases were searched by the corresponding author to identify all papers that mention MGS regardless of publication year and study design. Medical subject heading "Schistosomiasis" in Pubmed and Medline centrals was combined with the following terms: genital schistosomiasis, genital disease, lower reproductive tract, male/female, MGS, FGS, gender, testicular, prostatic, seminal, HIV, infertility. Publications on FGS were read to relate the theoretical background of the pathology. Efforts were made to contact corresponding authors of each paper to identify additional published studies not available online. All English language, clinical studies reporting about genital SH were examined when the topic was male schistosomal disease regardless of whether HIV status was reported and handsearch from reference lists of obtained articles was added for further pertinent articles. The frequencies of the following variables were registered: method of detection or diagnosis, clinical and paraclinical findings including detection of eggs in stool or urine, localization of lesions, symptoms, country of exposure, age group, number of participants, control group, time since exposure, treatment regimens and outcomes, active or chronic infestation, and schistosomal species.

Results

Available publications

The search including both FGS and MGS revealed 47 relevant publications, of which 40 publications specifically addressed MGS. Twenty-two case reports were found. We identified 10 observational and 4 clinical studies. Two reviews have been published: Rollinson's review on urinary schistosomiasis (Rollinson 2009), and a review by Richter (Richter 2000) analysing literature on genital manifestations of tropical diseases. Two postmortem studies from Africa in 1970 and 1988 serve as a base for almost all references to MGS pathology (Gelfand et al. 1970; Patil and Elem 1988) along with the review by Rollinson (Rollinson 2009). No randomized clinical trials have been conducted to date, and minimal research has focused on the possible association with HIV transmission. A graphic overview of summarizing estimates and descriptive information cannot be provided within the limits of this review due to the heterogeneity of the studies and the statistical uncertainty of findings. Important findings will be described in the following sections.

MGS

Current data on MGS prevalence rely on older postmortem histopathological studies and correlations to HIV status have not been researched. In SH-endemic areas, MGS was found in 58 % of male cadavers (Shebel et al. 2012). Vilana reported that 28 % of SH-infected Spanish travellers had genital symptoms and rectal ultrasonographic changes (Vilana et al. 1997). Barlow and Meleney recorded a diagnosis of schistosomiasis of the prostate in 19 % of known infected males (Barlow and Meleney 1949). Leutscher et al. found SH eggs in 43 % of semen samples from SH-infected men in Madagascar (Leutscher et al. 2000). As reflected by the dates of these reports, sporadic case reports

of MGS have been published. Nevertheless, the focus on MGS is rising with accumulating evidence of the association between FGS and HIV acquisition and transmission. Genitals are invaded by haematogenous or lymphatic spread and not necessarily associated with bladder infection, which explains why worm eggs are not always present in urine (Khafagy and Khalil 1970; Obel and Black 1994). There may be marked inflammation with only a few eggs and yet intensive oviposition may provoke little or no response, possibly reflecting different immunologic properties of the host (Gelfand et al. 1970; Vilana et al. 1997).

Symptoms and anatomical distribution of MGS

The epididymis, spermatic cord, testes and prostate can be affected, leading to initial enlargement of the organs. This is closely followed by fibrosis, shrinkage and calcification. Seminal vesicle cysts may remain asymptomatic and be discovered incidentally. Alternatively, they may cause symptoms such as voiding, chronic epididymitis, ejaculate duct dilatation, and haemospermia or prostatitis, possibly leading to increased risk of HIV transmission if co-infected. When caused by SH, patients complain of dysuria, haemospermia, frequent urination and lumpy semen. Four of 22 case reports reported a positive test for haemospermia, while four other case reports were negative for haemospermia. In 14 cases, this information was not reported. A considerable proportion of males with SH will exhibit some level of MGS, with or without macroscopic haemospermia (Leutscher et al. 2000). In the reviewed case reports, where information of anatomical site of lesions was available from histology or clinical manifestations, disease was most prevalent in the seminal vesicles (8/22) followed by the prostate (6/22) and testis (5/22).

Male infertility

SH has been proposed to cause male infertility (Adisa et al. 2012; Kini et al. 2009; Ugwu et al. 2014). The causality has been debated in the literature and perspectives that support no correlation include: (i) The magnitude of the problem is probably negligible as inflammation of seminal vesicles is often unilateral (Gelfand et al. 1970; Patil and Elem 1988); (ii) Use of fructose test, vesiculography and casting techniques in 40 schistosomiasis patients has failed to prove obstructive infertility (Aboul et al. 1977); (iii) Patil et al. found no correlation between intensity of infection and histological changes in 50 Zambian postmortem observances. They suggest that due to normal histological appearance an association with infertility is unlikely (Patil and Elem 1988). Perspectives opposing these arguments include: (i) A possible geographical variation explaining the discrepancies between the Zambian study and the Zimbabwean findings by Gelfand. According to Rollinson, SH hybridizes in nature and experimentally, which argues for a possible geographical variation explaining the demonstrated differences (Rollinson 2009); (ii) MGS has proven to be associated with seminal apoptosis and reduced seminal fluid quantity (Leutscher et al. 2009); (iii) A case of total azoospermia in a traveller returning from Uganda suggests that intense epididymitis can create obstructive azoospermia, inhibit spermatogenesis and cause irreversible male infertility with normal levels of gonadotrophins and testosterone (Kini et al. 2009); (iv) In 1992, Bornman et al. presented evidence of improved semen quality in an infertile man after treatment for schistosomiasis. Improvements included sperm motility and proper pH of the seminal fluid, suggesting improved function of the seminal vesicles after schistosomiasis treatment altered the biochemical composition of seminal fluid into a less hostile environment for the sperm. Direct semen-toxic effect of ova excretions is also postulated (Bornman et al. 1992); (v) Omer et al. found that 13.6 % of 59 sub-fertile men have schistosomiasis, partly due to spermatic arrest, which is a known cause of schistosomal inflammatory obstruction (Lembeli and Venkataramaiah 1981; Ogunbanjo et al. 1989; Omer 1985); (vi) Patients with schistosomal prostatitis often complain about weak erection, rapid ejaculation and diminished libido (Ghoneim 2002). In the current review, infertility was reported in two of 22 cases, normal fertility occurred in 6 of the 22 and information was missing in 14 of 22 case reports. Time span from pathogen exposure to disease diagnosis ranged from 2 months to 13 years in the nine case reports, where this information is available.

MGS morbidity

Of note, journals from multiple disciplines have published case reports about returned travellers, mainly from the African continent, who complained of watery, discoloured semen (Corachan et al. 1994; Durand et al. 2004; Hawary et al. 2012; Kini et al. 2009; Logan et al. 2013; Obel and Black 1994; Perignon et al. 2007; van Delft et al. 2007; Vilana et al. 1997). Many of the reported cases were initially misdiagnosed due to lack of haematuria, haemospermia or Katayama fever. Four studies were identified from urologic journals. They used computed tomography (CT) or ultrasound scan (USS) as diagnostic tools for genital schistosomiasis detecting classic radiographic calcifications pathognomonic of genitourinary schistosomiasis (Fataar et al. 1990; Jorulf and Lindstedt 1985; Vilana et al. 1997). Diagnosis is complicated by false negative examination for schistosomal eggs. In the reviewed literature, egg detection was reported positive in urine, faeces or semen in 7 of 22 case reports and undetected in 6 of 22 cases. Information

was missing in the remaining nine cases. Age range was between 10 and 68 years of age.

MGS and HIV transmission

Modifications to reduce HIV acquisition risk include antiretroviral therapy (ART), condom use, circumcision, and hypothetical treatment of sexually transmitted infections (STIs) (Hayes et al. 2010). Genital sores and inflammation with resultant abnormal blood vessels strongly suggest a risk factor for HIV infection. As shown by Leutscher et al. in Madagascar, egg-induced inflammation in the genitals recruits and activates great numbers of CD4+ immune cells (Leutscher et al. 2005), although these findings could not be reproduced by Kjetland et al. in Malawi. The infiltrating CD4+ T-cells express the CCR5 chemokine receptor required for HIV cell entry, and increased levels of IL-4, IL-6, IL-10, IFN-γ and TNF-α in semen of SH-positive subjects may induce accelerated replication of HIV in the human body via a stimulatory effect of IL-6 and TNF-α. Parasitic infection evokes an eosinophilic immune response. As eosinophils express CD4, this mechanism may facilitate viral transmission (Fincham et al. 1999; Kaul et al. 2008; Lucey et al. 1989; Wolff and Anderson 1988). Schistosomiasis has been shown to impair the killing of invading retroviruses by cytotoxic T-cells and the infection may thereby accelerate the natural history of HIV establishment in the body. Antigenic mimicry between schistosomes and HIV regulatory proteins have been reported (Capron and Dessaint 1992) and several studies have hypothesized an association between FGS and HIV (Downs et al. 2011; Kjetland et al. 2006), suggesting that egg-induced lesions of the mucosa facilitate cellular entry of HIV virions. SH is associated with abnormal blood vessels and increased density of HIV target cells, including CD4 + T-lymphocytes, eosinophils and macrophages in the mucosa of the cervix, and could facilitate uptake of HIV virions (Jourdan et al. 2011a, b). Theoretically, histological and pathophysiological changes described in females chronically infected with schistosomiasis are likely to be abundant in males also. This gives rise to the suspected increase of viral shedding in seminal fluids among SH/HIV co-infected individuals. This suspected increase, however, has never been systematically investigated in a clinical trial. Studies have shown increased seminal plasma HIV-1 RNA concentrations in men with *gonococcal, Chlamydial* and *T. vaginalis*-associated urethritis followed by a significant reduction after antibiotic therapy (Cohen et al. 1997; Moss et al. 1995; Price et al. 2003; Sadiq et al. 2002, 2005). Increased rates of HIV transmission occur when seminal viral burden is high due to genital inflammation (Chakraborty et al. 2001; Sadiq et al. 2005) and MGS may be regarded as a contributing risk factor for HIV transmission (Chakraborty et al. 2001). It has been demonstrated that MGS is associated with an increased leukocyte count in semen, and that the leukocyte count declines after PZQ treatment (Leutscher et al. 2005).

Treatment

Praziquantel (PZQ) is the drug of choice for treating all manifestations of schistosomal disease. One dose results in 90 % clearance of adult schistosomes but only a minimal effect on larval stages. It acts via increased cell-membrane calcium penetration, leading to paralysis and immune clearance by the host. Standard treatment is sometimes supplemented with a second dose (40 mg/kg) 6 weeks after the first treatment (Knopp et al. 2013; Poggensee and Feldmeier 2001; Zwang and Olliaro 2014). The WHO infection intensity definitions range from "light" to "moderate" to "heavy" according to the numbers of eggs/10 ml urine. In postmortem studies, definitions are quantified in relation to eggs/grams of tissue. Acute symptoms resolve quickly after treatment, but chronic tissue damage and fibrosis resolve slowly. Calcifications due to chronic inflammation appear refractory to conventional treatment of genital manifestations and have been proposed to require longer follow-up or higher doses (Dauda and Rafindadi 2006; Perignon et al. 2007). PZQ is widely used in national prevention programs that perform mass drug administrations (MDA) in schools throughout sub-Saharan Africa. Unfortunately, these programs do not include adults who are particularly prone to long-term genital complications of the infestation. The WHO goal for preventive therapy is that 75 % of at-risk populations receive preventive chemotherapy (World Health Organization 2013). Different conclusions on the comparison of cure rates of SH by artesunate and PZQ have been published, with the highest cure rate occurring in children treated with a combination of artesunate and PZQ in Nigeria (Inyang-Etoh et al. 2009). Trials testing combinations of PZQ with artesunate and mefloquine are pending (Kramer et al. 2014). Individual case reports may portray persisting pathology more than a decade after schistosomal exposure (Venz and Ruckner 1992), but little attention has been paid to evolution of lesions after anti-parasitic therapy (Vilana et al. 1997). Sub-curative treatment may result from one single course of PZQ and more than one dose of treatment should be considered (Cioli 1998; Feldmeier and Poggensee 1993). To date, all reported clinical studies regarding the treatment outcome of genital disease have been on FGS.

SH disease manifestations

Chronic SH infection primarily affects the urogenital organs (Edington et al. 1975; Gelfand et al. 1970, 1971;

Vennervald and Dunne 2004). Histopathological changes, including inflammatory lesions in the prostate and seminal vesicles without a correlation between egg load and grade of inflammation, have been established (Gelfand et al. 1970; Patil and Elem 1988). Surprisingly, only a few eggs were sufficient to provoke a substantial reaction, while intense infestation could be accompanied by a minimal inflammatory response. The bladder was most prone to inflammation followed by the seminal vesicles, vas deferens and the prostate, the latter of which may also become enlarged. Schistosome eggs cause a chronic irritation of the urothelium and cell proliferation, which results in bud-like polypoid structures, and in some cases mucin-secreting glands that develop into adenocarcinomas. Fibrosis may lead to urethral strictures, peri-urethral abscesses and fistulas in the peri-anal and scrotal area. Bladder abnormalities and urinary tract obstruction most frequently resolve after treatment or may heal spontaneously. Bladder and ureteric calcifications are prominent radiologic features of schistosomiasis, followed by involvement of the seminal vesicles, the spermatic cord, the prostate and vas deferens (Fataar et al. 1990). Reversal of urinary tract pathology, as determined by USS, is generally fast (Richter 2000). However, reversal of the minute lesions in bladder mucosa such as pathognomonic "sandy patches" has only been infrequently described (Silva et al. 2005). Furthermore, only one in nine cases of MGS showed significant resolution 9 months post-treatment (Doehring et al. 1986; Vilana et al. 1997).

Malignancy

The mechanism of schistosoma-induced carcinogenesis remains unclear, but may be associated with a change in the bladder's capacity to detoxify endogenous compounds or potentiate effects of external bladder carcinogens. The carcinogenic enzyme beta-glucuronidase has been found in patients with schistosomiasis (Al Adnani 1985). Bladder cancer is the most prevalent malignancy in SH-endemic countries of Africa and has a different cancer histology (squamous cell carcinomas) compared to non-African bladder cancers (transitional cell carcinomas) (Rollinson 2009). In a retrospective study of 80 Nigerian cases, the anatomical distribution of schistosomiasis revealed the urinary bladder being affected in 50 cases (62.5 %) and coexisting bladder carcinoma was found in 15 cases (30 %) with schistosomiasis distribution into the urinary bladder (Mohammed et al. 2007). Colorectal and renal cell carcinomas have also been found in conjunction with schistosomal infection (Ming-Chai et al. 1980; Smith et al. 1974). Two case reports describe co-existence of genital cancer and schistosomal inflammation, especially in the prostate. Cancers seem to arise at a younger age in people infected with schistosomes (Alexis and Domingo 1986; Cohen et al. 1995). Kjetland et al. proposed that the disrupted vascularization around deposited eggs eases transmission of human papilloma virus (HPV) (Kjetland et al. 1996, 2010). A mechanism of coordinate contributions to cancer by schistosomiasis and other factors has been suggested. These could include poor nutrition, frequent sepsis and environmental carcinogens (Cohen et al. 1995). Moreover, numerous reports have told the stories of patients presenting with prostatic or testicular masses leading to misdiagnosis of cancers with resultant orchiectomy or prostatectomy, where post-operational histology revealed MGS and no cancer cells (Rambau et al. 2011).

Field diagnostics

Genital SH prevalence is underestimated throughout Africa due to limited clinical infrastructures that generally rely on symptomatology and microscopy for diagnosis. Haemospermia has been suggested as a proxy for MGS (Feldmeier et al. 1999), although the association is questioned (Al-Saeed et al. 2003; Elem and Patil 1987). Detection of haemospermia requires active questioning and examination as this condition is seldom passively observed or even spontaneously reported by patients (Corachan et al. 1994). Numerous reports advocate for routine examination of semen in patients as urine or faeces microscopy may be negative even in serious schistosomal infections (Bornman et al. 1992; Corachan et al. 1994; Durand et al. 2004; Hawary et al. 2012; McKenna et al. 1997; Obel and Black 1994; van Delft et al. 2007). No significant associations were found between specific symptoms and eosinophilia in 79 cases of returned travellers from Lake Malawi (Logan et al. 2013). This is the most extensive case report published, but the report only analyses cases of acute schistosomiasis and does not mention any genital manifestations.

Advanced diagnostic tools

ELISAs for egg antigen detection of circulating cathodic antigen (CCA), membrane-bound antigen (MBA) or circulating anodic antigen (CAA), the latter of which has a high specificity, sensitivity and positive predictive value for egg excretion in urine and semen. Both CCA and CAA reflect relative infection intensity (Carey et al. 2001; Leutscher et al. 2008; Logan et al. 2013). Tests are positive approximately 12 weeks after infection. Commercially available diagnostic tools, such as strip tests for detecting CCA, soluble egg antigen (SEA) ELISA assays and dipsticks (MoAb) for urine and semen show promising results in small scale studies, but apart from the CCA strip test they are still too expensive for use in developing country settings (Ochodo et al. 2015). Eosinophil cationic protein

(ECP) in urine and semen reflects egg-induced inflammation with a limited clinical relevance in the field. Detection of haemoglobin-derived peptides in the urine of infected patients has been set up as a reverse-phase cation-exchange fractionation, followed by mass spectrometry. Ultrasound scan (USS), when performed with a 5- or 7.5-MHz biplanar endorectal probe is a generally accepted method of detection of genital pathology. Lesions often present as echogenic masses with diffuse punctate calcification and cystic changes, uni- or bilaterally (Corachan et al. 1994), although USS has been criticized for being less sensitive than biopsy followed by histopathological examination (Durand et al. 2004; Kini et al. 2009). Other radiological diagnostic methods of urinary or genital schistosomiasis exist in developed countries. The gold standard of FGS detection is made by colposcopic examination for grains, sandy patches or rubbery papules (Kjetland et al. 2014b; Norseth et al. 2014). Other detection methods include tissue biopsies, urinary filtration techniques, cystoscopy, cervical smears, classical histology and potassium hydroxide tissue digestion of postmortem tissue samples, CT, magnetic resonance imaging (MRI) and colposcopy (Richter 2000).

Discussion

MGS is a neglected manifestation of SH infection and could very well prove to be an important cofactor in HIV transmission in SH-endemic regions. Insufficient quantity and quality of studies exist and in the available publications correlation data are missing. One great challenge is defining diagnostic criteria for MGS. Endemic MGS frequency is difficult to ascertain because available diagnostic tools are few, and the unspecific nature of symptoms poses a great risk of disease burden underestimation. Incorrect diagnoses of cancer for MGS result in surgeries that alter the reproductive capacity of many men and delay effective SH treatment. The prevalence of genital involvement among women with urinary schistosomiasis ranges from 37 to 65 %, but this number is unknown in men (Ibisomi and Mudege 2014; Ndeffo Mbah et al. 2013b; Poggensee et al. 1999; Renaud et al. 1989). If examination is limited to a single urine test, 31 % of all FGS cases will be missed. Similar findings probably occur in MGS, but this has never been explored (Poggensee et al. 1998). To date, studies on HIV-SH co-infection have focused solely on FGS. The immunological background and mucosal changes shown in these studies may also apply to MGS. Young people most at risk of contracting HIV are not included in MDA programs and prevention should focus more on this matter. It remains unclear whether MGS symptoms are reversible after PZQ treatment and which treatment regimen is acquired. This and other details in understanding the possible risk factors attributed to MGS are yet to be explored and it is not yet possible to conclude that treatment of MGS is a neglected tool for HIV prevention.

Diagnostic challenges

Symptoms are non-specific for genital schistosomiasis and none are pathognomonic. Better field-applicable diagnostic tools for schistosomiasis are necessary. The gold standard of diagnosing schistosomiasis in the field is still the microscopic detection of eggs in tissue or body fluids. This is very specific and possible in low-technology settings, but time-consuming and observer dependent. Day-to-day variation of egg excretion is substantial and one urine sample per day on 3 consecutive days is required because, eggs are regularly washed out by urine flow, especially during mid-day where schistosome motility peaks in the bladder. Semen analyses demonstrated that in 62 % of SH-positive men whose semen samples were examined twice, one sample would be negative (Leutscher et al. 2008). This suggests that diagnosing MGS by adapting the tradition of three samples (after 3 days of sexual abstinence) could be the future way of seminal sampling. Haemospermia, defined by visual inspection or chemical test, as a diagnostic tool still awaits clinical validation in a larger scale designed to delineate whether HIV co-infection alters the egg load in semen, as has been suggested for urine (Mwanakasale et al. 2003). A clinical survey indicated that 23 % of Tanzanian women had eggs in the cervical region but no eggs in their urine (Poggensee et al. 1998). They also found that 32 % of SH-infected women had genital disease and 43 % of SH-infected subjects had haematuria. This means that long known tools, such as the detection of haematuria, haemospermia or eggs in urine or semen, are far from sensitive enough to detect cases of genital involvement, initiate treatment and reduce morbidity. Recorded prevalence will continue to be underestimated until improved diagnostic tools are widely available and used in SH-endemic regions (Poggensee et al. 1998). Schistosomal lesions in the male genitals are often abundant without giving rise to egg excretion, because eggs are trapped and only a few reach the lumen of the organs, as suggested by postmortem analyses (Gelfand et al. 1970).

Conclusion

Many unanswered questions remain regarding the possible association between HIV and genital schistosomiasis and researchers have worked intensively to turn the eyes of policy makers in sub-Saharan Africa towards this problem (Mbabazi et al. 2011; Ndeffo Mbah et al. 2013a). Unfortunately, scant data exist to support the hypothesis of an

HIV–schistosomiasis association. However, existing studies do suggest that FGS increases the risk of contracting and of transmitting HIV. More studies are needed to test whether PZQ treatment of schistosomiasis has an HIV prophylactic effect. An alternative explanation for the observed results could be other concurrent genital infections, which not all studies have considered. The diversity of study designs and aims makes it impossible to make simple generalizations from existing literature and further research is needed to assess the biological and disease-specific qualities of SH. If an association can be proved, the following preventive measures to break the life cycle of this disease-spreading parasite should be prioritized: development and implementation of mass drug administration programs; treatment and re-treatment strategies; education of people living in and travelling to rural endemic areas; sustainable vector snail control programs; improved sanitation and research into vaccines (Mohammed et al. 2007). In endemic areas, there is an urgent need for low-cost, low-sophistication diagnostic tools, or an alternative approach to mass treatment programs to include whole populations, especially young adults, to reduce morbidity and possibly prevent the spread of HIV. This review highlights the shortage of research and knowledge of MGS associated with SH and HIV transmission. Assessing the possible association of genital SH and HIV co-infection must be recognized as an important part of the global health agenda and a welcome alternative to preventing HIV spread (Colley and Secor 2007; Leutscher et al. 2005; Rollinson 2009). Clinical, randomized studies and epidemiological studies covering the possible association between MGS and HIV and using gold standard diagnostics and disease definitions are urgently needed.

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